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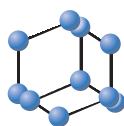
Survey of Drug Oxidation Activities in Hepatic and Intestinal Microsomes of Individual Common Marmosets, a New Nonhuman Primate Animal Model

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Abstract: *Background:* Common marmosets (*Callithrix jacchus*) are potentially useful nonhuman primate models for preclinical studies. Information for major drug-metabolizing cytochrome P450 (P450) enzymes is now available that supports the use of this primate species as an animal model for drug development. Here, we collect and provide an overview of information on the activities of common marmoset hepatic and intestinal microsomes with respect to 28 typical human P450 probe oxidations.

Results: Marmoset P450 2D6/8-dependent *R*-metoprolol *O*-demethylation activities in hepatic microsomes were significantly correlated with those of midazolam 1′- and 4-hydroxylations, testosterone 6β-hydroxylation, and progesterone 6β-hydroxylation, which are probe reactions for marmoset P450 3A4/5/90. In marmosets, the oxidation activities of hepatic microsomes and intestinal microsomes were roughly comparable for midazolam and terfenadine. Overall, multiple forms of marmoset P450 enzymes in livers and intestines had generally similar substrate recognition functionalities to those of human and/or cynomolgus monkey P450 enzymes.

Conclusion: The marmoset could be a model animal for humans with respect to the first-pass extraction of terfenadine and related substrates. These findings provide a foundation for understanding individual pharmacokinetic and toxicological results in nonhuman primates as preclinical models and will help to further support understanding of the molecular mechanisms of human P450 function.

1. INTRODUCTION

The human cytochrome *P450* gene superfamily comprises 57 functional genes and 58 pseudogenes [1]. The corresponding cytochrome P450 [P450 (EC 1.14.14.1)] enzymes are involved in the oxidative metabolism of a variety of endogenous and exogenous compounds and clinical medicines. In drug development, rodents are often used as preclinical animal models. However, it is well known that species differences exist in terms of drug oxidation activities mediated mainly by rodent and human P450 isoforms [2]. Common marmosets (*Callithrix jacchus*), New World monkeys, are attractive as small non-human primate models in drug metabolism studies due to genetic closeness, small body size, early sexual maturity, and high reproductive efficacy [3]. It has been reported that the metabolic profile of di(2-ethylhexyl)phthalate in marmosets was similar to that in humans, but not to that in rats [4]. Recently, an increasing amount of information on the characterization of cytochrome P450 enzymes has become available for marmosets, including information on P450 1A/B, 2A/B/C/D/E/F/J, 3A, and 4A/F [5, 6]. Toxicological research revealed that marmoset P450 2D6 activated and deactivated the potential pro-neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine [6]. It should be noted that all the P450s described in this study were named by the P450 Nomenclature Committee (http://drnelson.uthsc.edu/cytochromeP450.html) [7, 8]. Sequence similarity of P450 cDNA and amino acids between marmosets and humans are summarized in Table **1**.

In common marmosets, significantly faster *in vivo* clearance of *S*-warfarin than *R*-warfarin was observed after administration of racemic warfarin [9, 10], a finding consistent with warfarin stereoselectivity in humans [11]. In humans, warfarin is mainly metabolized by P450 2C9. However, marmosets do not possess the *P450 2C9* gene: instead, marmoset P450 2C19 mainly mediates the oxidations of human P450 2C9 and 2C19 substrates such as warfarin and omeprazole [12]. The *in vivo* pharmacokinetics of racemic warfarin and omeprazole have been shown to be related to marmoset P450 2C19 [F7L; S254L; I469T] [13]. The utility of physiologically based pharmacokinetic models was demonstrated in marmosets to help elucidate the inter-individual differences in the pharmacokinetics of *R*-omeprazole and *S*-warfarin associated with polymorphic P450 2C19 [14]. Moreover, the effects of aging or induction on some drug clearances mediated by marmoset P450 enzymes were evident in experiments on older animals and animals pretreated with rifampicin [15]. Additionally, marmoset P450 3A enzymes were strongly induced by exogenous rifampicin *in vitro* [16] and *in vivo* [15], just as human P450 3A enzymes are. Age-related pharmacokinetic changes in animal models could reveal important information during drug development for elderly patients.

Over the past few years, in separate studies, we have accumulated data on drug oxidation activities in hepatic microsomes and intestinal microsomes from marmosets [12-14, 17-33]. These data, along with the catalytic activities of recombinant P450 enzymes co-expressed with NADPH-cytochrome P450 reductase in bacterial membranes, are summarized in the current article. Moreover, we describe species and individual differences in marmoset P450 enzyme activities in hepatic and intestinal microsomes involved in

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Table 1.   Sequence similarity of P450 cDNA and amino acids between marmosets and humans.

