Faculty of Pharmaceutical Sciences[1], Okayama University, Okayama; Department of Biochemical Toxicology[2], Department of Clinical Pharmacy[3], Yokohama University of Pharmacy, Yokohama, Japan

Species and sex differences in propofol glucuronidation in liver microsomes of humans, monkeys, rats and mice

M. Mukai[1], T. Isobe[2], K. Okada[3], M. Murata[3], M. Shigeyama[3], N. Hanioka[2]

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Dr. Nobumitsu Hanioka, Professor, Department of Biochemical Toxicology, Yokohama University of Pharmacy, 601 Matano-cho, Totsuka-ku, Yokohama 245-0066, Japan
nhanioka@hamayaku.ac.jp

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Propofol (2,6-diisopropylphenol) is a short-acting anesthetic commonly used in clinical practice, and is rapidly metabolized into glucuronide by UDP-glucuronosyltransferase (UGT). In the present study, propofol glucuronidation was examined in the liver microsomes of male and female humans, monkeys, rats, and mice. The kinetics of propofol glucuronidation by liver microsomes fit the substrate inhibition model for humans and mice, the Hill model for monkeys, and the isoenzyme (biphasic) model for rats. The K_m, V_{max}, and CL_{int} values of human liver microsomes were 50 μM, 5.6 nmol/min/mg protein, and 110 μL/min/mg protein, respectively, for males, and 46 μM, 6.0 nmol/min/mg protein, and 130 μL/min/mg protein, respectively, for females. The rank order of the CL_{int} or CL_{max} (*in vitro* clearance) values of liver microsomes was mice » humans > monkeys > rats (high-affinity phase) » rats (low-affinity phase) in both males and females. Although no significant sex differences were observed in the values of kinetic parameters in any animal species, the *in vitro* clearance values of liver microsomes were males < females in humans, males = females in rats (low-affinity phase), and males > females in monkeys, rats (high-affinity phase), and mice. These results demonstrated that the kinetic profile of propofol glucuronidation by liver microsomes markedly differed among humans, monkeys, rats, and mice, and suggest that species and sex differences exist in the roles of UGT isoform(s), including UGT1A9, involved in its metabolism.

1. Introduction

Propofol (2,6-diisopropylphenol) is widely used as an intravenous anesthetic agent. It is rapidly eliminated from the body, and conjugation catalyzed by UDP-glucuronosyltransferase (UGT) in the liver is the main pathway for its metabolism in humans (Langley and Heel 1988; Vanlersberghe and Camu 2008). UGT1A9 has been identified as the predominant isoform for the glucuronidation of propofol in humans (Soars et al. 2003; Court 2005; Kiang et al. 2005). Human UGT1A9 is expressed not only in the liver, but also in extrahepatic tissues such as the kidney and small intestine (Ohno and Nakajin 2009; Harbourt et al. 2012). We recently reported that UGT1A9 expressed in the kidney as well as in the liver played an important role in propofol glucuronidation (Mukai et al. 2014). UGT1A8 expressed mainly in the digestive organs, but not in the liver has also been shown to glucuronidate propofol (Cheng et al. 1999; Kiang et al. 2005). *In vivo* studies previously identified marked species differences in the pharmacokinetic and metabolic profiles of propofol among rats, rabbits, and dogs (Simons et al. 1991, 1992; Cockshott et al. 1992), and these differences have been attributed to the levels of expression and function of the UGT isoform(s) responsible for propofol glucuronidation in each animal species. Several cDNAs of rodents and/or monkeys that encode the orthologs of human UGT1A8 and UGT1A9 have been cloned (http://www.flinders.edu.au/medicine/sites/clinical-pharmacology/ugt-homepage.cfm), and the functions of each UGT enzyme coded by cDNA have been characterized (Ritter 2000; Kiang at al. 2005). Previous studies suggested that large interindividual variability existed in the expression levels of UGT1A9 mRNA and protein in the livers of humans (Izukawa et al. 2009; Oda et al. 2012), and these variations may affect the plasma concentration, efficacy, and side-effects of propofol. Loryan et al. (2012) and Choong et al. (2013) demonstrated that the AUC of propofol glucuronide after a single bolus dose was 1.3-fold higher in female patients than in male patients. Thus, several *in vivo* studies have reported notable species and sex differences in propofol glucuronidation. However, the *in vitro* glucuronidation of propofol has not yet been examined in mammals. The aim of the present study was to clarify species and sex differences in the glucuronidation of propofol in the liver microsomes of humans, monkeys, rats, and mice.

