Radioprotective effects of valproic acid, a histone deacetylase inhibitor, in the rat brain

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Abstract. Radiotherapy is commonly used in the treatment of brain tumors but can cause significant damage to surrounding normal brain. The radioprotective effects of valproic acid (VPA) on normal tissue in the rat brain were evaluated following irradiation. Male Wistar rats were used in the present study and 48 rats were randomly divided into four groups consisting of 12 rats each. The whole-brain irradiation (WBI) was delivered by X-ray and the rats received the following treatment once a day for 5 days. The control group (sham-exposed group) received sham irradiation plus physiological saline. The VPA group received sham irradiation plus 150 mg VPA/kg. The X-ray group received WBI plus physiological saline. The combined group received WBI plus 150 mg/kg intraperitoneally VPA. A total of 6 months post-irradiation, the rats were sacrificed and the brains were harvested. Cell apoptosis in the cortex was determined by immunohistochemistry 24 h post-irradiation using an antibody for protein caspase-3. Transmission electron microscope (TEM) analyses were used to assess the effects of VPA on the radioprotection of rat normal brain cells 6 months post-irradiation. The weights of the animals in the TEM group measured over the two weeks after the first injection of VPA were also observed. Histological findings demonstrated that apoptosis occurred on the cortex 1 day after treatment, peaking in the X-ray group. The cells of the combined group showed a moderate caspase-3 staining compared to the X-ray group. There was a trend towards a lower body weight of the X-ray group following irradiation compared to either no-irradiation or rats of the combined group, although there was no significant difference in the average weight between the combined group and irradiated rats. Mild swelling of the capillary endothelial cells in the irregular lumen was observed in the combined group, whereas the X-ray group showed a severe structural disorder. In conclusion, VPA supplementation during radiotherapy may be beneficial for radioprotection following WBI by reducing normal brain cell injury.

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Introduction

Radiotherapy has an increasingly notable role in the treatment of the majority of malignant and a number of benign neurological neoplasms, and the treatment of select nonmalignant entities (1). However, the maximum radiation dose that can be used is limited by the tolerance of normal tissues surrounding the tumor (2). Thus far, in order to reduce radiotherapy-induced central nervous system (CNS) damage, several attempts are being made. One of these approaches is to apply the total dose locally in fractions, in order to preserve healthy neural tissue. Additionally, searches for novel treatment opportunities to prevent radiation damage are continuing. Following this, newer therapeutic methods may help diminish the risks of radiotherapy by not limiting the volume treated.

Histone deacetylase (HDAC) inhibitors represent a novel class of radiation protectors and mitigators against total-body irradiation and can produce a significant reduction in injury even when administered following the radiation exposure (3). Various mechanisms have been proposed for the radioprotective effects of HDAC inhibitors (4-6). Valproic acid (VPA) (Fig. 1), a HDAC inhibitor, is frequently prescribed as an anti-epileptic drug in patients with brain tumor due to its effectiveness, oral bioavailability and generally low toxicity profile (7-10). Previous findings have shown that VPA enhanced the radiation response of various brain tumor cell types *in vitro* and *in vivo* (11-14). Notably, VPA not only radiosensitizes tumor cells, but it may also protect normal brain from radiation.

Results from the study by Lai *et al* (15) indicate that VPA may decrease human neural cells vulnerability to cellular injury evoked by oxidative stress, possibly arising from putative mitochondrial disturbances involved in bipolar disorder. Similarly, VPA has neuroprotective effects in cultured cortical neurons undergoing spontaneous cell death. A previous study also indicated that the neuroprotective properties of VPA involve modulation of neurotrophic factors and receptors for melatonin, which is also believed to play a role in neuroprotection (16). However, it is also thought that VPA reduces DNA double-strand break repair capacity and increases radiosensitivity in fibroblasts obtained from healthy skin tissue (6).