Marmoset P450	GenBank Accession No.	Human P450	Homology to Human P450 (%)	
			cDNA	Amino Acids
1A1 [22]	KJ922553	1A1	93	90
1A2 [22]	NM_001204434	1A2	93	88
2A6 [39]	KJ922555	2A6	93	89
		2A7	91	86
		2A13	94	93
2B6 [30]	KJ922556	2B6	91	86
2C8 [12]	NM_001204437	2C8	93	88
2C18 [12]	KJ922558	2C18	94	93
2C19 [12]	KJ922561	2C9	92	86
		2C19	92	86
2C58 [12]	KJ922559	2C8	92	87
		2C9	84	79
		2C18	85	78
		2C19	84	78
2C76 [12]	KJ922560	2C8	76	68
		2C9	76	68
		2C18	78	70
		2C19	77	69
2D6 [18]	NM_001204438	2D6	92	91
2D8 [18]	KJ922562	2D6	89	85
2E1 [26]	NM_001267751	2E1	92	89
2J2 [23]	KX231948	2J2	94	91
3A4 [24]	NM_001204440	3A4	94	90
3A5 [24]	NM_001204442	3A5	93	89
3A90 [24]	NM_001204443	3A4	89	82
		3A5	92	88
		3A7	88	78
		3A43	83	74
4A11 [25]	KX231949	4A11	92	88
4F2 [19]	KX231950	4F2	93	93
4F3[19]	KX231951	4F3B	93	93
4F71[19]	KX231952	4F11	91	89
4F12 [19]	KX231953	4F12	91	87

drug oxidations associated with pharmacological and/or toxicological effects.

2. DRUG OXIDATION ACTIVITIES MEDIATED BY MARMOSET HEPATIC MICROSOMES

The oxidation activities of commercially available pooled hepatic microsomes from humans, monkeys, and marmosets and from individual marmosets obtained from the Central Institution for Experimental Animals (Kawasaki, Japan) for 26 substrates oxidized to 28 metabolites are plotted in Fig. (**1**). The numbers of available liver samples from individual marmosets ranged from 14 to 36 in these reactions. Marmoset hepatic microsomes catalyzed 7-ethoxyresorufin *O*-deethylation and 7-ethoxycoumarin *O*-deethylation (typical human P450 1A and 1B probe reactions) with similar activities to those of humans and cynomolgus monkeys [22, 33]. The catalytic activities

