Valproic acid induces apoptosis in differentiating hippocampal neurons by the release of tumor necrosis factor-α from activated astrocytes.

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Abstract
Human studies of neurodevelopment suggest that children exposed in utero to certain antiepileptic drugs (AEDs) suffer a variety of brain-behavior sequelae, such as neural tube defects, developmental delays, cognitive deficits, etc. Valproic acid (VPA), a commonly used AED, has greater risk for these side effects compared with other AEDs. However, the detailed molecular mechanisms underlying this developmental neurotoxicity of VPA is unclear despite previous research demonstrating that VPA could induce widespread apoptotic neurodegeneration in developing brains of animal models. This study characterizes the role of astrocytes in VPA-induced neurodegeneration. In developing brains, we evaluated the developmental neurotoxicity of VPA on differentiating neurons and astrocytes from neural progenitor cells cultured from the hippocampus of human fetuses. Exposure of a neuron-enriched culture to VPA at 250µM or 500µM did not cause neuronal apoptosis, but at 1mM and 7 days exposure, a slight increase in the percentage of apoptotic cells was observed. In contrast, VPA at 250µM to 1mM, selectively induced neuronal apoptosis in a neuron-astrocyte mixed cell culture model. The VPA-treated astrocytes showed morphological changes, and the level of tumor necrosis factor-α (TNF-α) was elevated in the supernatant. Both neuronal apoptosis and TNF-α release from astrocytes increased with concentration and exposure time to VPA, suggesting a synergism between the two cell types. Treatment of the neuron-astrocyte mixed culture exposed to VPA with TNF-α antibody partly prevented neuronal apoptosis, while the addition of exogenous TNF-α induced apoptosis in both cultures. Moreover, this pro-apoptotic effect was specific to VPA, as another AED, valpromide, failed to mimic this pro-apoptotic effect, nor did an inhibitor of histone deacetylase (iHDAC), sodium butyrate (NaB). We report a novel finding that astrocytes participate in VPA induced neurodegeneration by releasing TNF-α.

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