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Interindividual variations in levels and activities of cytochrome P-450 in liver microsomes of Chinese subjects[1]

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KEY WORDS liver microsomes; cytochrome P-450 CYP1A2; cytochrome P-450 CYP2C9; cytochrome P-450 CYP2D6; cytochrome P-450 CYP3A4; metabolism; Mongoloid race

ABSTRACT

AIM: To compare the level and/or activity of several important cytochrome P-450 (CYP) enzymes in liver microsomes prepared from different Chinese subjects. **METHODS**: Individual CYP contents, including CYP1A2, CYP2C9, and CYP3A4, in liver microsomes of 17 Han, 17 Zhuang, and 8 Miao subjects were determined by using Western blot analysis and densitometric scanning. The substrates for measuring the activity of individual CYP *in vitro* included phenacetin, tolbutamide, debrisoquine, and omeprazole. **RESULTS**: There was a large interindividual variability in the content and activity of CYP1A2, 2C9 and 3A4. And the activity of CYP2D6 also varied greatly between individual samples. CYP3A4 (32 %) is the most abundant CYP in Chinese liver microsomes, and the levels of CYP2C9 (19 %) and CYP1A2 (16 %) were also considerable. No clear ethnic, sex- and age-related differences in individual CYP content and catalytic activity were detected in 42 Chinese liver samples, except that there were somewhat ethnic and sex-related differences in the content and activity of CYP1A2. Good correlation between enzyme protein content and activity was found for CYP1A2, 2C9 and 3A4. **CONCLUSION**: Our results may provide useful information for the study of drug metabolism by liver microsomes in Chinese.

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INTRODUCTION

The cytochrome P450 (CYP) is a superfamily of hemoproteins that are the terminal oxidases of the mixed function oxidase system. At least 481 CYP genes and 22 pseudogenes are known to exist across all species[1]. The deduced amino acid sequences from these genes are compared and divided into families and subfamilies. Of the 35 known human CYP genes, only the eighteen forms comprising families 1 - 3 are currently thought to be responsible for the majority of hepatic metabolism of drugs and non-drug xenobiotics[1-4]. Representatives of these drug-metabolizing CYP include CYP1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, and 3A4.

People usually show large interindividual variations in drug oxidation reactions catalyzed by hepatic microsomal CYP, and these variations may lead to different sensitivities of people to pharmacologic and toxicologic actions of drugs[3,4]. Thus, it is of significance to determine the level and catalytic activity of the CYP important to drug metabolism and to summarize the patterns of their relative content in individual human livers. Up to now, there have been a few studies for such an end in a large number of liver samples from Caucasians[5,6], Japanese[5,6] and subjects whose ethnic origin was not clear[7,8]. But no similar study has been previously conducted in definitely Chinese livers. In consideration of commonly interethnic differences in drug response[9], systematic characterization of CYP level and activity in a relatively large number of Chinese livers is justifiable. In the present study, a total of 42 Chinese liver samples were examined with respect to level and/or catalytic activity of four different CYP enzymes.

MATERIALS AND METHODS

Chemicals and materials Phenacetin, acetaminophen, tolbutamide, NADP, glucose-6-phosphate, glucose-6-phosphate dehydrogenase were purchased from

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Sigma Chemical Co (St Louis, MO, USA). Debrisoquine, 4-hydroxydebrisoquine, and 4-hydroxytolbutamide were purchased from Ultrafine Chemicals (Manchester, UK). Omeprazole, 5-hydroxyomeprazole, omeprazole sulfone, and H259/36 were generous gifts from Astra Hässle AB (Mölndal, Sweden). Acetonitrile and methanol of HPLC grade were from Hunan Chemical Institute (Changsha, China). Recombinant CYP1A2, 2C9, and CYP3A4 expressed in human lymphoblast, and goat anti-rat CYP1A2, anti-rat CYP2C11, and anti-rat CYP3A2 were from Daiichi Pure Chemicals Co (Tokyo, Japan). All other supplies are of the highest grades available from commercial sources.