of recombinant marmoset P450 1A1 and 1A2 for these reactions were comparable to those of humans and cynomolgus monkeys (Table **2**). Marmoset hepatic microsomes did not show substantial coumarin 7-hydroxylation activities, unlike human and cynomolgus monkey hepatic microsomes [17]. This fact can be explained by the considerably low activity of this reaction mediated by recombinant marmoset P450 2A6 (Table **2**). Pooled hepatic microsomes from humans, cynomolgus monkeys, and marmosets catalyzed pentoxyresorufin *O*-depentylation, propofol 4-hydroxylation, and efavirenz 8-hydroxylation (typical human P450 2B6 substrates) [30]. However, the role of P450 enzymes in efavirenz 8-hydroxylation in marmoset and human livers may be different because of the low enzyme activity of recombinant marmoset P450 2B6 (Table **2**).
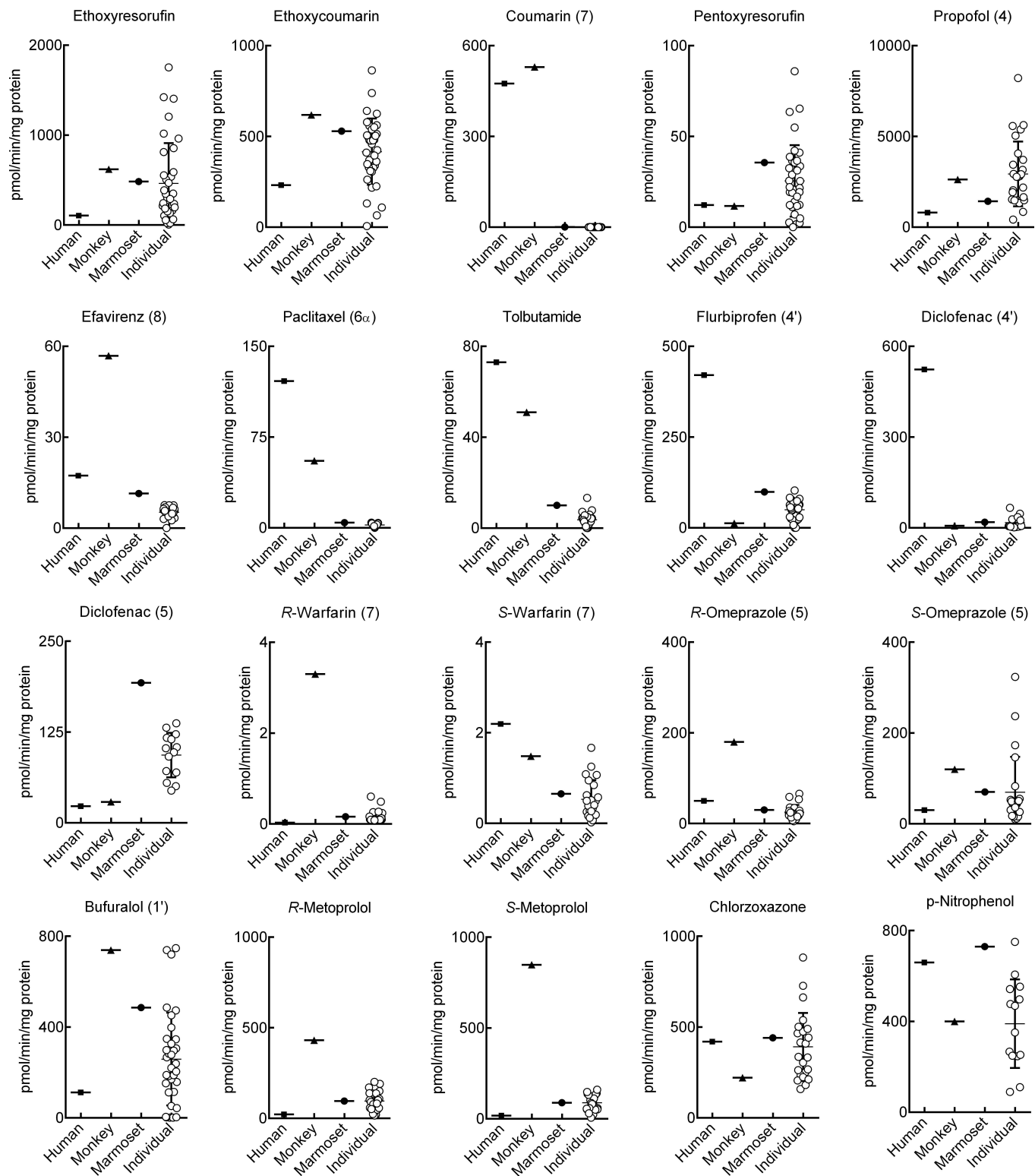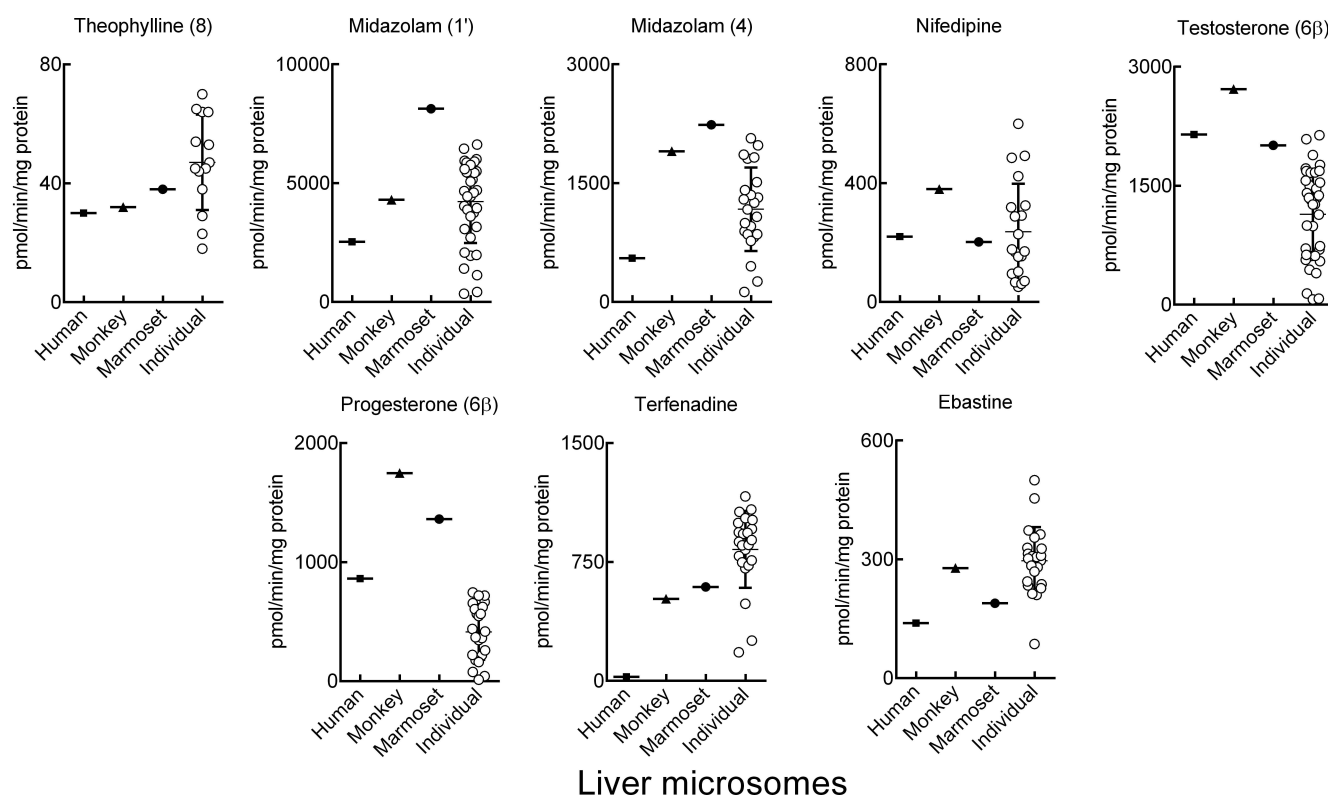
Fig. (1). Drug oxidation activities of commercially available pooled hepatic microsomes from humans, monkeys, and marmosets and from individual marmosets. For individual marmoset livers, individual plots and mean and SD bars are shown. Numbers in parentheses are the positions of drug oxidations. The substrate concentrations were: ethoxyresorufin (2.0 µM) [22], 7-ethoxycoumarin (20 µM) [30], coumarin (100 µM), pentoxyresorufin (10 µM) [30], propofol (20 µM) [30], efavirenz (20 µM) [30], paclitaxel (100 µM) [12], tolbutamide (100 µM) [12], flurbiprofen (20 µM) [12], diclofenac (10 µM for 4′-hydroxylation and 100 µM for 5-hydroxylation) [12], *R/S*-warfarin (10 µM) [41], *R/S*-omeprazole (10 µM) [12], bufuralol (20 µM) [24], *R/S*-metoprolol (10 µM) [27], chlorzoxazone (50 µM) [26], *p*-nitrophenol (50 µM) [26], theophylline (500 µM) [26], midazolam (20 µM) [24], nifedipine (50 µM) [24], testosterone (100 µM) [24], progesterone (100 µM) [24], terfenadine (2.0 µM) [23], and ebastine (20 µM) [19].

