Sodium valproate induces mitochondria-dependent apoptosis in human hepatoblastoma cells.

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Abstract

BACKGROUND: Sodium valproate inhibits proliferation in neuroblastoma and glioma cells, and inhibits proliferation and induces apoptosis in hepatoblastoma cells. Information describing the molecular pathways of the antitumor effects of sodium valproate is limited; therefore, we explored the mechanisms of action of sodium valproate in the human hepatoblastoma cell line, HepG2.

METHODS: The effects of sodium valproate on the proliferation of HepG2 cells were evaluated by the Walsh-schema transform and colony formation assays. Sodium valproate-induced apoptosis in HepG2 cells was investigated with fluorescence microscopy to detect morphological changes; by flow cytometry to calculate DNA ploidy and apoptotic cell percentages; with Western blotting analyses to determine c-Jun N-terminal kinases (JNK), p-JNK, Bcl-2, Bax, and caspase-3 and -9 protein expression levels; and using JC-1 fluorescence microscopy to detect the membrane potential of mitochondria. Statistical analyses were performed using one-way analysis of variance by SPSS 13.0 software.

RESULTS: Our results indicated that sodium valproate treatment inhibited the proliferation of HepG2 cells in a dose-dependent manner. Sodium valproate induced apoptosis in HepG2 cells as it: caused morphologic changes associated with apoptosis, including condensed and fragmented chromatin; increased the percentage of hypodiploid cells in a dose-dependent manner; increased the percentage of annexin V-positive/propidium iodide-negative cells from 9.52% to 74.87%; decreased JNK and increased phosphate-JNK protein expression levels; reduced the membrane potential of mitochondria; decreased the ratio of Bcl-2/Bax; and activated caspases-3 and -9.

CONCLUSION: Sodium valproate inhibited the proliferation of HepG2 cells, triggered mitochondria-dependent HepG2 cell apoptosis and activated JNK.