2. Investigations and results

2.1. Propofol glucuronidation activities in liver microsomes

The glucuronidation activities of propofol in human, monkey, rat, and mouse liver microsomes were determined at a substrate concentration of 50 μM (Fig. 1). Glucuronidation activities in male and female human liver microsomes were 2.7 and 3.0 nmol/min/mg protein, respectively. Activities in monkey liver microsomes were 1.6-fold for males and 1.3-fold for females

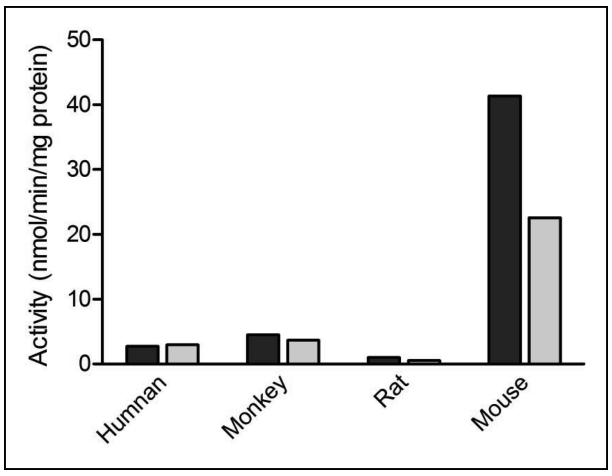

Fig. 1: Propofol glucuronidation activities in human, monkey, rat amd mouse liver microsomes. The substrate concentrations used was 50 μM. Each column represents the mean of three separate experiments performed in duplicate. ■, males; ■, females.

of those in human liver microsomes, respectively. Activities in male and female rat liver microsomes were 37% and 18% of those in human liver microsomes, respectively. Activities were markedly higher in male and female mouse liver microsomes (15- and 7.7-fold, respectively) than in human liver microsomes. Glucuronidation activities in male and female liver microsomes were similar between humans and monkeys. In rats and mice, activities were approximately 2-fold higher in male liver microsomes than in female liver microsomes.

2.2. Kinetics for propofol glucuronidation by liver microsomes

A kinetic analysis of propofol glucuronidation by the liver microsomes of humans, monkeys, rats, and mice was performed to obtain more detailed information. The plots (V-[S] and V-V/[S] plots) and parameters of the kinetics tested are shown in Figs. 2–5 and the Table 1, respectively. The kinetics for propofol glucuronidation by male and female human liver microsomes exhibited substrate inhibition with *K*si values of 530–550 μM. The K_m, V_{max}, and CL_{int} values of male human liver microsomes were 50 μM, 5.6 nmol/min/mg protein, and 110 μL/min/mg protein, respectively. The parameter values of female human liver microsomes were similar to those of male human liver microsomes. The kinetics by male and female monkey liver microsomes fit the Hill model with *n* of 1.5–1.6, and the S_{50}, V_{max}, and CL_{max} values of male monkey liver microsomes were 71 μM, 13 nmol/min/mg protein, and 93 μL/min/mg protein, respectively. The parameter values of female monkey liver microsomes were similar to those of male monkey liver microsomes.