Paclitaxel, tolbutamide, flurbiprofen, and diclofenac are typical human P450 2C9 and 2C19 substrates. Some species differences were seen in terms of the activities of hepatic microsomes between marmosets, cynomolgus monkeys, and humans with respect to paclitaxel 6α-hydroxylation, tolbutamide methyl hydroxylation, flurbiprofen 4′-hydroxylation, and diclofenac 4′-hydroxylation [12]. Compared with the activities in human livers, the paclitaxel 6α-hydroxylation and flurbiprofen 4′-hydroxylation activities were low in marmoset and cynomolgus monkey livers, respectively. This may be explained by the lower activities for these catalytic reactions in recombinant marmoset P450 2C19 and recombinant cynomolgus monkey P450 2C9 and 2C19 (Table **2**). Although tolbutamide methyl hydroxylation was catalyzed by marmoset P450 2C8 and 2C19 with high activity levels (Table **2**), the low tolbutamide methyl hydroxylation activity in marmoset livers compared with that in human livers may be accounted for by the lower capacity of marmoset P450 2C19 and the lower affinity of marmoset P450 2C8 compared to those of human P450 2C9 [12]. Marked diclofenac 5-hydroxylation activity was observed in marmoset liver [29]. Stereoselective oxidations of *R*- and *S*-omeprazole were mediated by hepatic microsomes from cynomolgus monkeys and common marmosets [21]. The roles of P450 2C19 and 3A4 enzymes for omeprazole 5-hydroxylation and sulfoxidation, respectively, were conserved between marmoset and human livers. However, there were conspicuous species differences in terms of the stereoselectivity of omeprazole 5-hydroxylation between human and marmoset livers: marmoset livers preferentially catalyzed *S*-omeprazole 5-hydroxylation, whereas human livers preferentially catalyzed *R*-

omeprazole 5-hydroxylation. The stereoselectivity for omeprazole 5-hydroxylation between human and marmoset livers may be accounted for by the respective activities of recombinant marmoset P450 2C19 and human P450 2C9 (Table **2**) [21].

Investigations of typical human P450 2D6 substrates showed that hepatic microsomes from humans, cynomolgus monkeys, and marmosets catalyzed regio- and stereoselective *R*- and *S*-metoprolol *O*-demethylation and bufuralol 1′-hydroxylation [27]. Recombinant human and marmoset P450 2D6 enzymes effectively catalyzed *R*-metoprolol *O*-demethylation, consistent with the activities of human and marmoset hepatic microsomes (Table **2**). Investigations of typical human P450 2E1 substrates showed that hepatic microsomes from humans, cynomolgus monkeys, and marmosets catalyzed *p*-nitrophenol 2-hydroxylation, chlorzoxazone 6-hydroxylation, and theophylline 8-hydroxylation at similar rates [26]. Recombinant human, cynomolgus monkey, and marmoset P450 2E1 catalyzed these drug oxidation reactions, suggesting that P450 2E1 plays a similar role in drug-related oxidation reactions in human and marmoset livers (Table **2**).

Analysis of typical human P450 3A probe substrates revealed that hepatic microsomes from marmosets catalyzed midazolam 1′- and 4-hydroxylation, nifedipine oxidation, testosterone 6β-hydroxylation, and progesterone 6β-hydroxylation in a similar manner to those from humans and cynomolgus monkeys [24, 29]. Moreover, recombinant marmoset P450 3A4, 3A5, and 3A90 also catalyzed these drug oxidation reactions in a similar manner to human P450 3A enzymes, which likely accounts for the similar

Table 2. **Drug oxidation activities of recombinant marmoset, cynomolgus monkey, and human P450 enzymes expressed in *Escherichia coli*.**

