High glucose-induced apoptosis in human vascular endothelial cells is mediated through NF-kB and c-Jun NH2-terminal kinase pathway and prevented by PI3K/Akt/eNOS pathway.

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摘要

Abstract

Our previous studies demonstrated that high glucose-induced apoptosis in human umbilical vein endothelial cells (HUVECs) is mediated by sequential activation of c-Jun N-terminal kinase (JNK) and caspase, and prevented by exogenous nitric oxide (NO). In this study we further elucidated the roles of the transcriptional factor NF-kappaB, phosphatidylinositol 3'-kinase (PI3K), Akt and endothelial nitric oxide synthase (eNOS) in the apoptosis of HUVECs induced by high glucose. The results showed that high glucose-induced apoptosis was significantly enhanced by PI3K inhibitors (wortmannin and LY294002), NOS inhibitor (NG-nitro-arginine methyl ester) and eNOS antisense oligonucleotide. In contrast, apoptosis was markedly reduced by NF-kappaB inhibitor (pyrrolidine dithiocarbamate, PDTC), NF-kappaB antisense oligonucleotide, NO donor (sodium nitroprusside, SNP), and overexpression of Akt. The high glucose-induced NF-kappaB activation and transient Akt phosphorylation were prevented by the presence of vitamin C. Moreover, high glucose-induced increase in eNOS expression was attenuated by PI3K inhibitors and the negative mutant of PI3K. The activity of JNK induced by high glucose was suppressed by NF-kappaB-specific antisense oligonucleotide. Taken together our results demonstrated that high glucose-induced HUVECs apoptosis is through NF-kappaB-dependent JNK activation and reactive oxygen species (ROS)-dependent Akt dephosphorylation. Activation of the ROS/PI3K/Akt/eNOS signaling pathway in

early phase exerts protective effects against the induction of apoptosis by high glucose.