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## Arachidonic acid promotes glutamate-induced cell death associated with necrosis by 12-lipoxygenase activation in glioma cells.

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### Abstract

Glutamate induced glutathione (GSH) depletion in C6 rat glioma cells, which resulted in cell death. This cell death seemed to be apoptosis through accumulation of reactive oxygen species (ROS) or hydroperoxides representing cytochrome c release from mitochondria and internucleosomal DNA fragmentation. A significant increase of 12-lipoxygenase enzyme activity was observed in the presence of arachidonic acid (AA) under GSH depletion induced by glutamate. AA promoted the glutamate-induced cell death, which reduced caspase-3 activity and diminished internucleosomal DNA fragmentation. Furthermore, AA reduced intracellular NAD, ATP and membrane potentials, which indicated dysfunction of the mitochondrial membrane. Protease inhibitors such as N-alpha-tosyl-L-phenylalanine chloromethyl ketone (TPCK) and 3,4-dichloroisocoumarin (DCI) but not Ac-DEVD, a caspase inhibitor, suppressed the glutamate-induced cell death. AA reduced the inhibitory effect of TPCK and DCI on the glutamate-induced cell death. These results suggest that AA promotes cell death by inducing necrosis from caspase-3-independent apoptosis. This might occur through lipid peroxidation initiated by ROS or lipid hydroperoxides generated during GSH depletion in C6 cells.

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