Marker Reaction	Substrate Concentration	Marmoset		Cynomolgus Monkey		Human	
	(µM)	P450	Activity, nmol product/min/ nmol P450	P450	Activity, nmol product/min/ nmol P450	P450	Activity, nmol product/min/ nmol P450
Ethoxyresorufin O-deethylation	2	1A1[a]	39	1A1[a]	4.5	1A1[a]	24
	-	1A2[a]	14	1A2[a]	4.4	1A2[a]	4.4
7-Ethoxycoumarin O-deethylation	20	2B6[b]	0.099	2B6[b]	0.023	2B6[b]	0.036
	50	2A6	2.6	2A23	9.0	2A6	0.53
	-	-	-	2A24	2.1	2A13	34
	-	-	-	2A26	4.7	-	-
	100	1A1[a]	54	1A1[a]	11	1A1[a]	88
	-	1A2[a]	71	1A2[a]	18	1A2[a]	8.3
Phenacetin O-deethylation	50	2A6	3.4	2A23	1.7	2A6	<0.1
	-	-	-	2A24	<0.1	2A13	6.0
	-	-	-	2A26	<0.1	-	-
	100	1A1[a]	24	1A1[a]	3.7	1A1[a]	8.2
	-	1A2[a]	26	1A2[a]	5.7	1A2[a]	14
Coumarin 7-hydroxylation	100	2A6	0.021	2A23	1.4	2A6	5.8
	-	-	-	2A24	0.4	2A13	0.28
	-	-	-	2A26	9.9	-	-
Pentoxyresorufin O-depentylation	20	2B6[b]	0.025	2B6[b]	0.014	2B6[b]	0.018
Propofol 4-hydroxylation	20	2B6[b]	1.7	2B6[b]	1.3	2B6[b]	4.1
Efavirenz 8-hydroxylation	20	2B6[b]	0.35	2B6[b]	0.014	2B6[b]	<0.001
Paclitaxel 6α-hydroxylation	100	2C8[c]	1.0	2C8[d]	0.26	2C8	29
	-	2C18[c]	<0.5	2C9[d]	<0.001	-	-
	-	2C19[c]	<0.5	2C19[d]	<0.001	-	-
	-	2C58[c]	<0.5	2C76[d]	<0.001	-	-
	-	2C76[c]	<0.5	2C93[d]	<0.001	-	-
Tolbutamide methyl hydroxylation	2500	2C8[c]	62	2C8	0.64	2C8	1.1
	-	2C18[c]	0.25	2C9	0.85	2C9	5.5
	-	2C19[c]	19	2C19	13	2C19	0.37
	-	2C58[c]	0.34	2C76	1.5	-	-
	-	2C76[c]	0.17	-	-	-	-

Marker Reaction	Substrate Concentration	Marmoset		Cynomolgus Monkey		Human	
	(μM)	P450	Activity, nmol product/min/ nmol P450	P450	Activity, nmol product/min/ nmol P450	P450	Activity, nmol product/min/ nmol P450
Flurbiprofen 4-hydroxylation	100	2C8[e]	0.54	2C8[d]	0.01	2C9	21
	-	2C18[e]	<0.01	2C9[d]	0.03	-	-
	-	2C19[e]	4.7	2C19[d]	1.32	-	-
	-	2C58[e]	0.42	2C76[d]	0.01	-	-
	-	2C76[e]	<0.01	2C93[d]	0.10	-	-
R-Warfarin 7-hydroxylation	100	2C8[e]	<0.0001	2C8[e]	0.001	2C9	0.0028
	-	2C18[e]	0.0028	2C9[e]	0.0023	-	-
	-	2C19[e]	0.0053	2C19[e]	5.0	-	-
	-	2C58[e]	<0.0001	2C76[e]	0.0024	-	-
	-	2C76[e]	<0.0001	-	-	-	-
S-Warfarin 7-hydroxylation	100	2C8[e]	<0.0001	2C8[e]	<0.00001	2C9	0.17
	-	2C18[e]	0.0056	2C9[e]	0.0029	-	-
	-	2C19[e]	0.17	2C19[e]	0.21	-	-
	-	2C58[e]	<0.0001	2C76[e]	0.0012	-	-
	-	2C76[e]	<0.0001	-	-	-	-
R-Omeprazole 5-hydroxylation	100	2C8[f]	<0.4	2C8[f]	1.5	2C8[f]	<0.4
	-	2C18[f]	1.3	2C9[f]	3.1	2C9[f]	<0.4
	-	2C19[f]	9.9	2C19[f]	27	2C19[f]	9.8
	-	2C58[f]	1.2	2C76[f]	7.5	-	-
	-	2C76[f]	<0.4	-	-	-	-
S-Omeprazole 5-hydroxylation	100	2C8[f]	<0.4	2C8[f]	1.7	2C8[f]	<0.4
	-	2C18[f]	9.6	2C9[f]	1.3	2C9[f]	1.1
	-	2C19[f]	17	2C19[f]	28	2C19[f]	3.7
	-	2C58[f]	1.9	2C76[f]	4.9	-	-
	-	2C76[f]	<0.4	-	-	-	-
Bufuralol 1′-hydroxylation	10	2D6	2.7	-	-	2D6	5.6
	-	2D8	1.6	-	-	-	-
	100	2D6[g]	8.5	-	-	2D6[g]	5.8
	-	2D8[g]	1.9	-	-	3A4[g]	0.13
	-	3A4[g]	1.9	-	-	3A5[g]	0.24
	-	3A5[g]	1.4	-	-	-	-
	-	3A90[g]	0.81	-	-	-	-
	200	-	-	2D6	8.9	-	-
	-	-	-	2D44	4.9	-	-
	-	-	-	3A4	0.99	-	-
	-	-	-	3A5	2.4	-	-

Table (2) contd….