Preparation of human liver microsomes Of the 42 native Chinese liver donors, 17 (10 men and 7 women) belong to the Zhuang minority group residing in the southwestern part of the Autonomous Region of Guangxi, 8 (3 men and 5 women) to the Miao minority group in the Autonomous Prefecture of Western Hunan, and the remaining 17 (13 men and 4 women) to the Han majority in Hunan Province. The collection and use of human liver tissue for studies had been approved by the Ethics Committee of Hunan Medical University. The criteria for selecting a liver sample into this study was strict as described previously[10], but detailed histories of some of the liver donors were not known. We therefore analyzed the CYP variations without considerations of disease states and drug intake, although they may contribute to the variations to some extent. Microsomes were prepared by differential centrifugation[10]. Microsomal protein concentrations were determined by the method of Lowry[11] and the total P450 contents were measured spectrally by the method of Omura & Sato[12].

Western blot analysis The protein levels of CYP1A2, CYP2C9, and CYP3A4 were determined using Western blot analysis and densitometric scanning with minor modifications[5]. In the present study, the goat anti-rat CYP1A2 antibody was used to detect CYP1A2, the anti-rat CYP2C11 antibody to detect CYP2C9 and the anti-rat CYP3A2 antibody to detect CYP3A4 (antibody dilution 1:500). Recombinant CYP1A2, CYP2C9, and CYP3A4 expressed in human lymphoblast were used as controls respectively.

Enzyme assays for CYP probes Substrates with high specificity for several CYP forms important to drug metabolism were selected: phenacetin *O*-deethylation for CYP1A2, tolbutamide 4-methyl-hydroxylation for CYP2C9, debrisoquine 4-hydroxylation for CYP2D6, and omeprazole sulfoxidation for CYP3A4. Rates of production of each metabolite were quantified by HPLC method using internal or external standard. The HPLC system used was described as previously[13].

Phenacetin *O*-deethylation (CYP1A2) Phenacetin *O*-deethylation was measured after 20-min incubations with human liver microsomes. After 1 min preincubation, reactions were initiated by adding microsomal protein (final protein concentration: 0.5 $g \cdot L^{-1}$) to incubation medium consisted of potassium-phosphate buffer 0.1 $mol \cdot L^{-1}$ (pH 7.4), microsome protein 0.5 $g \cdot L^{-1}$, NADP 5 $mmol \cdot L^{-1}$, glucose-6-phosphate 10 $mmol \cdot L^{-1}$, glucose-6-phosphate dehydrogenase 2 $kU \cdot L^{-1}$, $MgCl_2$ 10 $mmol \cdot L^{-1}$, and phenacetin 125 $\mu mol \cdot L^{-1}$ in a final volume of 500 μL. Duplicate incubations were used for each liver specimen. The enzyme reactions were terminated by cooling the samples in ice bath and by adding 3 mL ice-cold acetoacetic ester (extraction solution). Phenobarbital 100 μL (50.0 $\mu mol \cdot L^{-1}$) methanol solution were then added to the samples as internal standard for assaying acetaminophen. The aliquot of organic layer after shaking vigorously for 1 min and centrifugation for 10 min ($2500 \times g$) was transferred to another glass tube and evaporated to dryness under a gentle stream of nitrogen at 37 ℃. Residues were reconstituted by 100 μL of HPLC mobile phase. Acetaminophen and phenacetin were separated on a 5-μm Kromasil C18 column (4.6 mm × 250 mm, ID, Alltech, Dalian, China) at the wavelength of 240 nm at 40 ℃ of column temperature. The mobile phase was a mixture of methanol and double-distilled water (40/60, vol/vol) at a flow rate of 0.8 $mL \cdot min^{-1}$. The intraday and interday coefficients of detection variation were within 10 %.

Tolbutamide 4-hydroxylation (CYP2C9) The incubation method for tolbutamide hydroxylation was the same as that for the phenacetin *O*-deethylation, except that the incubation time was 1 h and that the substrate concentration was 250 $\mu mol \cdot L^{-1}$. In addition, extraction and HPLC analysis of samples for 4-hydroxytolbutamide were also similar to those for the acetaminophen with minor modifications. The mobile phase was a mixture of methanol and double-distilled water (60/40, vol/vol) at a flow rate of 0.8 $mL \cdot min^{-1}$. Detection was measured by UV absorbance at 230 nm. The intraday and interday coefficients of variation were less than 10 %.

