Abstract

Cancer cells are able to adapt to different stress factors such as hypoxia, which is caused by insufficient tumor vascularization. An increased acetylation status of histones H3 and H4 in UKF-NB-3 and UKF-NB-4 neuroblastoma cell lines was found to be a mechanism of adaptation of these cells to hypoxia. An increase in acetylation of histones H3 and H4 is suggested to cause changes in the structure of chromatin that lead to activation of gene transcription. In addition, cultivation of tested neuroblastoma cells under hypoxic conditions changes expression of proteins of a transcription factor N-myc, which is essential for development of neuroblastomas. This transcription factor is also responsible for a metabolic adaptation of neuroblastoma cells, increases their aggressiveness and its expression leads to a worse prognosis of the disease. Inhibitors of histone deacetylases (HDAC) are suggested to be the promising agents exhibiting various anticancer effects. They can induce cell cycle arrest, differentiation or programmed cell death in sensitive tumors. In this study, the effect of one of inhibitors of HDACs, valproate, on expression of proteins of transcription factors N-myc and hypoxia inducible factor 1α (HIF-1α) was investigated. Valproate decreases protein levels of both transcription factors in tested neuroblastoma cells, which confirms its anticancer efficiency.

Protein CD133 is a marker of cancer stem cells. The effect of valproate on expression of this protein was tested. Valproate increases protein levels of CD133 in a UKF-NB-3 cell line, which was associated with increased chemoresistance to cisplatin and vincristine in this cell line. In the UKF-NB-4 cell line, an increase in expression of CD133 protein was not produced by vaplroate, which might be caused by methylation of promoters P1 and P3 of a *PROM1* (CD133) gene. Inhibitors of HDAC are clinically promising, when used in a combination with convention cytostatics. Cultivation of a UKF-NB-4 neuroblastoma cell line with drugs damaging DNA such as cisplatin, etoposide and ellipticine in a combination with nontoxic concentrations of valproate leads to a synergistic effect of these drugs. In this study, a mechanism of chemoresistance of UKF-NB-4 cell line to ellipticine was also examined. Treatment of ellipticine-sensitive UKF-NB-4 cell line with ellipticine induced cytoplasmic vacuolization and ellipticine is concentrated (sequestrated) in these vacuoles. This sequestration results in lower cytoplasmic concentrations of ellipticine, less nuclear accumulation, and lower DNA damage by ellipticine, and therefore also lower toxic effects to these cells.