Marker Reaction	Substrate Concentration (µM)	Marmoset		Cynomolgus Monkey		Human	
		P450	Activity, nmol product/min/ nmol P450	P450	Activity, nmol product/min/ nmol P450	P450	Activity, nmol product/min/ nmol P450
R-Metoprolol	10	2D6[h]	4.9	-	-	2D6[h]	18
O-demethylation	-	2D8[h]	0.12	-	-	-	-
S-Metoprolol	10	2D6[h]	3.5	-	-	2D6[h]	5.7
O-demethylation	-	2D8[h]	0.095	-	-	-	-
Chlorzoxazone 6-hydroxylation	50	2E1[i]	0.68	2E1[i]	0.76	2E1[i]	1.3
p-Nitrophenol 2-hydroxylation	50	2E1[i]	0.42	2E1[i]	0.63	2E1[i]	0.40
Theophylline 8-hydroxylation	500	2E1[i]	0.017	2E1[i]	0.015	2E1[i]	0.49
Astemizole *O*-demethylation	20	2J2[j]	0.32	2J2[j]	0.76	2J2[j]	1.69
Midazolam	10	3A4[g]	29	3A4[g]	18	3A4[g]	11
1′-hydroxylation	-	3A5[g]	1.2	3A5[g]	36	3A5[g]	36
	-	3A90[g]	3.4	-	-	-	-
Midazolam	10	3A4[g]	9.1	3A4[g]	15	3A4[g]	2.3
4-hydroxylation	-	3A5[g]	0.051	3A5[g]	2.7	3A5[g]	1.4
	-	3A90[g]	0.11	-	-	-	-
Alprazolam	200	3A4[g]	1.4	3A4[g]	1.5	3A4[g]	0.74
4-hydroxylation	-	3A5[g]	0.022	3A5[g]	0.78	3A5[g]	0.46
	-	3A90[g]	0.054	-	-	-	-
Nifedipine	20	3A4[g]	25	3A4[g]	33	3A4[g]	22
oxidation	-	3A5[g]	1.1	3A5[g]	34	3A5[g]	7.8
	-	3A90[g]	2.8	-	-	-	-
Testosterone	50	3A4[g]	58	3A4[g]	50	3A4[g]	20
6β-hydroxylation	-	3A5[g]	5.4	3A5[g]	60	3A5[g]	19
	-	3A90[g]	4.9	-	-	-	-
Terfenadine *t*-butyl hydroxylation	20	2J2[j]	0.47	2J2[j]	0.54	2J2[j]	0.95
Ebastine	100	4F2[k]	0.013	4F2[k]	<0.01	4F2[k]	0.081
4-hydroxylation	-	4F3[k]	0.026	4F3v2[k]	0.013	4F3B[k]	0.043
	-	4F71[k]	0.38	4F11[k]	0.94	4F11[k]	1.1
	-	4F12[k]	6.6	4F12[k]	2.8	4F12[k]	2.5

Data are taken from [a] Uehara *et al.* [22]; [b] Oshio *et al.* [30]; [c] Uehara *et al.* [12] ; [d] Uno *et al.* [40]; [e] Hosoi *et al.* [41]; [f] Uehara *et al.* [21]; [g] Uehara *et al.* [24]; [h] Uehara *et al.* [27]; [i] Uehara *et al.* [26], [j] Uehara *et al.* [23]; and [k] Uehara *et al.* [19].

characteristics of P450 3A-dependent metabolism between human and marmoset livers (Table **2**). Hydroxylations of terfenadine and ebastine were effectively mediated by hepatic microsomes from marmosets and cynomolgus monkeys [19, 25, 32]. Recombinant human, cynomolgus monkey, and marmoset P450 2J2 and 4F12 enzymes effectively catalyzed terfenadine and ebastine hydroxylation, respectively (Table **2**).

The correlation coefficients among typical drug oxidation activities in hepatic microsomes from individual marmosets are summarized in Table **3**. This kind of wide correlation analysis has not previously been carried out in the course of developing marmoset P450 studies. We previously reported that the activities of marmoset hepatic microsomes with respect to *R*-metoprolol *O*-demethylation, a probe reaction for P450 2D6/8, were correlated to those of P450 2D6/8-dependent bufuralol 1′-hydroxylation, as expected [27]. The *R*-metoprolol *O*-demethylation activities mediated by individual marmoset hepatic microsomes were also significantly correlated to those of midazolam 1′- and 4-hydroxylations, testosterone 6β-hydroxylation, and progesterone 6β-hydroxylation, probe reactions for marmoset P450 3A4/5/90 (Table **3**) [27]. Interestingly, efavirenz 8-hydroxylation (a probe reaction for human P450 2B6) by marmoset hepatic microsomes was not mediated by marmoset P450 2B6 [30]. However, the activities for this reaction mediated by individual marmoset hepatic microsomes were correlated with those of marmoset P450 2C-dependent paclitaxel 6α-hydroxylation and *R*-omeprazole 5-hydroxylation, and marmoset P450 3A-dependent nifedipine oxidation (Table **3**), suggesting roles for marmoset P450 2C and 3A enzymes in efavirenz 8-hydroxylation.

