Advanced glycosylation end products induce NF-kappaB dependent iNOS expression in RAW 264.7 cells.

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Abstract

Advanced glycosylation end products (AGEs) have been implicated in the athogenesis of diabetic complications. Treatment of RAW 264.7 macrophages with bovine serum albumin (BSA)-derived AGEs caused dose- and time-dependent increases in nitrite production and inducible nitric oxide synthase (iNOS) expression. These effects were blocked by the nuclear factor-kappa B (NF-kappaB) inhibitor, pyrrolidone dithiocarbamate (PDTC). BSA-AGEs also stimulated the translocation of p65 NF-kappaB from cytosol to the nucleus. Electrophoretic mobility shift assay revealed that the NF-kappaB DNA-protein-binding activity was enhanced by AGEs. The tyrosine kinase inhibitor, genistein, the phosphatidylinositol-3-kinase (PI3-K) inhibitor, LY 294002, the protein kinase C (PKC) inhibitor, Ro 31-8220, and the p38 mitogen-activated protein kinase (MAPK) inhibitor, SB 203580, all inhibited GEs-stimulated iNOS expression, NO release, NF-kappaB translocation and NF-kappaB DNA binding activity. These results suggest that AGEs may activate NF-kappaB via an upstream signaling cascade composed of tyrosine kinase, PI3-K, PKC, and p38 MAPK, resulting in the induction of iNOS expression in RAW 264.7 macrophages.