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论著

酒精性肝损伤大鼠细胞色素P450 CYP2E1和细胞色素P450 CYP3A的代谢活性

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摘要 目的 观察酒精性肝损伤对大鼠细胞色素P450 CYP3A(CYP3A)和细胞色素P450 CYP2E1(CYP2E1)代谢活性的影响。方法 采用ig给予白酒制备大鼠酒精性肝损伤模型，检测血清中谷丙转氨酶（GPT）和谷草转氨酶（GOT）活性，采用HE染色法光镜下观测酒精对肝脏损伤程度。大鼠ip给予CYP3A探针药物咪达唑仑10 mg·kg^{-1}或ig给予CYP2E1探针药物氯唑沙宗50 mg·kg^{-1}后，采用高效液相色谱法测定不同时间点大鼠血浆中咪达唑仑和氯唑沙宗的血药浓度，并应用3P87软件计算其药代动力学参数，以考察CYP2E1和CYP3A的代谢活性的变化。大鼠ig给予氯唑沙宗80 mg·kg^{-1}后，热板方法测定大鼠添足次数和添足反射潜伏期。结果 酒精性肝损伤可致大鼠肝小叶结构不清，肝索排列紊乱，肝细胞体积增大，呈弥漫性中度水变性，肝窦受压，大部分肝细胞胞浆内见大小不等的脂肪空泡；与正常对照组相比，酒精性肝损伤组大鼠GPT和GOT活性分别增加了16.0%和20.0%(P<0.05, P<0.01)。酒精性肝损伤致大鼠CYP2E1对探针药物氯唑沙宗的代谢活性增强，AUC, $t_{1/2}$和c_{max}分别降低了38.0%, 30.5%和35.0%(P<0.05)；酒精肝损伤组大鼠氯唑沙宗镇痛效果明显降低；酒精性肝损伤致大鼠CYP3A对探针药物咪达唑仑的代谢活性增强， AUC, $t_{1/2}$和c_{max}分别降低了122.6%, 54.9%和56.9%(P<0.01, P<0.05)。结论 酒精性肝损伤可使大鼠CYP2E1和CYP3A代谢活性增强。

关键词 酒精性肝疾病 细胞色素P450 CYP2E1 细胞色素P450 CYP3A

分类号 R969.1, R595.5

Metabolic activities of cytochrome P-450 CYP2E1 and cytochrome P-450 CYP3A in hepatic alcohol-injuried rats

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Abstract

OBJECTIVE To study changes of metabolism activity of cytochrome P-450 CYP3A (CYP3A) and cytochrome P-450 CYP2E1 (CYP2E1) in alcohol-mediated hepatic injury rats. **METHODS** An alcohol-injured hepatic injury model was established after rats were ig given alcohol. Activities of glutamyl pyruvic transaminase (GPT) and glutamyl oxaloacetic transaminase (GOT) in serum were determined, and the liver tissues were collected for histopathological assessment under the light microscrope. Rats were given ip CYP3A probe drug midazolam 10 mg·kg^{-1} or CYP2E1 probe drug chlorzoxazone 50 mg·kg^{-1}. Concentrations of midazolam and chlorzoxazone in plasma were determined by HPLC, and their pharmacokinetic parameters were calculated by 3p87 software to evaluate metabolism activities of CYP3A and CYP2E1 indirectly. Rats were given ig chlorzoxazone 80 mg·kg^{-1}. The analgesic effect was assayed by hot plate test. **RESULTS** Liver cells were severely damaged by alcohol, resulting in alcoholic hepatitis and the fat liver. Compared with normal control group, activities of GPT and GOT increased by 16.0% and 20.0%, respectively (P<0.05, P<0.01); metabolism activities of CYP3A and CYP2E1 were increased, AUC, $t_{1/2}$ and c_{max} of chlorzoxazone decreased by 38.0%, 30.5% and 35.0% (P<0.05) and those of midazolam decreased by 122.6%, 54.9% and 56.9%(P<0.01, P<0.05). The analgesic effect significantly decreased in alcohol-induced hepatic injury group. **CONCLUSION** The CYP2E1 and CYP3A metabolism activity was reinforced in alcohol-induced hepatic injury rats.

Key words liver diseases alcoholic cytochrome P-450 CYP2E1 cytochrome P-450 CYP3A

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