3. DRUG OXIDATION ACTIVITIES MEDIATED BY MARMOSET INTESTINAL MICROSOMES

Marmoset intestine also exhibits several drug oxidation activities [18, 19, 23, 24, 32]. The oxidation activities of pooled intestinal microsomes from humans, monkeys, and marmosets and microsomes from individual marmosets (n = 16) with respect to 10 substrates forming 11 metabolites are plotted in Fig. (**2**). Small-intestinal microsomes from marmosets catalyzed midazolam 1′- and 4-hydroxylation and nifedipine oxidation activities in roughly similar manners to those of humans and/or cynomolgus monkeys. Additionally, marmoset small-intestinal microsomes more efficiently catalyzed terfenadine *t*-butyl hydroxylation than human small-intestinal microsomes did [32]. The activities of marmoset intestinal microsomes with respect to bufuralol 1′-hydroxylation (a probe reaction for P450 2D) and chlorzoxazone 6-hydroxylation (a probe reaction for P450 2E) were significantly correlated with those of midazolam 1′- and 4-hydroxylations, probe reactions for marmoset P450 3A4/5/90 (Table **4**). Moreover, marmoset P450 3A4/90 and 4F12 in small intestine played important roles in terfenadine *t*-butyl hydroxylation [32], suggesting that marmosets could be a human model for the first-pass extraction of terfenadine and related substrates.

4. OVERVIEW AND FUTURE ASPECTS

There are important similarities and differences among drug oxidations by human, monkey, and marmoset hepatic microsomes, as mentioned above. Additional differences also became evident during our extensive studies [34-41]. For example, caffeine is a typical P450 substrate differently metabolized among these primates, i.e., caffeine is *N*-3-demethylated by human livers, *N*-7-demethylated (to form theophylline) by monkey livers, and 8-hydroxylated by marmoset livers [34]. We also found that marmoset pulmonary P450 2F1 oxidized biphenyl and 7-ethoxycoumarin [31], and kidney P450 4A11 is a ω-hydroxylase with respect to arachidonic acid and lauric acid [25]. Furthermore, data for marmosets regarding other important drug-metabolizing enzymes and transporters (e.g., flavin-containing monooxygenases [35], aldehyde

Table 3.   **Correlation coefficients for drug oxidation activities of hepatic microsomes from individual marmosets.**

|	Pro-pofol	Efavi-renz	Pacli-taxel	Tolbu-tamide	Flur-bipro-fen	Diclo-fenac (4′)	Diclo-fenac (5)	S-War-farin	R-Ome-prazole	R-Me-toprolol	Theo-phyl-line	Mida-zolam (1′)	Mida-zolam (4)	Nifedip-ine	Testos-terone	Proges-terone
Efavirenz	0.05															
Paclitaxel	0.19	0.75**														
Tolbutamide	0.17	0.70*	0.72*													
Flurbiprofen	0.64*	0.22	0.29	0.43												
Diclofenac (4′)	0.13	0.57*	0.33	0.67*	0.15											
Diclofenac (5)	0.07	0.60*	0.67*	0.54	0.18	0.42										
S-Warfarin	0.22	0.48	0.48	0.77**	0.41	0.72*	0.35									
R-Omeprazole	0.31	0.71*	0.85**	0.82**	0.54*	0.51	0.47	0.81**								
R-Metoprolol	0.04	0.71*	0.76**	0.83**	0.06	0.68*	0.66*	0.72*	0.75**							
Theophylline	0.05	0.71*	0.71*	0.63	0.32	0.76**	0.72*	0.62*	0.69*	0.81**						
Midazolam (1′)	0.44	0.55*	0.80**	0.63	0.72*	0.11	0.48	0.42	0.79**	0.81**	0.58*					
Midazolam (4)	0.19	0.74*	0.94**	0.57	0.37	0.33	0.64*	0.43	0.83**	0.66*	0.75**	0.86**				
Nifedipine	−0.15	0.90**	0.91**	0.72*	0.07	0.54	0.69*	0.39	0.72*	0.78**	0.68*	0.53	0.83**			
Testosterone	0.35	0.67*	0.89**	0.66	0.53*	0.17	0.61*	0.41	0.81**	0.56*	0.63*	0.96**	0.95**	0.74*		
Progesterone	0.27	0.73*	0.91**	0.64	0.45	0.22	0.70*	0.41	0.79**	0.64*	0.67*	0.90**	0.95**	0.77**	0.98**	
Terfenadine	−0.12	0.62*	0.45	0.62	0.11	0.78**	0.48	0.65*	0.59*	0.75**	0.75**	0.11	0.41	0.72*	0.19	0.28

