Abstract

Cancers belong among the most serious problems of modern medicine and their occurrence is constantly increasing. Neuroblastoma is a malignant embryonal tumor in children, emerging from the peripheral nervous system and is the most frequent tumor in infants. Despite the significant development of therapeutic methods during recent years, this disease remains difficult to treat. It is treated surgically and also with chemotherapy using cytostatic drugs. The cytostatic drugs such as doxorubicin, ellipticine, cisplatin and vincristine have become very significant in treating cancer. However, they induced drug resistance in these neuroblastoma cells. This study investigates expression of the vacuolar H^+-ATPase (V-ATPase), in neuroblastoma cells and its role in the development of drug resistance. V-ATPase is a proton pump required for the acidification of vacuoles, as a sensor of cytosolic pH.

A sensitive neuroblastoma cell line (UKF-NB-4) and cells resistant to doxorubicin, ellipticine and cisplatin (UKF-NB-4^{DOX}, UKF-NB-4^{ELLI}, UKF-NB-4^{CDDP}) were exposed to these agents and the expression of the V-ATPase was studied by Western blot analysis and real-time quantitative reverse tarnscription polymerase chain reaction (RT-PCR). Ellipticine induces an increase in expression of the V-ATPase in neuroblastoma cells both on the transcriptional and the translational levels, while cisplatin causes a decrease in expression of this enzyme. Treatment with doxorubicin increases expression of the V-ATPase only at the translational level. Furthermore, it was found that a specific inhibitor of V-ATPase, bafilomycin A, potentiates the development of apoptosis generated by ellipticine and cisplatin. Doxorubicin and ellipticine induced formation of lysosomes, where these cytostatics accumulates (are sequestrated). This sequestration leads to a reduction of cytotoxicity of these agents.

In this study, we have shown that V-ATPase is one of the survival mechanisms of neuroblastoma cells in the presence of cytostatics, and seems to be a promising selective therapeutic target to be considered for future trials.

Keywords: neuroblastoma, drug rezistence, vacuolar ATPase, bafilomycin A