Glucuronidation of Thyroxine in Human Liver, Jejunum, and Kidney Microsomes

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ABSTRACT:

Glucuronidation of thyroxine is a major metabolic pathway facilitating its excretion. In this study, we characterized the glucuronidation of thyroxine in human liver, jejunum, and kidney microsomes, and identified human UDP-glucuronosyltransferase (UGT) isoforms involved in the activity. Human jejunum microsomes showed a lower \( K_{\text{m}} \) value (24.2 \( \mu \text{M} \)) than human liver (85.9 \( \mu \text{M} \)) and kidney (53.3 \( \mu \text{M} \)) microsomes did. Human kidney microsomes showed a lower \( V_{\text{max}} \) value (22.6 pmol/min/mg) than human liver (133.4 pmol/min/mg) and jejunum (184.6 pmol/min/mg) microsomes did. By scaling-up, the in vivo clearances in liver, intestine, and kidney were estimated to be 1440, 702, and 79 \( \mu \text{L} / \text{min/kg} \) body weight, respectively. Recombinant human UGT1A8 (108.7 pmol/min/unit), UGT1A3 (91.6 pmol/min/unit), and UGT1A10 (47.3 pmol/min/unit) showed high, and UGT1A1 (26.0 pmol/min/unit) showed moderate thyroxine glucuronosyltransferase activity. The thyroxine glucuronosyltransferase activity in microsomes from 12 human livers was significantly correlated with bilirubin O-glucuronosyltransferase (\( r = 0.855, p < 0.001 \)) and estradiol 3-O-glucuronosyltransferase (\( r = 0.827, p < 0.0001 \)) activities catalyzed by UGT1A1, indicating that the activity in human liver is mainly catalyzed by UGT1A1. Kinetic and inhibition analyses suggested that the thyroxine glucuronidation in human jejunum microsomes was mainly catalyzed by UGT1A8 and UGT1A10 and to a lesser extent by UGT1A1, and the activity in human kidney microsomes was mainly catalyzed by UGT1A7, UGT1A9, and UGT1A10. The changes of activities of these UGT1A isoforms via inhibition and induction by administered drugs as well as genetic polymorphisms may be a causal factor of interindividual differences in the plasma thyroxine concentration.

Thyroid hormones mediate many physiological processes including embryonic development, cellular differentiation, metabolism, and the regulation of cell proliferation (Hulbert, 2000; Wu and Koenig, 2000; Zhang and Lazar, 2000). The plasma concentrations of thyroid hormones are strictly controlled by thyroid-stimulating hormone, which is subjected to negative feedback regulation by thyroid hormones. The major form of thyroid hormone secreted from thyroid gland is thyroxine. In hypothyroidism, thyroxine is orally administered to keep the plasma thyroid hormone level normal. Thyroxine has little biological activity and is converted to the active form, triiodothyronine (T3) mainly in human liver and kidney (Leonard and Koehrle, 1996). In human, approximately 80% of the total plasma T3 is produced by thyroxine via outer ring deiodination (Fig. 1). In addition to deiodination, thyroxine is metabolized to sulfate and glucuronide by sulfotransferases and UDP-glucuronosyltransferases (UGTs), respectively (Fig. 1). The thyroxine sulfate hardly appears in bile, urine, or serum, because it is rapidly degraded by inner ring deiodination in the liver. In contrast to the sulfate, thyroxine glucuronide is readily excreted into bile and subsequently hydrolyzed by \( \beta \)-glucuronidases in the intestine, and may affect the enterohepatic circulation of thyroxine (Visser, 1994). It has been reported that administration of UGT inducers such as phenytoin, carbamazepine (Isojarvi et al., 1992), and rifampicin (Ohnhaus and Studer, 1983) markedly decreased serum thyroxine levels in patients. Thus, glucuronidation is a major metabolic pathway to control the serum thyroxine level.

In humans, UGTs are divided into two families: UGT1 and UGT2 (Mackenzie et al., 2005). The UGT1 and UGT2 genes appear to be structurally different in that the UGT1 proteins result from alternate splicing of the unique first exon with four common exons encoded by the UGT1 gene complex, whereas UGT2 proteins appear to be encoded by unique genes. In humans, there are nine functional UGT1A and seven UGT2B proteins (Mackenzie et al., 2005). Among them, human UGT1A1 and UGT1A9 have been reported to catalyze thyroxine glucuronidation (Findlay et al., 2000). However, a limitation of the study was that only two UGT isoforms were investigated. The first purpose of the present study is to investigate the catalytic activity of thyroxine glucuronidation by all human UGT isoforms for which recombinant proteins are currently available.

