

Nitric oxide from both exogenous and endogenous sources activates mitochondria-dependent events and induces insults to human chondrocytes.

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Abstract

During inflammation, overproduction of nitric oxide (NO) can damage chondrocytes. In this study, we separately evaluated the toxic effects of exogenous and endogenous NO on human chondrocytes and their possible mechanisms. Human chondrocytes were exposed to sodium nitroprusside (SNP), an NO donor, or a combination of lipopolysaccharide (LPS) and interferon-gamma (IFN-gamma) as the exogenous and endogenous sources of NO, respectively. Administration of SNP or a combination of LPS and IFN-gamma in human chondrocytes increased cellular NO levels but decreased cell viability. Exposure to exogenous or endogenous NO significantly induced apoptosis of human chondrocytes. When treated with exogenous or endogenous NO, the mitochondrial membrane potential time-dependently decreased. Exposure to exogenous or endogenous NO significantly enhanced cellular reactive oxygen species (ROS) and cytochrome c (Cyt c) levels. Administration of exogenous or endogenous NO increased caspase-3 activity and consequently induced DNA fragmentation. Suppression of caspase-3 activation by Z-DEVD-FMK decreased NO-induced DNA fragmentation and cell apoptosis. Similar to SNP, exposure of human chondrocytes to S-nitrosoglutathione (GSNO), another NO donor, caused significant increases in Cyt c levels, caspase-3 activity, and DNA fragmentation, and induced cell apoptosis. Pretreatment with N-monomethyl arginine (NMMA), an inhibitor of NO synthase, significantly decreased cellular NO levels, and lowered endogenous NO-induced alterations in cellular Cyt c amounts, caspase-3 activity, DNA fragmentation, and cell apoptosis. Results of this study show that NO from exogenous and endogenous sources can induce apoptotic insults to human chondrocytes via a mitochondria-dependent mechanism.