REST as a New Therapeutic Target for Neurodegenerative Disorders: REST Affords Protection Against Manganese-Induced Neurotoxicity

Eunsook Lee

Division of Pharmaceutical Sciences, College of Pharmacy and Pharmaceutical Sciences, and Institute of Public Health, Florida A&M University, Tallahassee, Florida, USA

Edward Pajarillo

Division of Pharmaceutical Sciences, College of Pharmacy and Pharmaceutical Sciences, and Institute of Public Health, Florida A&M University, Tallahassee, Florida, USA

Sanghoon Kim

Division of Pharmaceutical Sciences, College of Pharmacy and Pharmaceutical Sciences, and Institute of Public Health, Florida A&M University, Tallahassee, Florida, USA

Alexis Digman

Division of Pharmaceutical Sciences, College of Pharmacy and Pharmaceutical Sciences, and Institute of Public Health, Florida A&M University, Tallahassee, Florida, USA

Abstract:

Recent emerging evidence reveals that dysregulation of transcription factor RE1-silencing transcription factor/neuron-restrictive silencer factor (REST/NRSF) is linked to Alzheimer's disease (AD) and Parkinson's disease (PD). We investigated the role of REST in dopaminergic neurotoxicity induced by environmental neurotoxin manganese (Mn), causing neurological disorders with PD-like symptoms, as well as cognitive impairment which may contribute to the development of AD. Therefore, we focused on dopaminergic toxicity by investigating if REST modulates Mn toxicity using in vitro neuronal cultures and in vivo mouse models. Our findings reveal that Mn decreased REST expression along with its toxicities, such as oxidative stress and apoptosis, while REST overexpression attenuated Mn-induced toxicities in Cath. -a-differentiated (CAD) neuronal cells. In addition, REST increased the transcription of tyrosine hydroxylase (TH), a rate-limiting enzyme for dopamine synthesis in CAD neurons, while REST overexpression attenuated the Mn-decreased TH expression. To investigate the role of REST in vivo, we focused on dopaminergic REST as Mn preferentially accumulates in the basal ganglia of the brain and causes dopaminergic toxicity. We generated dopaminergic neuron-specific REST conditional knockout (REST-cKO) mice which were exposed to Mn (330 µg, intranasal, daily for 3 weeks). REST loxP mice were used as wild-type (WT) controls. The results showed that Mn decreased REST expression in the dopaminergic neuron-containing midbrain and caused behavioral deficits, such as impaired locomotor activity and motor coordination as well as novel object recognition in WT, which were further decreased in REST-cKO mice. Mn decreased dopamine levels in the nigrostriatal tissues of WT mice with exacerbation in REST cKO. At the cellular levels, Mn induced mitochondrial insults, apoptosis, and oxidative stress in WT, which were further pronounced in REST-cKO mice. On the other hand, REST restoration in the substantia nigra in the midbrain of REST-cKO mice with neuronal REST AAV vector infusion attenuated Mn-induced neurotoxicity. Given that REST appears to be critical for neuroprotection, we investigated if pharmacological agents increase REST expression. Tamoxifen, a selective estrogen receptor modulator, increased REST via Wnt signaling in CAD cells. These novel findings suggest that dopaminergic REST in the nigrostriatal pathway plays a critical role in protecting against Mn toxicity, as well as other neurological disorders associated with REST dysfunctions such as PD and AD.