Human UGTs are expressed in a tissue-specific manner. Table 1 summarizes the UGT isoforms expressed in human liver, intestine, and kidney (King et al., 2000; Tukey and Strassburg, 2000; Fisher et al., 2001; Levesque et al., 2001; Basu et al., 2004, Finel et al., 2005). In general, liver plays an important role in the glucuronidation of most

**ABBREVIATIONS:** T3, triiodothyronine; LC-MS/MS, liquid chromatography-mass/mass spectrometry; UGT, UDP-glucuronosyltransferase; UDP-GPA, UDP-glucuronic acid.
drugs, but extral hepatic tissues also contribute significantly to the glucuronidation of certain drugs in human (Krishna and Klotz, 1994).

It is conceivable that the glucuronidation of thyroxine occurs not only in liver but also in intestine and kidney. The second purpose of the present study is to characterize thyroxine glucuronidation in human liver, jejunum, and kidney microsomes, and to identify the UGT isoforms involved in the glucuronidation in each tissue.

Materials and Methods

Materials. Thyroxine, UDP-glucuronic acid (UDPGA), and alamethicin were purchased from Sigma-Aldrich (St. Louis, MO). Bilirubin, chenodeoxycholic acid, serotonin, imipramine hydrochloride, and propofol were purchased from Wako Pure Chemicals (Osaka, Japan). Morphine hydrochloride was from Takeda Chemical Industries (Osaka, Japan). Pooled human liver microsomes (lot H161), 12 individual human livers (H003, H023, H030, H043, H056, H064, H066, H070, H089, H093, H112, and HK23), recombinant human UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A7, UGT1A8, UGT1A9, UGT1A10, UGT2B4, UGT2B7, UGT2B15, and UGT2B17 expressed in baculovirus-infected insect cells (Supersomes), and UGT control Supersomes were purchased from BD Gentest (Woburn, MA). The human jejunum (lot HJM0023) or kidney (lot 045290170002) microsomes from an individual donor were purchased from KAC (Kyoto Japan). All other chemicals and solvents were of analytical or the highest grade commercially available.

Thyroxine Glucuronidation Assay. A typical incubation mixture (100 μl total volume) contained 100 mM Tris-HCl buffer (pH 7.4), 5 mM MgCl₂, 5 mM UDPGA, 25 μg/ml alamethicin, 0.4 mg/ml human liver, jejunum, or kidney microsomes or recombinant UGTs, and 50 μM thyroxine. Thyroxine was dissolved in dimethyl sulfoxide/0.05 M sodium hydroxide (50:50). The final concentration of the organic solvents in the incubation mixture was 1% (v/v). The reaction was initiated by the addition of UDPGA. After incubation at 37°C for 90 min, the reaction was terminated by adding 100 μl of ice-cold 94% acet nitrile/6% formic acid. After the centrifugation at 12,000 rpm for 5 min, the supernatant was filtered with a 0.22-μm filter (Ultrafree-MC centrifugal filter unit; Millipore, Eschborn, Germany). Aliquots of 10 μl were injected into the LC-MS/MS system.

LC-MS/MS Analysis for Thyroxine Glucuronides. LC was performed using an HP1100 system including a binary pump, an automatic sampler, and a column oven (Agilent Technologies, Waldbronn, Germany), which was equipped with a Mightsil RP-18 GP (4.6 × 150 mm; 5 μm) column (Kanto Chemical, Tokyo, Japan). The column temperature was 35°C. The mobile phase was 0.1% formic acid (A) and acetonitrile including 0.1% formic acid (B). The conditions for elution were as follows: 25% B (0–1 min); 25 to 70% B (1–4 min); 70% B (4–10 min); 70 to 25% B (10–11 min). Linear gradients were used for all solvent changes. The flow rate was 0.5 ml/min. The LC apparatus was connected to a PE Sciex API2000 tandem mass spectrometer (Applied Biosystems, Langen, Germany) in the positive electrospray ionization mode. The turbo gas was maintained at 450°C. Nitrogen was used as the nebulizing, turbo, and curtain gas at 50, 80, and 20 psi, respectively. Parent and/or fragment ions were filtered in the first quadrupole and dissociated in the collision cell using nitrogen as the collision gas. The collision energy was 20 V and 26 V for thyroxine and thyroxine glucuronides, respectively. Two mass/charge (m/z) ion transitions were recorded in the multiple reaction monitoring mode: m/z 778 and 778 for thyroxine, and m/z 954 and 778 for thyroxine glucuronide. The retention times of thyroxine glucuronide and thyroxine were 7.1 min and 8.9 min, respectively. For the quantification of thyroxine glucuronide, the eluate of the HPLC from the incubation mixture including thyroxine glucuronide was collected, referring to the retention time. A part of the eluate was incubated with 800 U/ml β-glucuronidase at 37°C for 24 h. The produced thyroxine was quantified by LC-MS/MS. Once we determined the peak area per known content of thyroxine glucuronide, the ratio was applied to the calculation of the thyroxine glucuronide formed in the incubation mixtures.

