Valproic Acid Mediated Neuroprotection and Neurogenesis after Acute Spinal Cord Injury

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Abstract

Spinal cord injury (SCI)-induced systemic inflammatory response affects multiple organs outside the spinal cord. Treatment options for such complications are lacking. Valproic acid (VPA) is a histone deacetylase inhibitor, acting directly at the level of gene transcription by inhibiting histone deacetylation and making transcription sites more accessible. Acetylation of histones is critical to cellular inflammatory and repair processes. A recent study demonstrated that VPA has effects on neuroprotection and neurogenesis for the treatment of the injured spinal cord. VPA can decreases glial apoptosis, neuroinflammation, neurotoxicity and autophagy during the secondary injury period, and upregulates prosurvival neurotrophic factors. The neuroprotective effects of VPA are interdepend and mediated by HDAC inhibition and GSK-3 inhibition. VPA increased several stages of neurogenesis, including the proliferation of endogenous neural stem cells, neuronal differentiation and maturation, neurite outgrowth, and synaptic integration. In addition, VPA can promote neurogenesis even after spinal cord cells are damaged, by controlling the expression of important transcriptional factors and the activation of multiple signaling pathways. Furthermore, the effects and mechanisms of VPA on neuronal excitation mediated neuroprotection and neurogenesis are cooperated and interconnected in treating SCI. It is necessary to optimize VPA treatment processes for SCI on aspects of therapeutic timing, effective dosage, and reliable administration route. Combinatory strategies should be established to maximize the benefits of VPA and to reduce adverse events. Specific criteria must be met prior to translating VPA treatment for SCI from animal experiments to clinical trials.

Keywords: Spinal Cord Injury, Valproic Acid, Secondary Injury, Neuroprotection, Neurogenesis.

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