Cardiac glycosides induced resistance to tubulin-dependent anticancer drugs in androgen-independent human prostate cancer

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Abstract

Due to high prevalence and mortality and the lack of effective therapies, prostate cancer is one of the most crucial health problems in men. Drug resistance aggravates the situation, not only in human prostate cancer but also in other cancers. In this study, we report for the first time that cardiac glycosides (e.g. ouabain and digitoxin) induced resistance of human prostate cancer cells (PC-3) in vitro to tubulin-binding anticancer drugs, such as paclitaxel, colchicine, vincristine and vinblastine. Cardiac glycosides exhibited amazing ability to reverse the G2/M arrest of the cell cycle and cell apoptosis induced by tubulin-binding agents. However, neither ionomycin (a Ca(2+) ionophore) nor veratridine (a Na(+) ionophore) mimicked the preventive action of cardiac glycosides, indicating that elevation of the intracellular Ca(2+) concentration and Na(+) accumulation were not involved in the cardiac glycoside action. Furthermore, cardiac glycosides showed little influence on the effects induced by actinomycin D, anisomycin and doxorubicin, suggesting selectivity for microtubule-targeted anticancer drugs. Using in situ immunofluorescent detection of mitotic spindles, our data showed that cardiac glycosides diminished paclitaxel-induced accumulation of microtubule spindles; however, in a non-cell assay system, cardiac glycosides had little influence on colchicine- and paclitaxel-induced microtubule dynamics. Using an isotope-labeled assay method, we found that ouabain modestly but significantly inhibited the transport of [(14)C]paclitaxel from the cytosol into the nucleus. It is suggested that cardiac glycosides inhibit the G2/M arrest induced by tubulin-binding anticancer drugs via an indirect blockade on microtubule function. The decline in transport of these drugs into the nucleus may partly explain the action of cardiac glycosides.