Kinetic Analyses of Thyroxine Glucuronidation in Human Liver, Jejunum, and Kidney Microsomes or Recombinant UGTs. Thyroxine glucuronosyltransferase activities were determined as described above with substrate concentrations from 2 μM to 100 μM. Kinetic parameters were estimated from the fitted curve using a computer program (KaleidaGraph; Synergy Software, Reading, PA) designed for nonlinear regression analysis. The following equations were applied for Michaelis-Menten kinetics (eq. 1) or substrate inhibition kinetics (eq. 2) (Houston and Kenworthy, 2000):

\[ V = V_{\text{max}} \times S/(K_s + S) \]  
\[ V = V_{\text{max}} \times S/(K_s + S + S^2/K_{ii}) \]

where \( V \) is the velocity of the reaction, \( S \) is the substrate concentration, \( K_s \) is the Michaelis-Menten constant, \( V_{\text{max}} \) is the maximum velocity, and \( K_{ii} \) is the

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**FIG. 1. Major metabolic pathways of thyroxine in human.**
substrate inhibition constant. Data are expressed as mean ± S.D. of three independent determinations.

Estimation of Tissue Clearances from in Vitro Data. In vivo clearance was scaled-up by an equation (Obach et al., 1997; Soars et al., 2002):

$$CL = \frac{V_{\text{max}}}{K_m} \times \frac{\text{Microsomal protein (mg/g)}}{\text{Tissue}} \times \frac{\text{Tissue weight (g/kg)}}{\text{Body weight}}$$

According to a previous study (Soars et al., 2002), 45, 3, and 45 mg/g tissue were used as the contents of the microsomal protein in liver, intestine, and kidney, respectively. For the weights of liver, intestine, and kidney, 20, 30, and 4.4 g/kg body weight, respectively, were used.

Immunoblot Analysis of Recombinant Human UGT1A Isoforms. SDS-polyacrylamide gel electrophoresis and immunoblot analysis of recombinant UGT1A isoforms were performed according to the method of Laemmli (1970). The microsomes from baculovirus-infected insect cells (0.5 μg) were separated on 10% polyacrylamide gel and transferred electrophotorectically to a polyvinylidene difluoride membrane Immobilon-P (Millipore, Bedford, MA). Rabbit anti-human UGT1A polyclonal antibodies (BD Gentest) react with all human UGT1A isoforms, since the antibodies recognize the conserved C-terminal region of UGT1A isoforms (Malfatti and Felton, 2004). Biotinylated anti-rabbit IgG and a VECTASTAIN ABC kit (Vector Laboratories, Burlingame, CA) were used for diaminobenzidine staining. The densities of the bands were determined using an ImageQuant (GE Healthcare Bio-Sciences Corp., Piscataway, NJ). For each isoform, the densities of multiple bands, possibly owing to variability in glycosylation (Malfatti and Felton, 2004), were summed for the quantification. The expression level of UGT1A was defined based on a standard curve using recombinant UGT1A1 (1 unit per 1 mg protein).

Other Glucuronidation Assays. Bilirubin O-glucuronosyltransferase (Katoh et al., 2007), imipramine N-glucuronosyltransferase (Nakajima et al., 2002), and serotonin O-glucuronosyltransferase (Fujiwara et al., 2007) activities in microsomes from 12 human livers were determined according to methods established in our laboratory. Chenodeoxycholic acid 24-O-glucuronosyltransferase activities in these human liver microsomes were determined according to the method of Trottier et al. (2006) with slight modifications. Estradiol 3-O-, propofol O-, and morphine 3-O-glucuronosyltransferase activities in these human liver microsomes were provided by the manufacturer.