Propofol glucuronidation by male and female rat liver microsomes exhibited isoenzyme (biphasic) kinetics. The K_m, V_{max}, and CL_{int} values of male rat liver microsomes were 8.0 μM, 0.6 nmol/min/mg protein, and 72 μL/min/mg protein for the high-affinity phase, and 170 μM, 2.1 nmol/min/mg protein, and 13 μL/min/mg protein for the low-affinity phase, respectively. The K_m and V_{max} values of female rat liver microsomes were lower than those of male rat liver microsomes (56% and 26% for the high-affinity phase, and 75% and 64% for high-affinity phase, respectively). The results revealed that the CL_{int} value of female rat liver microsomes in the high-affinity phase was approximately 50% that of male rat liver microsomes, whereas the value in the low-affinity phase was similar to that of male

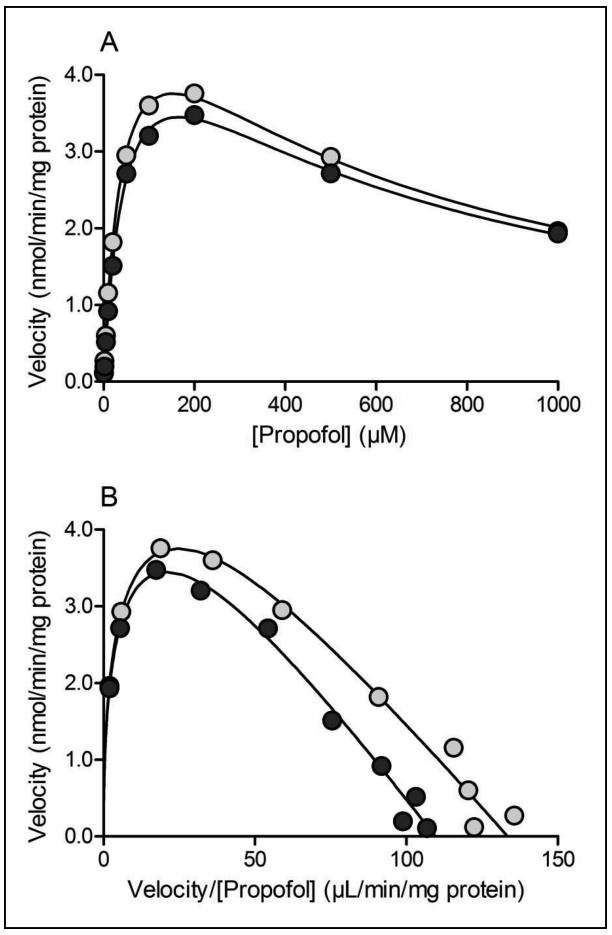

Fig. 2: Kinetics of propofol glucuronidation by human liver microsomes. Substrate concentrations were 1–1000 μM. Each point represents the mean of three separate experiments. ●, males; ●, females. (A) V-[S] plots; (B) V-V/[S] plots.

rat liver microsomes. The kinetics by male and female mouse liver microsomes exhibited substrate inhibition with *K*si values of 75–110 μM. The K_m, V_{max}, and CL_{int} values of male mouse liver microsomes were 40 μM, 97 nmol/min/mg protein, and 2400 μL/min/mg protein, respectively; and these values in female mouse liver microsomes were 76%, 58%, and 76% of those in male mouse liver microsomes, respectively.

3. Discussion

Propofol is intravenously administered for anesthetic induction and maintenance. It is rapidly metabolized, with the majority of the dose being excreted into urine as propofol glucuronide in humans (Langleyand and Heel 1988; Vanlersberghe and Camu 2008). Although *in vivo* studies have been performed on species and sex differences in propofol glucuronidation in mammals (Simons et al. 1991, 1992; Cockshott et al. 1992; Loryan et al. 2012; Choong et al. 2013), there is no information on the *in vitro* glucuronidation of propofol. Therefore, we herein examined the glucuronidation of propofol in the liver microsomes of humans, monkeys, rats, and mice.

To obtain basic information on species and sex differences in propofol glucuronidation, propofol glucuronidation activities were initially determined in the liver microsomes of humans, monkeys, rats, and mice at a single substrate concentration of 50 μM. The rank order of these activities in liver microsomes was mice » monkeys > humans > rats in both males and females. UGT1A9 has been identified as the predominant isoform for the

Table 1: Kinetic parameters for propofol glucuronidation by human, monkey, rat and mouse liver microsomes

