Resveratrol Via Sirtuin-1 Downregulates RE1-Silencing Transcription Factor (REST) Expression Preventing PCB-95- Induced Neuronal Cell Death

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Resveratrol (3,5,4'-trihydroxystilbene) (RSV), a polyphenol widely present in plants, exerts a neuroprotective function in several neurological conditions; it is an activator of class III histone deacetylase sirtuin1 (SIRT1), a crucial regulator in the pathophysiology of neurodegenerative diseases. By contrast, the RE1-silencing transcription factor (REST) is involved in the neurotoxic effects following exposure to polychlorinated biphenyl (PCB) mixture A1254. The present study investigated the effects of RSV-induced activation of SIRT1 on REST expression in SH-SY5Y cells. Further, we investigated the possiblerelationship between the non-dioxin-like (NDL) PCB-95 and REST through SIRT1 to regulate neuronal death in rat cortical neurons. Our results revealed that RSV significantly decreased REST gene and protein levels in a dose- and time-dependent manner. Interestingly, overexpression of SIRT1 reduced REST expression, whereas EX-527, an inhibitor of SIRT1, increased REST expression and blocked RSV-induced REST downregulation. These results suggest that RSV downregulates REST through SIRT1. In addition, RSV enhanced activator protein 1 (AP-1) transcription factor c-Jun expression and its binding to the REST promoter gene. Indeed, c-Jun knockdown reverted RSV induced REST downregulation. Intriguingly, in SH-SY5Y cells and rat cortical neurons the NDL PCB-95 induced necrotic cell death in a concentration-dependent manner byincreasing REST mRNA and protein expression. In addition, SIRT1 knockdown blocked RSV-induced neuroprotection in rat cortical neurons treated with PCB-95. Collectively, these results indicate that RSV via SIRT1 activates c-Jun, thereby reducing REST expression in SH-SY5Y cells under physiological conditions and blocks PCB-95-induced neuronal cell death by activating the same SIRT1/c-Jun/REST pathway.