中国药理学与毒理学杂志 2008 22 (4): 301-305 ISSN: 1000-3002 CN: 11-1115/R

实验方法

大鼠肝睾酮羟化酶体外诱导模型的建立

张呈菊*, 钱蓓丽, 顾性初, 马 璟

（上海医药工业研究院国家上海新药安全评价研究中心, 上海 201203）

收稿日期 2007-9-10 修回日期 网络版发布日期 2008-7-30 接受日期 2008-1-3

摘要 目的 建立大鼠原代培养肝细胞微粒体睾酮羟化酶系列同工酶(CYP2A1, CYP2B1/2, CYP2C11, CYP3A1/2)的体外诱导模型。方法 应用胶原酶原位灌流法分离大鼠肝细胞进行原代培养；用苯巴比妥钠（PB, 1 mmol·L^{-1}）、地塞米松(Dex, 10 μmol·L^{-1})和β-萘酚黄酮（β-NF, 50 μmol·L^{-1}）诱导培养肝细胞72 h，提取肝细胞微粒体，进行其肝CYP总量、肝微粒体蛋白含量和睾酮羟化酶比活性的测定。另外采用体内诱导方法，SD大鼠分别给予PB 80 mg·kg^{-1}, Dex 50 mg·kg^{-1}和β-NF 80 mg·kg^{-1}, ip, 每天1次，连续5 d，停药24 h后制备肝微粒体进行上述指标的测定。结果 在体外和体内实验中，PB, Dex和β-NF对肝微粒体蛋白含量、CYP总量和睾酮羟化酶同工酶活性均具有较高的诱导效应。PB对肝CYP总量在体外的诱导效应高于体内，对睾酮不同位置羟化作用的诱导效应体内外无显著性差异；Dex和β-NF对肝CYP总量及睾酮不同位置羟化作用的诱导效应体内外无显著性差异。结论 大鼠肝睾酮羟化酶体外诱导模型可替代体内实验，用于药物代谢、新药安全性评价及其他外源性化合物代谢和毒性研究。

关键词 肝 细胞色素P450 睾酮羟化酶 同工酶类 药物代谢 模型, 动物, 体外

分类号 R965

Establishment of in vitro induction model of rat hepatic microsomal testosterone hydroxylases

ZHANG Cheng-Ju*, QIAN Bei-Li, GU Xing-Chu, MA Jing

(National Shanghai Center for New Drug Safety Evaluation and Research, Shanghai Institute of Pharmaceutical Industry, Shanghai 201203, China)

Abstract

AIM To establish an in vitro induction model of rat hepatic microsomal testosterone hydroxylase (CYP2A1, CYP2B1/2, CYP2C11 and CYP3A1/2). **METHODS** Hepatocytes were isolated from adult SD rats by the collagenase in situ perfusion technique. Three kinds of inducers phenobarbital sodium (PB, 1 mmol·L^{-1}), dexamethasone (Dex, 10 μmol·L^{-1}) and β-naphthoflavone (β-NF, 50 μmol·L^{-1}) were added to the culture medium. After induction for 72 h, the cells were harvested to prepare liver microsomes, and then the total content of CYP, the protein concentration, and the specific activities of testosterone hydroxylases were assayed. For comparison with the *in vitro* induction, adult SD rats were treated with PB 80 mg·kg^{-1}, Dex 50 mg·kg^{-1} and β-NF 80 mg·kg^{-1}, respectively, ip, once a day for 5 d, respectively. **RESULTS** PB, Dex and β-NF significantly increased the concentration of microsomal protein, total content of CYP and activities of testosterone hydroxylases *in vitro* and *in vivo*. PB had a higher inductive effect on total content of CYP *in vitro* compared with *in vivo*, but no difference on activities of testosterone hydroxylases between *in vitro* and *in vivo*. The inductive effects of Dex and β-NF on total content of CYP and activities of testosterone hydroxylases had no significantly difference between *in vitro* and *in vivo*. **CONCLUSION** The *in vitro* induction model of rat hepatic microsomal testosterone hydroxylases can be used in metabolic and toxicologic studies of new drug candidates or other chemicals in stead of *in vivo* experiments.

Key words liver cytochrome P-450 testosterone hydroxylases isozymes drug metabolism model animal in vitro

DOI: 10.3867/j.issn.1000-3002.2008.04.10

通讯作者 张呈菊 zhangcjchina@163.com