Advanced glycosylation end products induce inducible nitric oxide synthase (iNOS) expression via a p38 MAPK-dependent pathway.

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摘要

Abstract

BACKGROUND: Advanced glycosylation end products (AGEs) accumulation in tissue has been implicated in diabetic related complications, including diabetic nephropathy. Activation of peroxisome proliferator activated receptor-gamma (PPAR-gamma) ameliorates diabetic nephropathy. METHODS: In the present study, we investigated the effects of AGEs on inducible nitric oxide synthase (iNOS) expression and nitric oxide production, and the effects of rosiglitazone, an activator of PPAR-gamma, on AGE-induced iNOS expression and nitrite release in glomerular mesangial cells. RESULTS: AGEs caused a dose- and time-dependent increase of iNOS induction and nitrite accumulation in mesangial cells. A protein tyrosine kinase inhibitor (genistein), or a p38 mitogen-activated protein kinase (MAPK) inhibitor (SB203580) suppressed AGE-induced iNOS expression and nitrite release from mesangial cells. Addition of bovine serum album in (BSA)-AGEs to mesangial cells increased p38 MAPK activities. Activation of PPAR-gamma by rosiglitazone inhibited AGE-induced iNOS expression, nitrite release, and p38 MAPK activation in mesangial cells. AGE-stimulated nitrite release was attenuated by pretreatment with anti-tumor necrosis factor-alpha (TNF-alpha) and anti-transforming growth factor-beta (TGF-beta) antibodies. AGE-induced iNOS expression was inhibited by treatment with a nuclear factor-kappaB (NF-kappaB) inhibitor, pyrrolidone dithiocarbamate. Addition of BSA-AGEs to mesangial cells stimulated p65 NF-kappaB translocation from the cytosol to the nucleus. CONCLUSION: These data suggest that cytokine release, NF-kappaB and p38 MAPK-dependent pathways may play a role in AGE-induced iNOS expression and subsequent nitric oxide production in mesangial cells. Rosiglitazone may prevent AGE-induced iNOS expression by interfering with p38 MAPK activity.