MS-275 inhibits A1254-induced SH-SY5Y neuronal cell toxicity by preventing the formation of the HDAC3/REST complex on the Synapsin-1 promoter

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PCB exposure has been associated with neurodegenerative diseases like Parkinson's disease, amyotrophic lateral sclerosis, and dementia. Neuronal death elicited by the PCB mixture Aroclor 1254 (A1254) has been attributed to an increase in RE-1-silencing transcription factor (REST), which, in turn, correlates with a decrease in Synapsin -1 promoter gene. Although histone deacetylase (HDAC) inhibitors are known to be neuroprotective in several neurological disorders, the core mechanisms governing this effect are not yet understood. Here, to examine how HDAC class I (MS-275) and HDAC class II (MC-1568) inhibitors prevent A1254-induced neuronal cell death, we exposed SH-SY5Y neuroblastoma cells to A1254. Exposure to A1254 (30.6 μM) for 24 and 48 h resulted in a time-dependent cell death. Indeed, after 48 h, MS-275, but not MC-1568, reverted A1254-induced cell death in a dose-dependent manner. Furthermore, A1254 significantly increased HDAC3, but not HDAC1 and HDAC2. Interestingly, REST physically interacted with HDAC3 after A1254 exposure. Chromatin immunoprecipitation assays revealed that MS-275 reverted the increased levels of HDAC3 binding and increased acetylation of histone H3 within the Synapsin-1 promoter region, thus reverting Synapsin-1 mRNA reduction. Moreover, REST knockdown by small interfering RNA (siRNA) prevented HDAC3 binding to the Synapsin-1 promoter. Likewise, HDAC3 siRNA significantly reduced A1254-induced cell toxicity in SH-SY5Y cells and cortical neurons. Hence, this study demonstrates that inhibition of HDAC class I attenuates A1254-induced neuronal cell death by preventing HDAC3 binding and histone deacetylation within the Synapsin-1 promoter region.