PHARMACOLOGY AND TOXICOLOGY

THE EFFECTS OF TAXOL AND STRESS RESPONSE/ HEAT SHOCK IN MULTIPLE DRUG RESISTANT C-6 GLIOMA [MAS]

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Multidrug-resistant cells are thought to maintain low intracellular cytoxic drug concentrations through the active efflux of drugs across the cell membrane. P-glycoprotein, encoded by the MDR1 gene, is believed to mediate this energy-dependent drug efflux by interacting directly with various amphipathic compounds. We have isolated a multidrug resistant strain of rat C-6 Glioma by exposing cells to progressively increasing concentrations of colchicine-a microtubule destabilizing compound that selectively kills MDR negative cells. Drug resistance was verified by determining ED_{50} values of both the parent (82.0 ± 23.5 ng/ml) and the drug resistant strain (1490.3 ± 157.7 ng/ml) upon exposure to increasing concentrations of taxola microtubule stabilizing agent. The drug resistant strain also exhibited a significant decrease ($p < 0.05$) in the rate of growth (cells/ml/24 hours) in comparison to the parent strain. To establish a correlation between multiple drug resistance and the stress response, both strains were subjected to heat shock at 42°C for 30 minutes. The presence of heat shock proteins (hsp 70, hsp 90, hsp 32) was assessed by SDS-PAGE; no significant differences were found in either of the treated and untreated parent and drug resistant strains. Protein concentrations were significantly increased in the heat treated and untreated drug resistant strains. In addition, glutamine synthetase (GS), cyclic nucleotide phosphohydrolase (CNP), and heme

oxygenase (HO) enzyme activities were significantly increased in both heat treated and untreated drug resistant strains. Exposure of both the parent and drug resistant strains to varying concentrations of verapamil, a substrate for p glycoprotein, was used to show resistance modification to taxol.

The results suggest that there is a correlation between the stress response to heat shock and multiple drug resistance. They also suggest that C-6 Glioma would be a model system for testing other antineoplastic drugs and other resistance modifying agents.