博士学位論文内容の要旨

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学位論文題名	Inhibitory Effects of Valproic Acid in Oxaliplatin-Induced Neuropathy in Rat Model （Oxaliplatinによる末梢神経障害に対するバルプロ酸の抑制効果の動物実験研究）
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【論文の内容の要旨】

BACKGROUND: Oxaliplatin is a third-generation platinum-based chemotherapy drug in various solid tumors, in particular, it was introducedfor the management of the advanced stages of metastatic colorectal cancer. Repeated administration of oxaliplatin induced acute and chronic peripheral neuropathy can persist from months to years beyond chemotherapy completion, causing significant challenges for cancer survivors due to negative influence on function and quality of life. Valproic acid (VPA) is a neurotherapeutic drug prescribed worldwide as therapy for seizures, bipolar disorder, and migraine, including children, adult and women of reproductive age. Recently, VPA exerts protective effects for various neurological diseases, including spinal cord injury, stroke, traumatic brain injury, and motor neuron, Parkinson's, Alzheimer's, Huntington'sdiseases. However, the effect of VPA on the oxaliplatin-induced neuropathy remains unexplored.

MATERIALS AND METHODS: In the present study, we investigated the effect of VPA in prevention of oxaliplatin-induced periphery neuropathy in the rat model. We demonstrated that VPA (300 mg/kg) relievedthe oxaliplatin (4mg/kg)-induced peripheral neuropathy using behavioral tests, biochemical tests, and histopathological and immunohistochemical evaluations.

RESULTS: VPA administration significantly attenuated the mechanical hyperalgesia by oxaliplatin-induced in rats. VPAexerted a significant protective effect by reducing the occurrence of multinucleolated neurons and the nucleolar eccentricity caused on lumbar dorsal root ganglionfrom oxaliplatin-treated rats. Itrevealed an inhibitory effect of VPA on the number and activation of microglia and astrocytes in the dorsal horn of the spinal cord. However, VPA was unable to prevent demyelination and degeneration of nerve fibersfrom oxaliplatin-induced peripheral neurotoxicity.

COLUSION: The present results demonstrated for the first time thatVPA administration ameliorated the oxaliplatin-induced behavioral, biochemical and histopathological changes in rats. The VPA-mediated effects in this study may be attributed to neuroprotection properties and ameliorating oxaliplatin-induced astrocytes and microglial activation. VPA may offer a dual protective approach against etiological factors and resulting maladaptative plasticity.