Correlation Analyses. Correlation between thyroxine glucuronidation and the other glucuronosyltransferase activities was determined by unpaired Student’s t test. A p value of less than 0.05 was considered statistically significant.

Inhibition Analysis of Thyroxine Glucuronosyltransferase Activities in Human Liver, Jejunum, and Kidney Microsomes or Recombinant UGTs. Bilirubin is a typical substrate of UGT1A1 (King et al., 2000). Imipramine is a substrate of UGT1A3 and UGT1A4 (Green and Tephly, 1998). Emodin is a substrate of UGT1A1, UGT1A3, UGT1A8, and UGT1A9 (King et al., 2000). Propofol is a substrate of UGT1A8 and UGT1A9 (King et al., 2000). Trogilitrazone is a substrate of UGT1A1, UGT1A8, and UGT1A10 (Watanabe et al., 2002). Bilirubin was dissolved in 0.1 M sodium hydroxide. Imipramine hydrochloride was dissolved in water. Emodin and trogilitrazone were dissolved in dimethyl sulfoxide. Propofol was dissolved in methanol. These compounds were added to the incubation mixtures described above to investigate their inhibitory effects on the thyroxine glucuronosyltransferase activities in human liver, jejunum, and kidney microsomes or recombinant UGTs. The final concentration of the organic solvents in the incubation mixture was <2% (v/v). The substrate concentration was 20 μM.

**Results**

Thyroxine Glucuronosyltransferase Activities in Human Liver, Jejunum, or Kidney Microsomes. The formation of thyroxine glucuronide increased in a microsomal protein concentration- and time-dependent manner. The formations were linear at least for 0.5 mg/ml microsomal protein and 120 min incubation (data not shown). Unless specified, the typical incubation mixture containing 0.4 mg/ml microsomal protein was incubated at 37°C for 90 min. The kinetics of thyroxine glucuronosyltransferase activities in human liver, jejunum, and kidney microsomes were fitted to the Michaelis-Menten equation (Fig. 2A). The Eadie-Hofstee plots were monophasic (Fig. 2B). The apparent $K_m$ and $V_{\text{max}}$ values are summarized in Table 2. Human jejunum microsomes showed a lower $K_m$ value (24.2 μM) than did human liver (85.9 μM) and kidney (53.3 μM) microsomes. Human kidney microsomes showed a lower $V_{\text{max}}$ (22.6 pmol/min/mg) value than did human liver (133.4 pmol/min/mg) and jejunum (184.6 pmol/min/mg) microsomes. The in vitro intrinsic clearances ($V_{\text{max}}/K_m$) of thyroxine glucuronidation in human liver, jejunum, and kidney microsomes were 1.6, 7.8, and 0.4 μl/min/mg, respectively. By scaling-up, the in vivo clearances in liver, intestine, and kidney were estimated to be 1440, 702, and 79 μl/min/kg body weight, respectively.

Thyroxine Glucuronosyltransferase Activities by Recombinant UGT Isosforms. Eleven recombinant UGT isoforms expressed in baculovirus-infected insect cells were used to determine their thyroxine glucuronosyltransferase activities. As shown in Fig. 3A, UGT1A8 exhibited the highest thyroxine glucuronosyltransferase activity (87 pmol/min/mg), followed by UGT1A1 (26 pmol/min/mg), UGT1A10 (20 pmol/min/mg), UGT1A3 (18 pmol/min/mg), UGT1A9 (5 pmol/min/mg), and UGT1A7 (5 pmol/min/mg). To quantify the expression level of UGT1A1 in each expression system, immunoblot analysis was performed (Fig. 3B). In accordance with previous studies (Malfatti and Felton, 2004; Fujiwara et al., 2007), the recombinant UGT1A isoforms showed multiple bands, possibly owing to variability in glycosylation. Based on a UGT1A1 level of 1.00 unit/mg, the expression levels of the other isoforms were determined as follows: UGT1A3, 0.20 unit/mg; UGT1A4, 0.38 unit/mg; UGT1A6, 0.95 unit/mg; UGT1A7, 0.60 unit/mg; UGT1A8, 0.80 unit/mg; UGT1A9, 0.68 unit/mg; and UGT1A10, 0.42 unit/mg. By normalization with the UGT expression levels (Fig. 3C), UGT1A8 (108.7 pmol/min/unit) and UGT1A3 (91.6 pmol/min/unit) exhibited the highest thyroxine glucuronosyltransferase activities, followed by UGT1A10 (47.3 pmol/
Kinetic parameters of thyroxine glucuronosyltransferase activities in human liver, jejunum, and kidney microsomes, and by recombinant UGTs

