PROSTAGLANDIN-J₂ INDUCES THE ENDOTHELIAL SYNTHESIS OF IL-8 INDEPENDENTLY OF PPARγ ACTIVATION

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Prostaglandin-J₂ is a natural ligand of PPARγ, a transcription factor involved in inhibition of inflammatory response. We examined the influence of 15-deoxy-Δ¹²,₁₄-prostaglandin-J₂ (15d-PGJ₂) on generation of interleukin-8 (IL-8), one of the principal mediators of inflammation, by human microvascular endothelial cells (HMEC-1). After 24 h incubation, resting and LPS-treated HMEC-1 released about 150 and 1000 pg/ml of IL-8, respectively. PPARγ was expressed in HMEC-1 and could be activated by ciglitazone (exogenous PPARγ agonist) and 15d-PGJ₂. Both basal and LPS-induced expression of IL-8 mRNA and protein were potently and dose-dependently increased by 15d-PGJ₂, as well as by prostaglandin-F₂ (inhibitor of PPARγ) and prostaglandin-E₁ (does not influence PPARγ). Ciglitazone did not exert any effect, even in cells overexpressing PPARγ cDNA. In contrast, production of IL-8 in response to 15d-PGJ₂ was reduced in HMEC-1 treated with antioxidants or transfected with Cu/Zn-SOD, whereas xanthine/xanthine oxidase stimulated IL-8 synthesis. 15d-PGJ₂ elevated cAMP level and its effect on IL-8 was potentiated by IMBX, inhibitor of cAMP degradation. Induction of cAMP by forskolin imitated effect of 15d-PGJ₂, resulting in increased IL-8 expression, whereas inhibition of cAMP or blockage of p38 kinase activity completely prevented response to 15d-PGJ₂. Surprisingly, SN-50, a NFκB inhibitor, did not attenuate IL-8 release and 15d-PGJ₂ did not influence the NFκB nuclear translocation or DNA binding. 15d-PGJ₂ potently increases IL-8 production in HMEC-1. This effect is independent of PPARγ, but is possibly connected with induction of oxidative stress, upregulation of cAMP and activation of p38 kinase. NFκB is not involved in this pathway.