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PEROXISOME PROLIFERATOR-ACTIVATED RECEPTORγ INHIBITS ANGIOGENESIS BY SUPPRESSING CREB-MEDIATED CYCLOOXYGENASE-2 EXPRESSION IN HUMAN ENDOTHELIUM

Scoditti E[1,2], Massaro M[1,2], Carluccio MA[1], Distante A[1], Storelli C[2], and De Caterina R[3].

[1]C.N.R. Institute of Clinical Physiology, Pisa and Lecce, Italy.
[2]Department of Biology-University of Lecce, Italy.
[3]Institute of Cardiology, "G. d'Annunzio" University, Chieti, Italy.

Objetives. Neoangiogenesis contributes to diabetic vasculopathy and intraplaque hemorrhage in atherosclerosis. The activation of Peroxisome Proliferator-Activated Receptor(PPAR)γ is known to inhibit angiogenesis. We therefore examined the effects of PPARγ agonists on the pro-angiogenic enzyme cyclooxygenase(COX)-2 in human umbilical vein endothelial cells challenged with vascular endothelial growth factor (VEGF) and phorbol 12-myristate 13-acetate (PMA).
Methods and Results.A 24 h exposure of HUVEC to the PPARγ agonists rosiglitazone (RSG) and GW1929 significantly attenuated VEGF- and PMA-stimulated COX-2 activity (by 30%, immunoassay for 6-keto-PGF1α), as well as protein (by 50%, Western analysis) and mRNA expression (by 50%, RT-PCR). This effect was abolished by the PPARγ antagonists bisphenol A diglycidyl ether and GW9662. COX-2 promoter activity experiments revealed that the induction of COX-2 promoter was significantly inhibited by RSG through an interference with the cAMP response element (CRE) site. COX-2 downregulation after siRNA knockdown of the transcription factor CRE binding protein (CREB) confirmed the role of CREB in mediating COX-2 transcription. Correspondingly, PPARγ agonists also attenuated CREB phosphorylation/activation. Since Protein Kinase(PK)C is involved in VEGF-induced COX-2 expression and CREB activation, we also investigated which isoforms of PKC were affected by RSG. While the inhibition of both conventional PKCα and β suppressed VEGF- and PMA-stimulated CREB activation and COX-2 expression, RGS only reduced VEGF- and PMA-stimulated PKCα membrane translocation.
Conclusions. The anti-angiogenic effect of PPARγ agonists is due, at least in part, to their interference with the PKCα-mediated activation of CREB and the related expression of COX-2. PKCα may therefore be a novel therapeutic target for antidiabetic drugs in atherosclerosis.