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Valproic acid up-regulates p75NTR and sortilin expression to induce neuronal cell death

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Background. Valproic acid (VPA) is widely used for the treatment of epilepsy, bipolar mood disorder and pain. Although several studies have shown that VPA can exert neuroprotective effects against a variety of brain insults, there is also evidence that this drug can adversely affect neuronal growth and survival through mechanisms still not completely understood. Moreover, VPA administration during pregnancy has been associated with increased incidence of children with neurodevelopmental defects and autism spectrum disorder. The common neurotrophin receptor p75NTR, which belongs to the tumor necrosis factor receptor superfamily, and its co-receptor sortilin have been shown to regulate neuronal viability and function. In the present study we report that in neuronal cells VPA up-regulates the expression of p75NTR and sortilin and this effect is associated with apoptotic cell death.

Methods. The drug effects were examined in human SH-SY5Y and LAN-1 neuroblastoma cells and mouse cerebellar granule cells. The expression of p75NTR and sortilin, the activation of the apoptotic cascade and histone acetylation were examined by using western blot, immunofluorescence. and cytofluorimetry.

Results. Exposure of SH-SY5Y and LAN-1 cells to VPA enhanced the whole cell protein levels of p75NTR and sortilin in a time- and concentration-dependent manner. Cell surface protein biotinylation experiments indicated that VPA increased the plasma membrane expression of both receptor proteins. The effects of VPA occurred within the same concentration range required to induce histone acetylation. Moreover, other histone deacetylase (HDAC) inhibitors, such as thricostatin A, sodium butyrate, MS-275 and MC1568 mimicked the effect of VPA on p75NTR expression. In both neuroblastoma cells and cerebellar granule cells proNGF, a potent ligand of p75NTR/sortilin receptor complex, failed to affect cell viability per se. Cell pre-treated with VPA to induce up-regulation of p75NTR and sortilin exhibited activation of the apoptotic pathway, as indicated by increased formation of active caspase 9 and 3 forms and cleavage of poly (ADP ribose) polymerase. The exposure to proNGF significantly potentiated the pro-apoptotic effect of VPA.

Conclusions. These data indicate that in neuronal cells VPA enhances the expression of the p75NTR/sortilin receptor complex to promote proNGF-induced apoptotic cell death.