

P005 HSP70 and IEG expression following exposure of human and rat proximal tubular cell cultures to platinum analogues: correlation with toxicity

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Platinum based drugs are used to treat cancer but exhibit dose-limiting nephrotoxicity. HSP70 levels and IEG activation are detectable early protective responses to toxicity. Cisplatin was more toxic to rat proximal tubule cells (RPT) than to human proximal tubule (HPT) cells, 24 h IC₅₀ 77±4 µM, 121±10 µM respectively. HSP 72 induction was maximal (2.5 fold increase) at 8h and correlated with platinum analogue toxicity in RPT cells (n=3±SD). *c-fos* and *c-jun* mRNA were detected at an earlier time point than the protein products. Maximal induction in RPT cells as arbitrary units was at 1h for *c-fos* (1.25±0.25) and 2h for *c-jun* (1.5±0.39) (n=3±SD). *c-fos* protein levels were maximal at 8h (ODU per mm² 0.37±0.05) and correlated with toxicity (n=4±SD). *C-jun* protein was not detected in RPT cells. At no time-point was AP-1 activity detected in RPT cell cultures (n=3±SD). *c-jun* protein and functional AP-1 were however detected in HPT cell cultures. This observation may explain the difference in platinum analogue sensitivity between RPT and HPT cell cultures. The formation of functional AP-1 in HPT cells would provide cellular protection, in part, through increased GSH synthesis. The *c-fos* and *c-jun* response exhibited greater sensitivity than that of HSP72.