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Research article

MC1568 Inhibits Thimerosal-Induced Apoptotic Cell Death by Preventing HDAC4 Up-Regulation in Neuronal Cells and in Rat Prefrontal Cortex

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ABSTRACT

Ethylmercury thiosalicylate (thimerosal) is an organic mercury-based compound commonly used as an antimicrobial preservative that has been found to be neurotoxic. In contrast, histone deacetylases (HDACs) inhibition has been found to be neuroprotective against several environmental contaminants, such as polychlorinated biphenyls, di-2-ethylhexyl phthalate, and methylmercury. The aim of this study was to investigate the effect of HDAC inhibition on thimerosal-induced neurotoxicity in neuroblastoma cells and cortical neurons. Interestingly, we found that thimerosal, at 0.5 μM in SH-SY5Y cells and at 1 μM in neurons, caused cell death by activation of apoptosis, which was prevented by the HDAC class IIA inhibitor MC1568 but not the class I inhibitor MS275. Furthermore, thimerosal specifically increased HDAC4 protein expression but not that of HDACs 5, 6, 7, and 9. Western blot analysis revealed that MC1568 prevented thimerosal-induced HDAC4 increase. In addition, both HDAC4 knocking-down and MC1568 inhibited thimerosal-induced cell death in SH-SY5Y cells and cortical neurons. Importantly, intramuscular injection of 12 μg/kg thimerosal on postnatal days 7, 9, 11, and 15 increased HDAC4 levels in the prefrontal cortex (PFC), which decreased histone H4 acetylation in infant male rats, in parallel increased motor activity changes. In addition, coadministration of 40 mg/kg MC1568 (intraperitoneal injection) moderated the HDAC4 increase which reduced histone H4 deacetylation and caspase-3 cleavage in the PFC. Finally, open-field testing showed that thimerosal-induced motor activity changes are reduced by MC1568. These findings indicate that HDAC4 regulates thimerosal-induced cell death in neurons and that treatment with MC1568 prevents thimerosal-induced activation of caspase-3 in the rat PFC.

Key words: HDAC; MC1568; thimerosal.