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Valproate Attenuates 25-kDa C-Terminal Fragment of TDP-43-Induced Neuronal Toxicity via Suppressing Endoplasmic Reticulum Stress and Activating Autophagy

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Abstarc :

Amyotrophic lateral sclerosis (ALS) is a fatal adult-onset neurodegenerative disease. To date, there is no any effective pharmacological treatment for improving patients' symptoms and quality of life. Rapidly emerging evidence suggests that C-terminal fragments (CTFs) of TAR DNA-binding protein of 43 kDa (TDP-43), including TDP-35 and TDP-25, may play an important role in ALS pathogenesis. Valproate (VPA), a widely used antiepileptic drug, has neuroprotective effects on neurodegenerative disorders. As for ALS, preclinical studies also provide encouraging evidence for multiple beneficial effects in ALS mouse models. However, the potential molecular mechanisms have not been explored. Here, we show protective effects of VPA against TDP-43 CTFs-mediated neuronal toxicity and its underlying mechanisms in vitro. Remarkably, TDP-43 CTFs induced neuronal damage via endoplastic reticulum (ER) stress-mediated apoptosis. Furthermore, autophagic self-defense system was activated to reduce TDP-43 CTFs-induced neuronal death. Finally, VPA attenuated TDP-25-induced neuronal toxicity via suppressing ER stress-mediated apoptosis and enhancing autophagy. Taken together, these results demonstrate that VPA exerts neuroprotective effects against TDP-43 CTFs-induced neuronal damage. Thus, we provide new molecular evidence for VPA treatment in patients with ALS and other TDP-43 proteinopathies.

Key Word :
Amyotrophic lateral sclerosis, Valproate, 25 kDa C-terminal fragment of TDP-43, Endoplasmic reticulum stress, Autophagy

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