Apoptosis on hepatoma cells but not on primary hepatocytes by histone deacetylase inhibitors valproate and ITF2357.

BACKGROUND/AIMS: Due to a particular resistance against conventional chemotherapeutics, palliative treatment of hepatocellular carcinomas (HCC) is highly ineffective. Recent demonstration of both proliferation-inhibition and apoptosis of hepatoma cells by a histone deacetylase inhibitor (HDAC-I) treatment opens up a promising new approach. However, little is known about tumor cell death mechanisms and HDAC-I influences on healthy hepatocytes. METHODS: HDAC-I substances with favourable in vivo profiles, valproate (VPA) and ITF2357, were investigated on HCC cell lines and primary human hepatocytes (PHH). Histone acetylation and apoptosis-modulating proteins were investigated by western-blotting, proliferation by sulforhodamin B binding, toxicity by enzyme release, apoptosis by FACS analysis.

RESULTS: VPA and ITF2357 inhibited proliferation in HCC cell lines. Both substances induced considerable cellular damage in HCC-derived cells, but PHH tolerated these substances well. A downregulation of anti- and upregulation of proapoptotic factors was found. Moreover, Bcl-X(L) transfection into HCC cells abrogated apoptosis induced by both substances, indicating that modulation of intracellular pro- and anti-apoptotic proteins is a key event in VPA or ITF2357 induced tumor-cell death.

CONCLUSIONS: Preferential
induction of cell death in HCC-derived cell lines, without toxicity in PHH, demonstrates the potential of VPA and ITF2357 to become promising new tools in the fight against HCC.