	K_m or S_{50} (μM)	V_{max} (nmol/min/mg protein)	n	CL_{int} or CL_{max} (μL/min/mg protein)	K_{si} (μM)	Model
Human						
Male	50.2 ± 9.6	5.62 ± 0.64		110 ± 13	546 ± 105	Substrate inhibition
Female	45.8 ± 8.8	6.02 ± 0.59		134 ± 15	531 ± 115	Substrate inhibition
Monkey						
Male	71.4 ± 8.2	12.5 ± 1.0	1.61 ± 0.23	92.5 ± 8.7		Hill
Female	83.1 ± 9.5	11.7 ± 0.5	1.53 ± 0.16	75.1 ± 3.6		Hill
Rat						
Male						Isoenzyme
High-affinity phase	8.00 ± 1.22	0.58 ± 0.12		72.0 ± 8.9		
Low-affinity phase	169 ± 20	2.07 ± 0.37		12.5 ± 3.2		
Female						Isoenzyme
High-affinity phase	4.45 ± 1.65	0.15 ± 0.05		35.4 ± 8.9		
Low-affinity phase	127 ± 36	1.33 ± 0.20		12.9 ± 7.0		
Mouse						
Male	40.1 ± 1.9	97.1 ± 7.8		2420 ± 180	114 ± 19	Substrate inhibition
Female	30.5 ± 4.3	56.2 ± 6.2		1850 ± 130	75.4 ± 7.5	Substrate inhibition

Each value represents the mean ± SD of three separate experiments.

glucuronidation of propofol in humans (Court 2005; Kiang et al. 2005), and is extensively expressed in hepatic and extrahepatic tissues (Ohno and Nakajin 2009; Harbourt et al. 2012; Fallon et al. 2013). The cDNAs of monkeys and mice that encode the ortholog of human UGT1A9 have been cloned; however, rat UGT1A9 cDNA has been identified as a pseudogene (Emi et al. 1995; Albert et al. 1999; Zhang et al. 2004). The weak

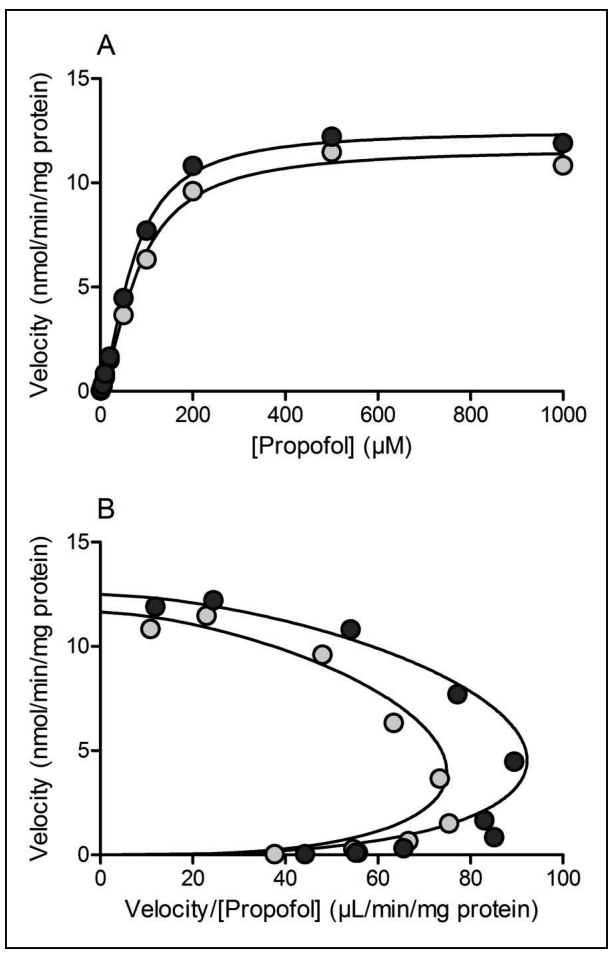

Fig. 3: Kinetics of propofol glucuronidation by monkey liver microsomes. Substrate concentrations were 1–1000 μM. Each point represents the mean of three separate experiments. ●, males; ●, females. (A) V-[S] plots; (B) V-V/[S] plots.