Debrisoquine 4-hydroxylation (CYP2D6) Microsomal protein 0.5 – 1.0 mg in 500 μL was incubated with debrisoquine 250 $\mu mol \cdot L^{-1}$ in the presence of

$MgCl_2$ 10 mmol·L^{-1}, NADP 5 mmol·L^{-1}, glucose-6-phosphate 10 mmol·L^{-1}, glucose-6-phosphate dehydrogenase 2 kU·L^{-1} in potassium-phosphate buffer 0.1 mol·L^{-1}, pH 7.4. Incubations were terminated after 90 min of incubation by placing the reaction tubes in ice bath and by adding 100 μL of acetonitrile to precipitate mirosomal protein. 4-Hydroxydebrisoquine formed in the incubations was also determined using HPLC as described by others[14] except that microsomal incubation instead of urine samples were used.

Omeprazole sulfoxidation (CYP3A4) Omeprazole sulfoxidation was evaluated at the substrate concentration of 100 mol·L^{-1} according to our method described previously[13].

Statistical analysis Data were expressed as $\bar{x} \pm s$. ANOVA, paired or unpaired Student's t-test, and Dunnett t-test were applied to analyze data, when appropriate. Correlation analyses were performed by least-squares linear regression. A P value less than 0.05 was considered statistically significant.

RESULTS

Variations in content of total CYP and individual CYP in Chinese microsomes The individual CYP analyzed in this part were CYP1A2, 2C9, and 3A4. Their contents were determined by using Western blot analysis and densitometric scanning (Fig 1). The recovery of CYP contents determined immunochemically accounted for about 62 % of the total CYP determined spectrally (Tab 1), and good correlation was observed between recovered CYP contents and total CYP content ($r = 0.73$, $P < 0.05$) (Fig 2). CYP determined spectrally in liver microsomes were (0.32 ± 0.15) μmol·g^{-1} protein with an interindividual variability of 6 folds. No ethnic, sex- and age-related differences in total CYP content were found. The mean CYP1A2, 2C9, and 3A4 levels were about 16 %, 19 %, and 32 % of total CYP, respectively, in Chinese liver microsomes (Tab 1). There was a large interindividual variability in the content of each CYP examined, namely, 9.4-, 6.4-, and 4.6-time for CYP1A2, 2C9, and 3A4, respectively. The CYP1A2 content in men was lower than that in women (0.033 ± 0.019) *vs* (0.056 ± 0.038) μmol·g^{-1} protein, $P < 0.05$. In addition, the samples of Han (0.027 ± 0.019) μmol·g^{-1} protein contained a lower CYP1A2 content than those of Zhuang (0.056 ± 0.037) μmol·g^{-1} protein, $P < 0.05$ and Miao (0.042 ± 0.014) μmol·g^{-1} protein, $P < 0.05$. Although the content of CYP1A2 appeared to be lower in men than in women both in the Zhuang and in the Miao samples, the variance is too great to reach a conclusion at the $P < 0.05$ level. No significant ethnic and sex-related differences in protein content were found for CYP2C9 and CYP3A4. Any age-related differences in the levels of these three CYP could not be detected.

Fig 1. Western blot analysis of CYP1A2, 2C9, and 3A4. The fifth lane (from left to righu) of each nitrocellulose sheet is the recombinant CYP1A2, 2C9, and CYP3A4 (1 pmol) expressed in human lymphoblast, respectively. CYP1A2 90 μg, 2C9 60 μg, and 3A4 45 μg, and the sample numbers for lane 1 – 4 and 6 – 9 are 40, 11, 23, 28, and 33, 7, 32, 29 in turn. In the panel of CYP2C9, the above lanes represent CYP2C9, the bottom lanes represent CYP2C19 (unpublished data).

