DEFERIPRONE AMELIORATES CISPLATIN INJURY TO RENAL TUBULAR EPITHELIAL CELLS

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Nephrotoxicity is one of the major adverse events resulting from the use of the chemotherapeutic agent cisplatin (cis-diamminedichloroplatinum II). Our previous studies have demonstrated that oxidative mechanisms of cisplatin injury to kidney tubular epithelial cells are mediated by cytotoxic endogenous endonucleases. Since endonuclease inhibitors are not available, antioxidant therapy may provide nephroprotection. Iron, by its ability to undergo redox cycling, plays an important role in the generation of powerful oxidant species. The purpose of our study was to determine whether an iron chelator (deferiprone--DFP, L1) can be used for protecting renal tubular epithelial cells from cisplatin-induced injury. Lactate dehydrogenase (LDH) release, endonuclease activation, and DNA fragmentation were used as endpoints to assess the DFP effect on cisplatin toxicity. Immortalized mouse tubular epithelial (TKPTS) cells exposed to cisplatin concentrations of 25 μM and above induced significant cell death associated with leakage of endonuclease G from mitochondria to cytoplasm and then to nuclei. The nuclear import of endonuclease G was associated with the increase of DNA fragmentation measured using a TUNEL assay. DFP (3-100 μM) provided significant protection against cytotoxic effects of cisplatin on TKPTS cells. 100 μM DFP provided the highest protection (~50%), which was equal to the effect of 1 mM desferoxamine (DFO). In conclusion, deferiprone, an iron chelator with better tissue penetration than desferoxamine, may be an important therapeutic modality for prevention of cisplatin nephrotoxicity.