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>$K_m$ (μM)</th>
<th>$V_{max}$ (pmol/min/mg)</th>
<th>Corrected $V_{max}$ (pmol/min/unit)</th>
<th>$V_{max}/K_m$ (μl/min/unit)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLM</td>
<td>85.9 ± 6.9</td>
<td>133.4 ± 9.8</td>
<td>75.7 ± 0.7</td>
<td>1.6 ± 0.0</td>
</tr>
<tr>
<td>HJM</td>
<td>24.2 ± 4.1</td>
<td>184.6 ± 7.0</td>
<td>204.0 ± 11.9</td>
<td>6.2 ± 0.1</td>
</tr>
<tr>
<td>HKM</td>
<td>53.3 ± 5.4</td>
<td>22.6 ± 1.8</td>
<td>13.7 ± 0.4</td>
<td>0.4 ± 0.0</td>
</tr>
</tbody>
</table>

$K_m$, $V_{max}$, and $V_{max}/K_m$ values vary from 24.1 μM to 104.9 μM. UGT1A8 (6.6 μl/min/unit) exhibited the highest clearance, followed by UGT1A9 (6.2 μl/min/unit) and by UGT1A10 (3.7 μl/min/unit). UGT1A1 (0.7 μl/min/unit), UGT1A9 (0.4 μl/min/unit), and UGT1A7 (0.4 μl/min/unit) exhibited low intrinsic clearance.

**These inhibitors were used at effective concentrations according to previous studies (Watanabe et al., 2002; Kuehl et al., 2005; Yamanaka et al., 2005).** The thyroxine glucuronosyltransferase activity in human liver microsomes was significantly correlated with bilirubin ($r = 0.855$, $p < 0.001$), estradiol ($r = 0.827$, $p < 0.0001$), and serotonin ($r = 0.522$, $p < 0.05$) glucuronidation.

**Inhibitory Effects of Typical Substrates for UGT Isoforms on Thyroxine Glucuronosyltransferase Activity in Human Liver, Jejunum, and Kidney Microsomes.** The inhibitory effects of bilirubin, imipramine, emodin, propofol, and troglitazone on thyroxine glucuronosyltransferase activity were investigated. These inhibitors were used at effective concentrations according to previous studies (Watanabe et al., 2002; Kuehl et al., 2005; Yamanaka et al., 2005). The thyroxine glucuronosyltransferase activity in human liver microsomes was strongly inhibited by bilirubin (29% of control) and emodin (15% of control), and was moderately inhibited by troglitazone (51% of control), but was activated by...
TABLE 3  
Correlation coefficients between thyroxine glucuronidation and other glucuronidations in microsomes from 12 human livers

<table>
<thead>
<tr>
<th>Activity (Isoform)</th>
<th>Substrate Concentration</th>
<th>r</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin O-glucuronidation (UGT1A1)</td>
<td>10</td>
<td>0.855</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Estradiol 3-O-glucuronidation (UGT1A1)</td>
<td>100</td>
<td>0.827</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cheno-3-O-glucuronidation (UGT1A3)</td>
<td>10</td>
<td>−0.700</td>
<td>0.27</td>
</tr>
<tr>
<td>Imipramine N-glucuronidation (UGT1A3 and UGT1A4)</td>
<td>500</td>
<td>0.135</td>
<td>N.S.</td>
</tr>
<tr>
<td>Serotonin O-glucuronidation (UGT1A6)</td>
<td>1000</td>
<td>0.522</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Propofol O-glucuronidation (UGT1A9)</td>
<td>30</td>
<td>0.330</td>
<td>N.S.</td>
</tr>
<tr>
<td>Morphine 3-O-glucuronidation (UGT2B7)</td>
<td>250</td>
<td>−0.084</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

N.S., not significant.