*P<0.05; **P<0.01.
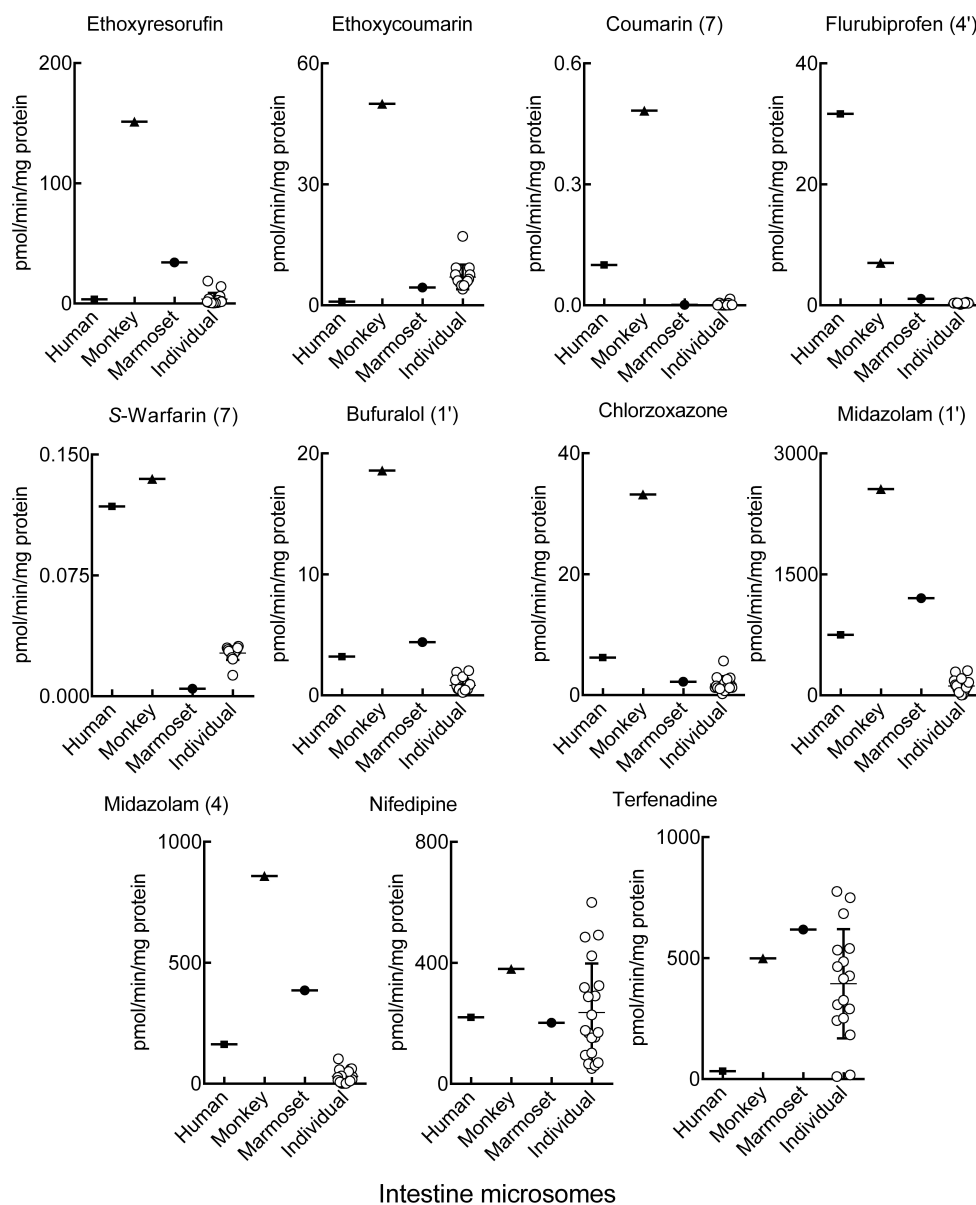
Fig. (2). Drug oxidation activities of pooled intestinal microsomes from humans, monkeys, and marmosets and from individual marmosets. For individual marmoset intestines, individual plots and mean and SD bars are shown. Numbers in parentheses are the positions of drug oxidations. The substrate concentrations are the same those shown in the legend for Fig. (**1**).

Table 4. **Correlation coefficients for drug oxidation activities of intestinal microsomes from individual marmosets.**

-	Bufuralol	Chlorzoxazone	Midazolam (1′)	Midazolam (4)	Nifedipine
Chlorzoxazone	0.10	-	-	-	-
Midazolam (1′)	0.66**	0.54*	-	-	-
Midazolam (4)	0.24	0.71**	0.65**	-	-
Nifedipine	0.71**	0.30	0.55*	0.42	-
Terfenadine	0.72**	0.31	0.55*	0.44	0.50*

*P<0.05; **P<0.01.

oxidases [36], catechol-*O*-methyltransferase [37], and ABC transporters [38]) are now available. Investigations of marmoset UDP-glucuronosyltransferases, glutathione *S*-transferases, and carboxy esterases are ongoing projects to help elucidate drug metabolism and disposition in marmosets as a model animal.

CONCLUSION

Taken together, the current surveys of the inter-individual variability of marmoset P450-dependant drug oxidation activities in hepatic and intestinal microsomes should help to further

our understanding of apparent species differences in drug metabolism and disposition in humans and nonhuman primates. Moreover, the information summarized here will help inform the extrapolation to humans of preclinical data obtained using common marmosets.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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