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论著

双丙戊酸钠和丙戊酸钠对HepG2细胞的毒性作用及机制

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摘要 目的 探讨双丙戊酸钠和丙戊酸钠对肝细胞的毒性作用及其可能的作用机制。方法 肝癌细胞株HepG2加入双丙戊酸钠和丙戊酸钠0.1，0.3，1和3 mmol·L^{-1}，培养24 h后，MTT法测定HepG2的细胞存活；双丙戊酸钠和丙戊酸钠0.3，0.5和1.0 mmol·L^{-1}作用HepG2细胞24 h，丙酮酸法测定培养液中乳酸脱氢酶(LDH)活性，赖氏法测定培养液中谷丙转氨酶(GPT)和谷草转氨酶(GOT)活性；双丙戊酸钠和丙戊酸钠62.5，125，250，500和1000 μmol·L^{-1}作用24 h，实时定量逆转录聚合酶链反应(RT-PCR)测定细胞色素P450家族中CYP1A1 mRNA和CYP1A2 mRNA表达的变化。结果 与溶剂对照组比较，双丙戊酸钠和丙戊酸钠0.1，0.3，1和3 mmol·L^{-1}均显著抑制细胞的存活($P<0.05$，$P<0.01$)，且存在浓度依赖关系。双丙戊酸钠与丙戊酸钠0.3，0.5和1 mmol·L^{-1}使HepG2细胞培养液中GPT，GOT和LDH的活性明显升高($P<0.05$，$P<0.01$)，且随浓度升高，肝酶活性进一步升高。双丙戊酸钠与丙戊酸钠62.5，125，250，500和1000 μmol·L^{-1}使HepG2细胞中CYP1A1 mRNA和CYP1A2 mRNA的表达水平亦逐渐升高。结论 双丙戊酸钠和丙戊酸钠对HepG2细胞都有明显的毒性作用，CYP1A1 mRNA和CYP1A2 mRNA表达水平的升高可能是丙戊酸类药物诱发肝毒性的机制之一。

关键词 双丙戊酸钠 丙戊酸钠 HepG2细胞 细胞色素P450酶系统 细胞毒性

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Cytotoxicity and mechanisms of divalproex sodium and sodium valproate on HepG2 cells

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Abstract

OBJECTIVE To investigate the cytotoxicity of divalproex sodium and sodium valproate on HepG2 cells and its underlying mechanisms. **METHODS** The cytotoxicity of divalprox sodium and sodium valproate were investigated using HepG2 cell lines. After HepG2 cells were cultured with divalproex sodium or sodium valproate 0.1, 0.3, 1 and 3 mmol·L^{-1} for 24 h, cell viability was measured by MTT assay. After HepG2 cells were cultured with divalproex sodium or sodium valproate 0.3, 0.5 and 1.0 mmol·L^{-1} for 24 h, lactate dehydrogenase (LDH) activity in the culture medium was tested by the pyruvic acid method, and the activity of glutamic pyruvic transaminase (GPT) and glutamic oxaloacetic transaminase (GOT) in the culture medium was determinated by malate dehydrogenase method. After HepG2 cells were cultured with divalproex sodium or sodium valproate 62.5, 125, 250, 500 and 1000 μmol·L^{-1} for 24 h, the gene expressions of cytochrome P4501A1 (CYP1A1) and cytochrome P4501A2 (CYP1A2) were measured by real time quantitive reverse transcription-polymerase chain reaction (RT-PCR) assay. **RESULTS** After treatment with divalproex sodium or sodium valproate 0.1, 0.3, 1 and 3 mmol·L^{-1} for 24 h, the viability of HepG2 cells was obviously inhibited compared with solvent control group and there was a good concentration-effect relationship. After HepG2 cells were treated with divalproex sodium or sodium valproate 0.3, 0.5 and 1 mmol·L^{-1} for 24 h, the activity of GPT, GOT and LDH in culture medium was significantly increased. With the increase in

concentrations, the activities of GPT, GOT and LDH increased. The gene expressions of CYP1A1 and CYP1A2 was gradually increased after HepG2 cells were treated with divalproex sodium and sodium valproate 62.5, 125, 250, 500 and 1000 μmol • L^{-1} for 24 h. **CONCLUSION** Growth inhibition is