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PPARγ ACTIVATION SUPPRESSES ANGIOTENSIN II-INDUCED PRODUCTION OF KLF5 IN RAT VASCULAR SMOOTH MUSCLE CELLS

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Objective The mechanisms underlying the inhibitory effects of PPARγ agonists on Ang II-induced VSMC proliferation and the Ang II/KLF5-dependent signalling pathway remain unclear.

Methods Sprague–Dawley rats received Ang II (150 ng/kg/min) with or without rosiglitazone (5 mg/kg/day) for seven days. Real-time RT-PCR, immunohistochemistry, western blot, and DNA binding assay were performed in rat aorta or cultured vascular smooth muscle cells. MTT assay and flow cytometry were used to measure cell proliferation.

Results We found that, in growth-arrested VSMCs, PPARγ agonists (rosiglitazone and 15d-PGJ2) dose-dependently attenuated Ang II-induced cell proliferation and expression of KLF5 and cyclin D1. These suppressive effects were attenuated by the PPARγ antagonists GW9662, BADGE and PPARγ specific siRNA. Furthermore, PPARγ agonists inhibited Ang II-induced protein kinase C (PKC) ζ and phosphorylation of ERK1/2 and EGR transcription activity but had no effect on PKCε phosphorylation. In aortas of Ang II-infused rats, KLF5 expression was markedly increased, and its target gene cyclin D1 was overexpressed. Cotreatment with rosiglitazone diminished these changes, whereas nuclear PPARγ expression was increased in VSMCs.

Conclusion PPARγ agonists might have an antiproliferative effect through mechanisms that include reducing KLF5 expression, and a crosstalk between PPARγ and PKCζ and ERK1/2 may be involved in the inhibitory effects.