Tab 1. Contents of total P-450 determined spectrally and individual P-450 forms determined immunochemically in liver microsomes of 42 Chinese samples. Values represent $\bar{x} \pm s$. a: Percentage of total P-450. b: Determined spectrally. c: Determined immunochemically. d: Sum of individual forms of P-450 determined immunochemically.

	P-450 content/ μmol·g^{-1} protein	% of total P-450[a]
Total P-450[b]	0.32 ± 0.15	–
CYP1A2[c]	0.042 ± 0.021	16 ± 11
CYP2C9[c]	0.06 ± 0.04	19 ± 13
CYP3A4[c]	0.12 ± 0.04	32 ± 11
Total[d]	0.22 ± 0.08	66 ± 24

Variations in enzyme activity of individual CYP in Chinese microsomes The catalytic activities of CYP1A2, 2C9, and 3A4 were determined in 42 Chinese liver samples using probe substrates. Although the content of CYP2D6 was not determined because we

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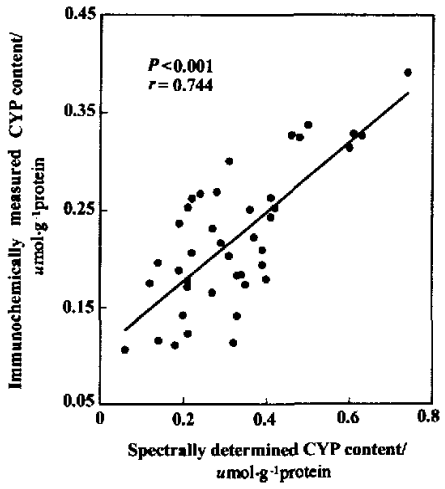

Fig 2. Correlation between total P-450 determined spectrally and sum of the individual forms of P-450 determined immunochemically (CYP1A2, 2C9, and 3A4) in liver microsomes of 42 Chinese samples.

could not obtain an anti-CYP2D6 antibody, its catalytic activity was still measured due to its importance in drug metabolism. At the substrate concentrations of 125 (phenacetin), 250 (tolbutamide), 250 (debrisoquine) and 100 $\mu mol \cdot L^{-1}$ (omeprazole), the activities of CYP1A2, 2C9, 2D6 and 3A4 could vary greatly in ranges of 3.4-, 11.8-, 7.5-, and 9.8-folds, respectively. There were no significant sex-related differences in enzyme activity for the four CYP examined, except that in the Zhuang samples the phenacetin *O*-deethylation showed a lower activity in men than in women ($P < 0.05$). In accordance with the results of protein content, the CYP1A2 activity of Han samples (350 ± 170) $nmol \cdot g^{-1} \cdot min^{-1}$ was lower than those of Zhuang (590 ± 79) $nmol \cdot g^{-1} \cdot min^{-1}$, $P < 0.05$ and Miao samples (490 ± 97) $nmol \cdot g^{-1} \cdot min^{-1}$, $P < 0.05$. Possibly due to the great variance, any other ethnic and age-related differences in enzyme activity was not detected.

Correlation analysis Correlations between contents of individual CYP and their activities by probe substrates were determined in liver microsomes of 42 Chinese samples. Good correlations were observed between CYP1A2 content and phenacetin *O*-deethylation activity ($r = 0.72$, $P < 0.05$), CYP2C9 content and tolbutamide 4-hydroxylation activity ($r = 0.80$, $P < 0.05$), and CYP3A4 content and omeprazole sulfoxidation activity ($r = 0.79$, $P < 0.05$), respectively. No other significant correlation between CYP content and drug oxidation activity was found (Tab 2).

Tab 2. The enzyme activities of CYP1A2, 2C9, 2D6, and 3A4 in liver microsomes of 42 Chinese subjects. Values represent $\bar{x} \pm s$. Reactions with high specificity were selected to determine individual P450 activities: phenacetin ($125\ \mu mol \cdot L^{-1}$) 4-methyl-hydroxylation for CYP2C9, debrisoquine ($250\ \mu mol \cdot L^{-1}$) 4-hydroxylation for CYP2D6, and omeprazole ($100\ \mu mol \cdot L^{-1}$) sulfoxidation for CYP3A4.

