Arsenite stimulates cyclooxygenase-2 expression through activating IkB kinase and nuclear factor kB in primary and ECV304 endothelial cells.

梁有志

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Abstract

Epidemiological studies have shown that chronic exposure to arsenic can result in liver injury, peripheral neuropathy, arteriosclerosis, and an increased incidence of cancer of the lung, skin, bladder, and liver. The overexpression of inducible cyclooxygenase-2 (Cox-2) has been associated with vascular inflammation and cellular proliferation. However, the effect of arsenite on Cox-2 gene expression in endothelial cells was left to be investigated. Western Blot analysis of HUVECs revealed a two-fold induction of Cox-2 protein by arsenite. This induction was associated with a two-fold increase of prostaglandin E2 in the media. Furthermore, the level of Cox-2 mRNA was correspondingly elevated as demonstrated by both Northern blot and reverse transcriptase-polymerase chain reaction (RT-PCR) analyses. Transfection of an immortalized human endothelium cell line (ECV304) with Cox-2 reporter gene constructs demonstrated that the transcription of Cox-2 gene was enhanced by arsenite. This induction was attenuated by pyrrolidine dithiocarbamate (PDTC), an inhibitor of NFkappaB. In addition, electrophoretic mobility shift assays indicated that NFkappaB activity was induced by arsenite. The kinase activity assay also indicated that IkappaB kinase (IKK) activity was induced by arsenite. These findings indicated that the induction of Cox-2 gene transcription by arsenite was through the stimulation of NFkappaB activity. Arsenite could induce IKK activity, which leads to the phosphorylation and degradation of IkappaB in ECV304 cells. Therefore, it appears that IKK signaling pathway is involved in arsenite-mediated Cox-2 expression.