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Autophagy induced by valproic acid is associated with oxidative stress in glioma cell lines

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▶ Abstract

Autophagy represents an alternative tumor-suppressing mechanism that overcomes the dramatic resistance of malignant gliomas to radiotherapy and proapoptotic-related chemotherapy. This study reports that valproic acid (VPA), a widely used anti-epilepsy drug, induces autophagy in glioma cells. Autophagy, crucial for VPA-induced cell death, is independent of apoptosis, even though apoptotic machinery is proficient. Oxidative stress induced by VPA occurs upstream of autophagy. Oxidative stress also activates the extracellular signal-regulated kinase 1/2 (ERK1/2) pathway, whereas blocking this pathway inhibits autophagy and induces apoptosis. VPA-induced autophagy cannot be alleviated by inositol, suggesting a mechanism different from that for lithium. Moreover, VPA potentiates autophagic cell death, but not apoptosis, when combined with other autophagy inducers such as rapamycin, Ly294002, and temozolomide in glioma cells both in vitro and in vivo, which may warrant further investigation toward possible clinical application in patients with

malignant gliomas.

Keywords: autophagy, glioma, oxidative stress, valproic acid

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