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# Angiotensin II or Uric Acid-induced Apoptosis of Human Vascular Endothelial Cells is inhibited by Peroxisome Proliferator-Activated Receptor γ (PPAR γ) Agonist

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**Background :** Endothelial cell injury is considered a critical event in the pathogenesis of atherosclerotic vascular disease. In atherosclerosis, the turn-over rates of endothelial cells are accelerated and local endothelial cell apoptosis is implicated in this process. Our recent studies demonstrated that both angiotensin II (AII) and uric acid (UA) are associated with early endothelial dysfunction and pathologic vascular remodeling with decreased endothelial nitric oxide (NO) release. PPAR γ agonist, which was originally known as an insulin-sensitizing medication, is reported to exert diverse beneficial effects on vasculature including stimulation of endothelial NO release.

**Methods :** To investigate the effect of PPAR γ on AII or UA-induced endothelial dysfunction with potential mechanism of vaso-protective effect of PPAR γ, we examined the effect of PPAR γ agonist rosiglitazone on endothelial apoptosis, NO release, eNOS expression and activity in human umbilical vein endothelial cell (HUVEC) stimulated by AII (2 μM) or UA (9 mg/dL). Apoptosis was evaluated by FACS analysis after annexin-V staining and cell cycle (Sub G1) analysis, and eNOS activity was quantified by measuring conversion of [$^3$H]-L-arginine to [$^3$H]-L-citrulline.

**Results :** AII (2 μM) or UA (9 mg/dL) induced both early and late apoptosis of HUVEC at 24 hours, which was significantly attenuated with co-stimulation of rosiglitazone (10 μM). AII- or UA-induced decrease in NO release was also reversed with rosiglitazone. However, treatment of AII, UA or rosiglitazone was not associated with the changes in eNOS expression by Western blotting. Treatment of HUVEC with rosiglitazone resulted in an increase in citrulline conversion and eNOS phosphorylation, suggesting rosiglitazone-induced eNOS activity without increasing eNOS expression. Interestingly, we also observed that UA stimulated AII release from 12 hours of stimulation.

**Conclusion :** Our results suggest that PPAR γ increased eNOS activity of HUVEC without affecting eNOS expression itself and protected HUVEC from apoptosis. Uric acid-induced apoptosis and impaired NO release in vascular endothelial cells can be mediated by an increase in angiotensin II production by uric acid.