Advanced glycosylation end products induce nitric oxide synthase expression in C6 glioma cells Involvement of a p38 MAP kinase-dependent mechanism

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Abstract

The mitogen-activated protein kinase (MAPK) pathway is believed to function as an important mediator of inducible nitric oxide synthase (iNOS) expression. In the present study, we investigated the role of the p38 MAPK signaling pathway in advanced glycosylation end products (AGEs)-induced iNOS expression in C6 glioma cells. AGEs caused a dose-dependent increase of nitrite accumulation in C6 glioma cells. The AGEs-stimulated nitrite production from C6 glioma cells was inhibited by actinomycin D, cyclohexamide, and the NO synthase inhibitor, Nv -nitro- L -arginine methyl ester (L-NAME), suggesting that the increase of AGEs-induced nitrite release is due to iNOS up-regulation. Consistently, treatment of C6 glioma cells with AGEs induced iNOS protein expression. AGEs-stimulated nitrite production was inhibited by pretreatment of C6 glioma cells with anti-AGEs antibodies (1:100 or 1:50). The tyrosine kinase inhibitor (genistein and tyrphostin), the Ras-farnesyl transferase inhibitor (FPT inhibitor-II), or the p38 MAPK inhibitor (SB203580) suppressed AGEs-induced iNOS expression and nitrite release from C6 glioma cells. AGEs activated p38 MAPK in C6 glioma cells, and this effect was blocked by genistein (20 MM), tyrphostin (30 m M), FPT inhibitor-II (20 m M), and SB203580 (10 m M). Taken together, our data suggest that AGEs may activate the pathways of tyrosine kinase and Ras to induce p38 MAPK activation, which in turn induces iNOS xpression and NO production in C6 glioma cells.