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论著

补骨脂素和异补骨脂素对体外细胞色素P450酶活性的抑制和诱导作用

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摘要 目的 探讨补骨脂素(PSO)和异补骨脂素(IPSO)对细胞色素P450(CYP)活性的抑制和诱导作用。方法 将人肝微粒体或鼠肝微粒体与PSO或IPSO以及CYP特异性探针底物共孵育30 min, 分别以非那西丁*O*-脱乙基、甲苯磺丁脲4-羟基化、美芬妥因-4-羟基化、右美沙芬*O*-脱甲基化和咪达唑仑1'-羟基化为同工酶CYP1A2, CYP2C9, CYP2C19, CYP2D6(大鼠2D2)和CYP3A4(大鼠3A1/2)代谢活性的标志, 用HPLC-MS/MS法检测相应代谢产物的生成量并计算相应的IC_{50}值, 评价PSO和IPSO对5种CYP同工酶的潜在抑制作用。将PSO和IPSO或阳性诱导剂与"三明治"培养大鼠肝原代细胞共孵育72 h后, 再加入CYP探针底物孵育1 h, 检测相应代谢产物的生成量, 与阳性诱导剂组比较, 评价二者对CYP1A和CYP3A的诱导作用。结果 PSO和IPSO对人肝微粒体和鼠肝微粒体的CYP1A2均有较强的抑制作用, 在人肝微粒体中的IC_{50}值分别为0.17和0.13 μmol·L^{-1};在鼠肝微粒体中的IC_{50}值分别为0.47和0.36 μmol·L^{-1}。二者对人肝微粒体的CYP2D6也有中等强度的抑制作用, IC_{50}值分别为3.59和9.51 μmol·L^{-1}。PSO和IPSO 100 μmol·L^{-1}可分别将大鼠肝细胞的CYP3A活性提高1.18和0.96倍, 有一定的诱导作用。结论 PSO和IPSO能显著抑制CYP1A2酶活性, 对CYP3A有一定的诱导作用。

关键词 补骨脂素类 异补骨脂素 细胞色素类 药物相互作用 微粒体, 肝

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Evaluation of cytochrome P450 inhibition and induction by psoralen and isopsoralen *in vitro*

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Abstract

OBJECTIVE To evaluate inhibitory and inductory activities of psoralen (PSO) and isopsoralen (IPSO) on cytochrome P450 (CYP) isoforms. METHODS PSO or IPSO was incubated with human liver microsomes (HLM) or rat liver microsomes (RLM) for 30 min in the presence of NADPH and CYP probe substrates for CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. Phenacetin-*O*-deethylation, tolbutamide methyl hydroxylation, mephenytoin 4-hydroxylation, dextromethorphan-*O*-demethylation and midazolam 1'-hydroxylation were used as marked reactions to measure enzyme activities. The relative activities of CYP isoforms were determined by analyzing the formation of the probe metabolites in the incubation system. IC_{50} was calculated to assess the inhibitory potency of PSO and IPSO on these CYP isoenzymes. To evaluate CYP induction effect, PSO, IPSO or known CYP inducers were incubated with sandwich-cultured rat hepatocytes for 72 h, followed by 1 h incubation of the hepatocytes with CYP1A or 3A substrates to measure the relative activities of CYP isoforms. The enzyme activities in PSO and IPSO groups were compared with those of known inducers to assess the induction potentials. RESULTS PSO and IPSO showed a strong inhibitory activity on CYP1A2 in both HLM and RLM incubations *in vitro*. IC_{50} of PSO and IPSO in HLM was 0.17 and 0.13 μmol·L^{-1}, 0.47 and 0.36 μmol·L^{-1} in RLM, respectively. A moderate inhibitory activity of PSO and IPSO on CYP2D6 in HLM was also observed, with IC_{50} of 3.59 and 9.51 μmol·L^{-1}. PSO and IPSO 100 μmol·L^{-1} demonstrated inductory activity on rat CYP3A. After incubation with rat hepatocytes for 72 h, PSO and IPSO increased CYP3A activity 1.18 and 0.96 times, respectively. CONCLUSION PSO and IPSO are strong inhibitors of CYP1A2 but moderate inhibitors for CYP2D6. They also show induction potency on rat CYP3A.

Key words psoralens isopsoralen cytochromes drug interactions microsomes liver

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