P450 isoform	Enzyme activity/$nmol \cdot g^{-1} \cdot min^{-1}$
CYP1A2	470 ± 160
CYP2C9	210 ± 140
CYP2D6	94 ± 81
CYP3A4	280 ± 150

Tab 3. Correlation coefficients (r) between levels and activities in liver microsome of 42 Chinese. a: Determined spectrally. b: Determined immunochemically. c: Sum of individual forms of P-450 determined immunochemically. PA: phenacetin; TB: tolbutamide; DR: debrisoquine; OP: omeprazole.

	PA	TB	DR	OP
Total P-450[a]	0.47	0.3	0.14	0.63
CYP1A2[b]	0.72	0.08	−0.05	0.44
CYP2C9[b]	0.10	0.80	0.09	0.24
CYP3A4[b]	0.33	0.49	0.32	0.79
Total[c]	0.63	0.56	0.24	0.78
PA	1.00	0.18	0.28	0.49
TB		1.00	0.21	0.13
DR			1.00	0.44
OP				1.00

DISCUSSION

In this study, we presented large interindividual variations in the contents and activities of total CYP and CYP1A2, 2C9, and 3A4 in Chinese liver microsomes. In addition, the activity of CYP2D6 also varied greatly between individual samples. These results can be used to explain, at least in part, the large interindividual variability in the disposition and response of certain drugs[4]. It is well recognized that the variability of drug metablism results from multiple factors, including genetic variations, sex, ethnicity, age, disease states, drug interactions and so on[15]. Of these factors, genetic variations of drug-metabolizing enzymes have been emphasized mostly for the past twenty years[16]. Much has been

learned about the genetic mutations in CYP2C9, CYP2C19, and CYP2D6 genes that lead to marked differences in enzyme activity. Recently, two genetic polymorphisms in CYP1A2 gene have also been associated with its activity and/or inducibility[17,18]. Nevertheless, until now no mutation in the CYP3A4 gene definitely relating to enzyme activity has been reported. Genetic variations may contribute greatly to the large variability in the contents and activities of CYP in the present study. However, a conclusion can not be reached until genotypes of individual samples are available with respect to each reported CYP allele, and in general until the regulation and function of CYP genes is better understood.

Consistent with the previous findings from Japanese and Caucasian liver microsomes[5], our results indicated that CYP3A4 (32 %) was the most abundant CYP in Chinese liver microsomes, and the levels of CYP2C9 (19 %) and CYP1A2 (16 %) were also considerable. In addition, the level of CYP2C19 was determined to be about 2 % of total CYP in Chinese liver microsomes in our laboratory (unpublished data), which was also similar to those in Japanese and Caucasian liver microsomes[6]. However, the total CYP level in liver microsomes of Chinese (0.32 $\mu mol \cdot g^{-1}$ protein) appears to be lower than that of Caucasians (0.43 $\mu mol \cdot g^{-1}$ protein)[5,6] but slightly higher than that of Japanese (0.26 $\mu mol \cdot g^{-1}$ protein)[5,6]. Our results may thus serve as evidence for ethnic differences in the metabolism of certain drugs between Caucasians and Orientals[9]. China is a multi-national country with 55 ethnic minorities besides the Han majority. It is of interest to determine whether the protein content and activity of CYP varies among these different ethnic groups in the same country. In this study, there was no ethnic differences in CYP content and activity between the three ethnic groups examined, except that the protein content and activity of CYP1A2 in the Han samples was somewhat lower than both in the Zhuang and in the Miao samples. Because the sex proportion of Han (13 men and 4 women) was different from those of Zhuang (10 men and 7 women) and Miao (3 men and 5 women), the ethnic differences of CYP1A2 in this study was, at least in part, due to the sex-related differences described below. More studies are required to elucidate the ethnic differences of CYP1A2 *in vivo* and *in vitro*.