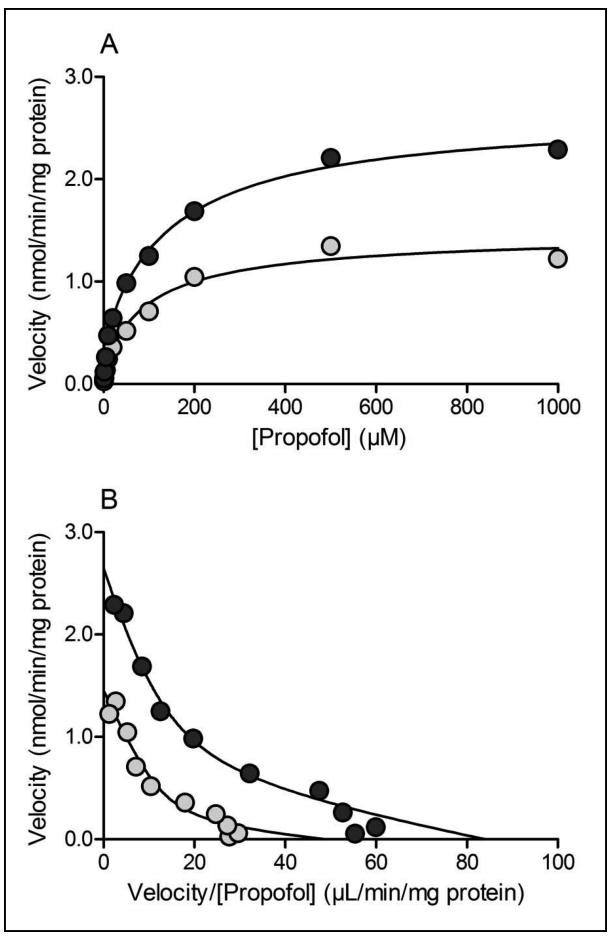

Fig. 4: Kinetics of propofol glucuronidation by rat liver microsomes. Substrate concentrations were 1–1000 μM. Each point represents the mean of three separate experiments. ●, males; ●, females. (A) V-[S] plots; (B) V-V/[S] plots.

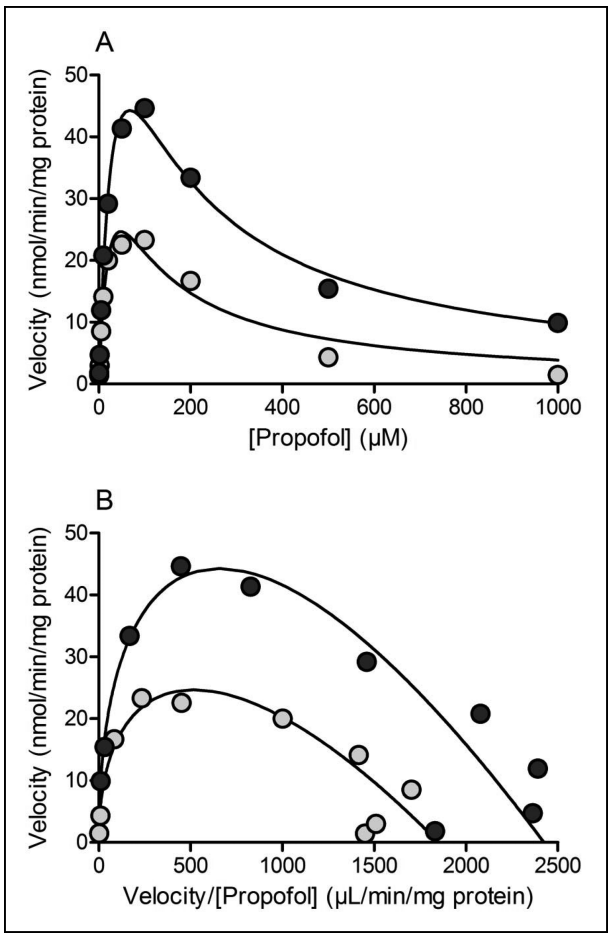

Fig. 5: Kinetics of propofol glucuronidation by mouse liver microsomes. Substrate concentrations were 1–1000 μM. Each point represents the mean of three separate experiments. ●, males; ○, females. (A) V-[S] plots; (B) V-V/[S] plots.

glucuronidation of propofol by rat liver microsomes has been attributed to a deficiency in the UGT1A9 enzyme in rats.