Discussion

In this study, we extensively investigated thyroxine glucuronidation in human liver, jejunum, and kidney microsomes and recombinant UGTs. The tissue clearances in liver, intestine, and kidney were estimated to be 1440, 702, and 79 l/min/kg body weight, respectively. Although the UGT activities are not the same in the region of intestine (Strassburg et al., 2000), it was first demonstrated that intestine exhibited approximately one half the clearance of liver for thyroxine glucuronidation. The glucuronidation in intestine may affect the enterohepatic circulation of thyroxine. In kidney, thyroxine is highly converted to T3 with $K_m = 3.0 \text{ M}$, $V_{max} = 26.1 \text{ pmol/min/mg}$, and $V_{max}/K_m = 8.7 \text{ M} \mu \text{mol/min/mg}$ (Boye, 1986). In addition to the outer ring deiodination, this study demonstrated that thyroxine is glucuronidated in kidney.

This is the first study demonstrating that human UGT1A8, UGT1A10, and UGT1A3 have high, and UGT1A1 has moderate catalytic activity toward thyroxine glucuronidation. Since UGT isoforms are expressed differently in human liver, jejunum, and kidney, it was conceivable that UGT isofrom(s) responsible for the thyroxine glucuronidation might be different between these tissues. If the absolute protein levels of each UGT isoform in human tissues are available, quantitative estimation of the contribution of each isoform to the concerned activity can be accomplished as for cytochrome P450 (Becquemont et al., 1998). Unfortunately, for UGT, a methodology of quantification is lacking. In addition, specific antibodies against each UGT1A isoform are limited. In the present study, we qualitatively identified the UGT isoforms that are responsible for the thyroxine glucuronidation in human tissues by kinetic, correlation, and inhibition analyses as well as tissue distribution of each UGT isoform.

The Eadie-Hofstee plots of thyroxine glucuronosyltransferase activities in human liver, jejunum, and kidney microsomes were monophasic, suggesting that one or more UGT isoforms would be involved in the activities. In human liver microsomes, the apparent $K_m$ value was similar to that of recombinant UGT1A1. The activity in a panel of human liver microsomes was significantly correlated with the bilirubin O- and estradiol 3-O-glucuronosyltransferase activities catalyzed by UGT1A1. Although the thyroxine glucuronosyltransferase activity was also correlated with the serotonin O-glucuronosyltransferase activity catalyzed by UGT1A6, it might be a fortuitous result, because the serotonin O-glucuronosyltransferase activity was significantly ($r = 0.627, p < 0.005$) correlated with the estradiol 3-O-glucuronosyltransferase activity in the panel of human liver microsomes. These results suggested that a major UGT isoform responsible for the thyroxine glucuronidation in human liver microsomes would be UGT1A1. We could not exclude the possibility that UGT1A9 might also contribute to the thyroxine glucuronosyltransferase activity in human liver microsomes. Interestingly, propofol activated the thyroxine glucuronosyltransferase activity in human liver microsomes. It has been reported that propofol activated 4-methylunbelliferone glucuronidation by recombinant UGT1A1 (Mano et al., 2004). Thus, the result supported the finding that a major isoform responsible for thyroxine glucuronidation in human liver microsomes would be UGT1A1. We used propofol as an inhibitor of UGT1A8 and UGT1A9. However, our previous study found that propofol can activate trans-3'-hydroxycotinine O-glucuronidation by recombinant UGT1A9 (Yamanaka et al., 2005). Propofol might not be an
appropriately inhibited by bilirubin. These results suggested that the thyroxine glucuronidation in human jejunum microsomes might be catalyzed mainly by UGT1A8 and UGT1A10, and to a minor extent by UGT1A1. In human kidney microsomes, the apparent $K_m$ value was similar to that of recombinant UGT1A7. The thyroxine glucuronidation in human kidney microsomes was inhibited by troglitazone and emodin. It was suggested that the thyroxine glucuronidation in human kidney microsomes might be catalyzed by UGT1A7, UGT1A9, and UGT1A10. In summary, the contribution of each UGT1A isomorph would vary between human tissues, depending on the relative abundance of each isoform.

In conclusion, we characterized the thyroxine glucuronidation in human liver, intestine, and kidney microsomes and found that UGT1A1 in the liver, UGT1A8 and UGT1A10 in the intestine, and UGT1A7, UGT1A9, and UGT1A10 in the kidney mainly contribute to the activity. The change of activities of these UGTs via inhibition and induction by administered drugs (Kiang et al., 2005) as well as genetic polymorphisms (Miners et al., 2002) may be a causal factor of interindividual differences in the plasma thyroxine concentration.

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References


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