It is interesting to note that the protein content and activity of CYP1A2 in men was lower than those in women in this study. This is inconsistent with the results of recent population studies *in vivo* which suggested a higher CYP1A2 activity in men[19,20]. The reason for this discrepancy is not clear. Further studies with a great sample size and liver specimens of detailed histories may be helpful to clarify it. However, large population studies also showed that sex differences only had a small effect on the interindividual variability of CYP1A2 activity[20]. And it has been suggested that there are no marked sex-related differences in CYP activities in humans[21]. In addition, Wrighton *et al* has demonstrated that no clear sex differences exist in CYP3A content and activity[22], and we only observed a marginal sex difference in CYP2C19 activity recently[23]. These observations, in consistence with the present results of no sex-related differences of CYP2C9, 2D6, and 3A4, suggest that sex differences may contribute to the interindividual variability of CYP content and activity to a very minor extent. In this study, we did not detect any age-related differences in liver microsomes of patients aged from 33 a to 67 a (45 ± 10), indicating that age may also not be an important reason for the interindividual variability in adults. In summary, we characterized the level and/or catalytic activity of several CYP important to drug metabolism in liver microsomes from 42 Chinese samples and analyzed the data with respect to interindividual variations and ethnic, sex- and age-related differences. Our results may provide useful information for the study of drug metabolism by liver microsomes in Chinese.

REFERENCES

1 Nelson DR, Koymans L, Kamataki T, Stegeman JJ, Feyereisen R, Waxman DJ, *et al*. P450 superfamily: update on new sequences, gene mapping, accession numbers and nomenclature. Pharmacogenetics 1996; 6: 1-42.

2 Wrighton SA, Stevens JC. The human hepatic cytochrome P450 involved in drug metabolism. Crit Rev Toxicol 1992; 22: 1-21.

3 Gonzalez FJ. Human cytochromes P450: Problems and prospects. Trends Pharmacol Sci 1992; 13: 346-52.

4 Cholerton S, Daly AK, Idle JR. The role of individual human cytochromes P450 in drug metabolism and clinical response. Trends Pharmacol Sci 1992; 13: 434-9.

5 Shimada T, Yamazaki H, Mimura M, Inui Y, Guengerich FP. Interindividual variations in human liver cytochrome P-450 enzymes involved in the oxidation of drugs, carcinogens and toxic chemicals: studies with liver microsomes of 30 Japanese and 30 Caucasians. J Pharmacol Exp Ther 1994; 270: 414-23.

6 Inoue K, Yamazaki H, Imiya K, Akasaka S, Guengerich FP, Shimada T. Relationship between CYP2C9 and 2C19 genotypes and tolbutamide methyl hydroxylation and *S*-mephenytoin