Kinetic analyses of propofol glucuronidation by the liver microsomes of humans, monkeys, rats, and mice were subsequently performed at a broad range of substrate concentrations. Soars et al. (2003) previously reported that the kinetics of propofol glucuronidation by human liver microsomes fit the Michaelis–Menten model with K_m values of 190–280 μM. In the present study, the kinetics by both male and female human liver microsomes exhibited substrate inhibition. Although no marked differences were observed in the values of kinetic parameters between male and female human liver microsomes, the CL_{int} value of female human liver microsomes was 1.2-fold higher than that of male human liver microsomes, supporting the *in vivo* studies by Loryan et al. (2012) and Choong et al. (2013). The kinetics for propofol glucuronidation by monkey liver microsomes exhibited a distinctive "hook" on V-V/[S] plots, suggesting the mechanism of allosteric activation, and the data obtained were found to fit the Hill model best. The kinetic profile differed from that of human liver microsomes, although the *in vitro* clearance values were similar for both sexes. We recently reported that the *in vitro* clearance value for propofol glucuronidation by recombinant monkey UGT1A9 was 2% of recombinant human UGT1A9 (Yamamoto et al. 2014). Our previous and present results indicated that UGT isoform(s), except for UGT1A9, predominantly contributed to the glucuronidation of propofol in the monkey liver. On the other hand, the S_{50}, V_{max}, CL_{max}, and n values of male and female monkey liver microsomes were similar, and no marked sex difference was observed in the *in vitro* kinetics of propofol glucuronidation.

In rat liver microsomes, the kinetics for propofol glucuronidation fit a biphasic model, suggesting the contribution of one or more UGT isoforms for its metabolism. The V_{max} and CL_{int} values for the low- and high-affinity phases were the lowest among the liver microsomes of the animal species examined in this study in both males and females. Since the UGT1A9 enzyme is deficient in rats (Emi et al. 1995), plural UGT isoforms, except for UGT1A9, glucuronidated propofol. The kinetic profile of substrate inhibition was observed in mouse as well as in human liver microsomes, and the K_{si} values obtained were approximately 10–20% of human liver microsomes. The K_m values of mouse liver microsomes were similar to those of human liver microsomes, whereas the V_{max} and CL_{int} values were approximately 15–20-fold higher than those of human liver microsomes. The V_{max} and CL_{int} values of female mouse liver microsomes were approximately 25–40% lower than those of male mouse liver microsomes. These results imply that UGT1A9 expression levels were markedly higher in the mouse liver than in the human liver, and differed between males and females.

The mRNA and protein of human UGT1A9 were previously found to be expressed in not only the liver, but also in extrahepatic tissues such as the kidney and intestines (Ohno and Nakajin 2009; Harbourt et al. 2012; Fallon et al. 2013). We recently reported the *in vitro* glucuronidation of propofol by human liver, intestinal, and kidney microsomes, and found that UGT1A9 expressed in the kidney as well as in the liver played an important role in propofol glucuronidation (Mukai et al. 2014). Additionally, the efficiency of propofol glucuronidation by intestinal microsomes was suggested to less than that of liver and kidney microsomes. Human UGT1A8, which is mainly expressed in the intestines, has also been shown to contribute to the glucuronidation of propofol, although the *in vitro* clearance value is estimated to be lower than that of UGT1A8 (Cheng et al. 1999; Soars et al. 2003; Court 2005; Kiang et al. 2005). Therefore, UGT1A9 was confirmed to be the main enzyme responsible for the glucuronidation of propofol in the human liver. Information on the tissue distribution of the mRNAs and proteins of each UGT isoform is limited in monkeys, rats, and mice. Among the cDNAs of monkeys, rats, and encoding orthologs of human UGT1A8 and UGT1A9 cloned to date (http://www.flinders.edu.au/medicine/sites/clinical-pharmacology/ugt-homepage.cfm), rat UGT1A9 has been identified as a pseudogene (Emi et al. 1995). Further studies are required to clarify the roles of hepatic and extrahepatic UGT isoforms including UGT1A8 and UGT1A9 in propofol glucuronidation using recombinant enzymes of each animal species.

