

Am J Physiol Renal Physiol 271: F209-F215, 1996;
0363-6127/96 \$5.00

AJP - Renal Physiology, Vol 271, Issue 1 209-F215, Copyright © 1996 by American Physiological Society

ARTICLES

Role of reactive oxygen metabolites in DNA damage and cell death in chemical hypoxic injury to LLC-PK1 cells

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Hypoxia is considered to result in a necrotic form of cell injury. We have recently demonstrated a role of endonuclease activation, generally considered a feature of apoptosis, to be almost entirely responsible for DNA damage in hypoxic injury to renal tubular epithelial cells. The role of reactive oxygen metabolites in endonuclease-induced DNA damage and cell death in chemical hypoxic injury has not been previously examined. LLC-PK1 cells exposed to chemical hypoxia with antimycin A resulted in enhanced generation of intracellular reactive oxygen species as measured by oxidation of a sensitive fluorescent probe, 2',7'-dichlorofluorescein diacetate. Superoxide dismutase, a scavenger of superoxide radical, significantly reduced the fluorescence induced by antimycin A and provided significant protection against chemical hypoxia-induced DNA strand breaks (as measured by the alkaline unwinding assay). Pyruvate, a scavenger of hydrogen peroxide, provided significant protection against chemical hypoxia-induced DNA strand breaks and DNA fragmentation (as measured by agarose gel electrophoresis). The interaction between superoxide anion and hydrogen peroxide in the presence of a metal catalyst leads to generation of other oxidant species such as hydroxyl radical. Hydroxyl radical scavengers, dimethylthiourea, salicylate, and sodium benzoate, and two metal chelators, deferoxamine and 1,10-phenanthroline, also provided marked protection against DNA strand breaks and DNA fragmentation. These scavengers of reactive oxygen metabolites and metal chelators provided significant protection against cell death as measured by trypan blue exclusion and lactate dehydrogenase release. Taken together, these data indicate that reactive oxygen species play an important role in the endonuclease activation and consequent DNA damage, as well as cell death in chemical hypoxic injury to renal tubular epithelial cells.

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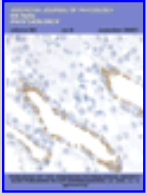
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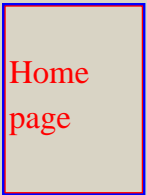
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