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4′-hydroxylation activities in livers of Japanese and Caucasian populations. Pharmacogenetics 1997; 7: 103 – 13.
7 Beaune P, Kremers PG, Kaminsky LS, De Graeve J, Albert A, Guengerich FP. Comparison of monooxygenase activities and cytochrome P-450 isozyme concentrations in human liver microsomes. Drug Metab Dispos 1986; 14: 437 – 42.
8 Guengerich FP, Turvy CG. Comparison of levels of several human microsomal cytochrome P-450 enzymes and epoxide hydroxylase in normal and disease states using immunochemical analysis of surgical liver samples. J Pharmacol Exp Ther 1991; 256: 1189 – 94.
9 Wood AJ, Zhou HH. Ethnic differences in drug disposition and responsiveness. Clin Pharmacokinet 1991; 20: 350 – 73.
10 Shu Y, Xu ZH, Xie HG, Zhu RH, Zhao JP, Zhou HH. Enzyme kinetic analysis and inhibition of amitriptyline *N*-demethylation in human liver microsomes *in vitro*. Chin J Pharmacol Toxicol 1998; 12: 260 – 5.
11 Lowry OH, Rosebrough NJ, Farr AL, Randall RJ. Protein measurement with the Folin phenal reagent. J Biol Chem 1951; 193: 265 – 75.
12 Omura T, Sato R. The carbon monoxide-binding pigment of liver microsomes. I. Evidence for its hemoprotein nature. J Biol Chem 1964; 239: 2370 – 8.
13 Shu Y, Wang LS, Xiao WM, Wang W, Huang SL, Zhou HH. Probing CYP2C19 and CYP3A4 activities in Chinese liver microsomes by quantification of 5-hydroxyomeprazole and omeprazole sulphone. Acta Pharmacol Sin 2000; 21: 753 – 8.
14 Frye RF, Branch RA. Improved high-performance liquid chromatographic determination of debrisoquine and 4-hydroxydebrisoquine in human urine following direct injection. J Chromatogr B Biomed Appl 1996; 677: 178 – 82.
15 Almira CM. Drug biotransformation. In: Katzung BG, editor. Basic and clinical pharmacology. 7th ed. Stamford: Connecticut Appleton & Lange; 1998.
16 Daly AK, Fairbrother KS, Smart J. Recent advances in understanding the molecular basis of polymorphisms in genes encoding cytochrome P450 enzymes. Toxicol Lett 1998; 102 – 3: 143 – 7.
17 Nakajima M, Yokoi T, Mizutani M, Kinoshita M, Funayama M, Kamataki T. Genetic polymorphism in the 5′-flanking region of human CYP1A2 gene: Effect on the CYP1A2 inducibility in humans. J Biochem 1999; 125: 803 – 8.
18 Sachse C, Brockmoller J, Bauer S, Roots I. Functional significance of a C→A polymorphism in intron 1 of the cytochrome P450 CYP1A2 gene tested with caffeine. Br J Clin Pharmacol 1999; 47: 445 – 9.
19 Ou-Yang DS, Huang SL, Wang W, Xie HG, Xu ZH, Shu Y, *et al*. Phenotypic polymorphism and gender-related differences of CYP1A2 activity in a Chinese population. Br J Clin Pharmacol 2000; 49: 145 – 51.
20 Tantcheva-Poór I, Zaigler M, Rietbrock S, Fuhr U. Estimation of cytochrome P-450 CYP1A2 activity in 863 healthy Caucasians using a saliva-based caffeine test. Pharmacogenetics 1999; 9: 131 – 44.
21 Sita DS. Human drug metabolism *in vivo*. Pharmacol Ther 1989; 43: 363 – 75.
22 Wrighton SA, Brian WR, Sari MA, Iwasaki M, Guengerich FP, Raucy JL, *et al*. Studies on the expression and metabolic capacibilities of human liver cytochrome P450IIIA5 (HLp3). Mol Pharmacol 1990; 38: 207 – 13.
23 Xie HG, Huang SL, Xu ZH, Xiao ZS, He N, Zhou HH. Evidence for the effect of gender on activity of *S*-mephenytoin 4′-hydroxylase (CYP2C19) in a Chinese population. Pharmacogenetics 1997; 7: 115 – 9.

中国人肝微粒体中细胞色素 P450 酶含量和活性的个体间差异[1]

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关键词 肝微粒体；细胞色素 P450 CYP1A2；细胞色素 P450 CYP2C9；细胞色素 P450 CYP2D6；细胞色素 P450 CYP3A4；代谢；蒙古人种

目的：比较不同中国人肝微粒体中几种重要细胞色素 P450 (CYP) 的酶含量和活性. **方法**：运用 Western 斑点分析和光密度扫描，对 17 个汉族、17 个壮族和 8 个苗族受试者肝微粒体中的细胞色素 P4501A2 (CYP1A2)、2C9 及 3A4 进行定量；非那西丁、甲磺丁脲、异喹胍和奥美拉唑分别用于体外测量 CYP1A2、2C9、2D6 及 3A4 的活性. **结果**：CYP1A2、2C9 及 3A4 的含量和活性具有很大的个体间变异，另外 CYP2D6 的活性在各样本间也有很大差异；CYP3A4 (32 %)是中国人肝微粒体中含量最丰富的 CYP，CYP2C9 (19 %)和 CYP1A2 (16 %)的含量也很可观；除了 CYP1A2 的含量和活性具有一定的种族和性别差异外，未发现其它 CYP 具有种族和性别差异；CYP1A2、2C9 和 3A4 的酶蛋白含量分别和它们的活性具有很好的相关性. **结论**：我们的结果为在中国人中进行药物代谢研究提供了非常有价值的信息.

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