Abstract

Histone deacetylase inhibitor trichostatin A (TSA) increases cytotoxicity of antineoplastic agent ellipticine to human neuroblastoma cells. Its mechanism of action has not yet been explained. One of the possible mode of action is conformational change in chromatin, which leads to changes in DNA that is more accessible to covalent modification and intercalation. The aim of this work is to study another mode of action, which can explain this phenomenon. The question is, if TSA can increase cytotoxicity of ellipticine to human neuroblastoma cells by modulation of activities and expression of cytochromes P450 and peroxidases. These enzymes are responsible for cytotoxicity of ellipticine to human neuroblastoma cells. TSA has no effect on oxidation of ellipticine mediated by cytochromes P450 leading to metabolites responsible for formation of ellipticine-DNA adducts and detoxication metabolites. TSA increases formation of ellipticine dimer, which is a detoxication metabolite, forming during its oxidation by peroxidases. TSA has no effect on activities of CYP1A1, CYP1A2, CYP3A, which significantly participate in oxidation of ellipticine. TSA modulates expression of enzymes oxidizing ellipticin in human neuroblastoma cells. TSA in the presence of ellipticine increases expression of CYP1A1 a CYP3A4 in UKF-NB-3 and UKF-NB-4 human neuroblastoma cells. On the contrary, TSA decreases expression levels of lactoperoxidase in these cells.