Prediction of drug disposition by human drug metabolizing enzymes

2000 Fiscal Year Final Research Report Summary

PREDICTION OF DRUG DISPOSITION BY HUMAN DRUG METABOLIZING ENZYMES

Research Project

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11557191

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Grant-in-Aid for Scientific Research (B).

Allocation Type

Single-year Grants

Section

展開研究

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医薬分子機能学

Research Institution

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Research Abstract

Drug oxidation activities of twelve recombinant human cytochrome P450 (P450) coexpressed with human NADPH-P450 reductase (NPR) in bacterial membranes (P450/NPR membranes) were determined and compared with those of other recombinant systems and of human liver microsomes. Addition of exogenous membrane-bound NPR to the P450/NPR membranes enhanced the catalytic activities of CYP2C8, CYP2C9, CYP2C19, CYP3A4, and CYP3A5 ; however, enhancement of activities of CYP1A1, CYP1A2, CYP1B1, CYP2A6, CYP2B6, CYP2D6, and CYP2E1 in membranes was not observed after the addition of NPR in 4-molar excess to each P450. Exogenous

purified human cytochrome b_5 (b_5) further enhanced catalytic activities of CYP2A6, CYP2B6, CYP2C8, CYP2E1, CYP3A4, and CYP3A5/NPR membranes. Catalytic activities of CYP2C9 and CYP2C19 were enhanced by addition of b_5 in reconstitution systems but not in the P450/NPR membranes. Apo b_5 (devoid of heme) enhanced catalytic activities when added to the both systems, except for CYP2E1/NPR membranes and the reconstituted systems containing purified CYP2C8 or CYP2E1 in comparison with b_5. Catalytic activities in P450/NPR membranes plus b_5 systems were roughly similar to those measured with microsomes of insect cells coexpressing P450 with NPR (and b_5) and/or of human liver microsomes, based on equivalent P450 contents. These results suggest that interactions of P450 and NPR coexpressed in membranes and reconstituted systems appear to be different in some human CYP2 family enzymes, possibly due to a conformational role of b_5. P450/NPR membrane systems containing b_5 are useful models for prediction of the rates for liver microsomal P450-dependent drug oxidations.

Research Products (12 results)

All | Other

All | Publications

[Publications] Komatsu,T. et al.: "Formation of a dihydroxy metabolite of phenytoin by human liver microsomes/cytosol : roles of cytochrome P450 2C9, 2C19, and 3A4"Drug Metab.Dispos.. 28. 1361-1368 (2000)

[Publications] Komatsu,T. et al.: "Roles of cytochrome P450 1A2, 2A6, and 2C8 in 5-fluorouracil formation from tegafur, an anti-cancer prodrug, in human liver microsomes"Drug Metab.Dispos.. 28. 1457-1463 (2000)

[Publications] Ohyama,K. et al.: "A significant role of human cytochrome P450 (CYP) 2C8 in amiodarone and N-deethylation : an approach to predect the contribution with reactive activity factor (RAF)"Drug Metab.Dispos.. 28. 1303-1310 (2000)

[Publications] Inoue,K. et al.: "CYP2A6 genetic polymorphism and liver microsomal coumarin and nicotine oxidation activities in Japanese and Caucasians"Arch.Toxicol... 73. 532-539 (2000)

[Publications] Yamazaki,H. et al.: "In vitro inhibitory effects of troglitazone and its metabolites on drug oxidation activities of human cytochrome P450 enzymes : comparison with pioglitazone and rosiglitazone"Xenobiotica. 30. 61-70 (2000)

[Publications] 山崎浩史: "ヒトチトクロムP450の薬物代謝学・毒性学的研究"薬学雑誌. 120. 1347-1357 (2000)

[Publications] Komatsu, T.et al.: "Formation of a dihydroxy metabolite of phenytoin by human liver microsomes/cytosol : roles of cytochrome P450 2C9, 2C19, and 3A4"Drug Metab. Dispos.. 28. 1361-1368 (2000)

[Publications] Komatsu, T.et al.: "Roles of cytochrome P450 1A2, 2A6, and 2C8 in 5-fluorouracil formation from tegafur, an anticancer prodrug, in human liver microsomes"Drug Metab. Dispos.. 28. 1457-1463 (2000)

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[Publications] Yamazaki, H.: "Roles of human cytochrome P450 enzymes involved in drug metabolism and toxicological studies."J.Pharm.Soc.J.. 120. 1347-1357 (2000)

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