In conclusion, propofol glucuronidation in male and female human, monkey, rat, and mouse liver microsomes was examined using a kinetic analysis. The kinetics for propofol glucuronidation by liver microsomes fit the substrate inhibition model for humans and mice, the Hill model for monkeys, and the biphasic model for rats. Species differences in the *in vitro* clearance values of liver microsomes were mice » humans > monkeys > rats (the high-affinity phase) » rats (the low-affinity phase) in both sexes. Sex differences in the *in vitro* clearance values of liver microsomes were males < females in humans, males = females in rats (the low-affinity phase), and males > females in monkeys, rats (the high-affinity phase), and mice. These results demonstrated that the kinetic profile of propofol glucuronidation by liver microsomes markedly differed between humans, monkeys, rats, and mice, and suggested that species and sex differences exist in the roles of UGT isoform(s), including UGT1A9, involved in its metabolism.

4. Experimental

4.1. Materials

Propofol and propofol glucuronide were obtained from Santa Cruz Biotechnology (Santa Cruz, CA, USA). The pooled liver microsomes of humans (race, Caucasian, Hispanic, and African American; age, 20–78 years old), monkeys (strain, cynomolgus; age, 3–8 years old), rats (strain, Wistar; age, 8–10 weeks old), and mice (strain, CD1; age, 8–11 weeks old) were purchased from XenoTech (Lenexa, KS, USA). All other chemicals and reagents used were of the highest quality commercially available.

4.2. Assay for propofol glucuronidation activity

Propofol glucuronidation activities were determined in the liver microsomes of humans, monkeys, rats, and mice according to a previously described method with minor modifications (Mukai et al. 2014). The incubation mixture contained propofol (1–1000 μM), microsomes (200 μg protein/mL for human liver microsomes, 100 μg protein/mL for monkey liver microsomes, 500 μg protein/mL for rat liver microsomes, and 10 μg protein/mL for mouse liver microsomes), alamethicin (20 μg/mL), 10 mM $MgCl_2$, and 2 mM UDP-glucuronic acid in a final volume of 200 μL of 50 mM Tris-HCl buffer (pH 7.4). After preincubation for 2 min at 37 °C, the reaction was initiated by adding UDP-glucuronic acid. Incubation was performed for 20 min at 37 °C and terminated by adding 50 μL of 10% phosphoric acid and vortexing. Propofol was dissolved in methanol/dimethyl sulfoxide (50:50, v/v) and the final concentration of the organic solvent (methanol and dimethyl sulfoxide) in the incubation mixture was 1% (v/v). The samples were centrifuged at 12000 g for 10 min at 4 °C. The supernatant was filtered with a polytetrafluoroethylene membrane filter (0.45 μm), and 50 μL of the filtrate was subjected to high-performance liquid chromatography with an Inertsil ODS-SP column (4.6 mm i.d. × 150 mm; GL Sciences, Tokyo, Japan). The column was maintained at 40 °C. Propofol glucuronide was isocratically eluted with 0.1% acetic acid/acetonitrile (60:40, v/v) at a flow rate of 1.0 mL/min. UV detection was performed at 220 nm. Standard curve samples spiked with propofol glucuronide were prepared in the same manner as incubation samples.

4.3. Data analysis

Kinetic parameters (K_m or S_{50}, and V_{max}), the Hill coefficient (n), and K_{si} for propofol glucuronidation were calculated by constructing velocity versus substrate concentration (V-[S]) plots using SigmaPlot v8.02 software (Systat Software, San Jose, CA, USA). The kinetic profile was estimated from the respective coefficient of determination and/or Akaike's information criterion values for the Michaelis–Menten, isoenzyme, substrate inhibition, and Hill equations. *In vitro* clearance values were CL_{int} (V_{max}/K_m) or CL_{max} ($V_{max}/S_{50}*(n\text{-}1)/(n(n\text{-}1)^{1/n})$. All values are expressed as the mean ± SD of three separate experiments performed in duplicate.

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