Characterization of human liver thermostable phenol sulfotransferase (SULT1A1) allozymes with 3,3′,5-triiodothyronine as the substrate

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Abstract

Sulfotransferase 1A1 (SULT1A1) (thermostable phenol sulfotransferase, TS PST1, P-PST) is important in the metabolism of thyroid hormones. SULT1A1 isolated from human platelets displays wide individual variations not only in the levels of activity, but also in thermal stability. The activity of the allelic variant or allozyme SULT1A1*1, which possesses an arginine at amino acid position 213 (Arg213) has been shown to be more thermostable than the activity of the SULT1A1*2 allozyme which possesses a histidine at this position (His213) when using p-nitrophenol as the substrate. We isolated a SULT1A1*1 cDNA from a human liver cDNA library and expressed both SULT1A1*1 and SULT1A1*2 in eukaryotic cells. The allozymes were assayed using iodothyronines as the substrates and their biochemical properties were compared. SULT1A1*1 activity was more thermostable and more sensitive to NaCl than was SULT1A1*2 activity when assayed with 3,5,3′-triiodothyronine (T3). Sensitivities to 2,6-dichloro-4-nitrophenol (DCNP) and apparent K_{m} values for SULT1A1*1 and for SULT1A1*2 with iodothyronines were similar. Based on K_{m} values, the preferences of these SULT1A1 allozymes for iodothyronine substrates were the same (3,3′-diiodothyronine (3,3′-T_{2})>3′, 5′,3′-triiodothyronine (rT_{3})>T_{3}>thyroxine (T_{4})>>3,5-diiodothyronine (3,5-T_{2})). SULT1A1*1 activity was significantly higher than the SULT1A1*2 activity with T_{3} as the substrate. Potential differences in thyroid hormone sulfation between individuals with predominant SULT1A1*1 versus SULT1A1*2 allozymes are most likely due to differences in catalytic activity rather than substrate specificity.

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Introduction

Sulfation contributes to the inactivation of 3,5,3′-triiodothyronine (T_{3}) and other iodothyronines by the addition of a sulfuryl moiety to the 4′-hydroxyl group. 3′-Phosphoadenosine-5′-phosphosulfate (PAPS) donates the sulfuryl group in the reaction. T_{3} sulfate (T_{3}S) is a major product of human T_{3} metabolism (Chopra et al. 1992, LoPresti & Nicollof 1994). T_{3}S is a better substrate than T_{3} for type I 5′-deiodinase (5′DI), and this results in enhancement of deiodination. Several human sulfotransferases (SULTs) are capable of sulfating thyroid hormones. These include SULT1A1 (thermostable phenol SULT, TS PST1, P-PST) (Young et al. 1988, Anderson et al. 1995, Kester et al. 1999a), SULT1A3 (TL PST, M-PST) (Young et al. 1988, Kester et al. 1999a), SULT1B1 (Fujita et al. 1997, Wang et al. 1998), SULT1C1 (Li et al. 2000), SULT1E1 (EST) (Li & Anderson 1999, Kester et al. 1999b), and SULT2A1 (DHEA ST) (Li & Anderson 1999). Endogenous human liver SULT1A1 has been shown to sulfate T_{3} and other thyroid hormones (Young et al. 1988, Anderson et al. 1995, Kester et al. 1999a), but there have not been detailed characterizations of the biochemical properties of recombinant human liver SULT1A1 with iodothyronines as the substrates.

An added complexity in the understanding of sulfation of thyroid hormone by SULT1A1 is the occurrence of SULT1A1 allozymes (allelic variants that result in amino acid changes in the enzyme). There are at least seven known SULT1A1 allozymes (Wilborn et al. 1993, Zhu et al. 1993, Hwang et al. 1995, Jones et al. 1995, Ozawa et al. 1995, Raftogianis et al. 1997, 1999). It is not clear whether these allozymes have different specificities for iodothyronines.

SULT1A1 from the human platelet displayed wide individual variations, not only in the level of activity, but
also in thermal stability (Van Loon & Weinshilboum 1984, Price et al. 1989, Anderson & Liebentritt 1990). Segregation analysis of data from family studies showed human platelet SULT1A1 activity and individual variations in its thermal stability were controlled by genetic polymorphisms (Price et al. 1989). The most common SULT1A1 allozyme is SULT1A1*1, a variant with the amino acid arginine (Arg) at position 213 (0.67 gene frequency) (Ozawa et al. 1995, Raftogianis et al. 1997, 1999). The second most common SULT1A1 allozyme is SULT1A1*2 (His213, 0.31 gene frequency) (Zhu et al. 1993, Raftogianis et al. 1997, 1999). SULT1A1*1 (Arg213) and SULT1A1*2 (His213) allozymes have been reported in Caucasians, Asians and Africans (Raftogianis et al. 1997, Coughtrie et al. 1999, Ozawa et al. 1999). Isolation of cDNAs of the SULT1A1*1 and SULT1A1*2 allozymes was accomplished by cloning and sequencing DNA from leukocytes and livers of individuals identified by specific human platelet SULT1A1 phenotypes. Individuals homozygous for SULT1A1*2 allozyme (His/His213) showed phenotypes of lower thermal stability and lower activity, when the enzyme was assayed with p-nitrophenol, than did individuals homozygous for SULT1A1*1 allozyme (Arg/Arg213) (Raftogianis et al. 1997). Individual differences in thyroid hormone metabolism occur, and a difference in substrate specificity or enzyme activity of SULT1A1 allozymes might contribute to these differences.

Using bacterially expressed SULT1A1 allozymes isolated from human liver, Ozawa et al. (1999) showed that SULT1A1*1 was more thermostable than SULT1A1*2. However, contrary to results with platelet samples, the differences in activities with recombinant enzymes were minimal when assayed with 4 μM p-nitrophenol (Ozawa et al. 1999). On the other hand, it was recently reported that recombinant SULT1A1 allozymes had very different effects on activation of promutagens (Glatt et al. 2000). Another group tested SULT1A1 allozymes that contained the common Arg213 and His213 changes and found different specificities for 3,3′-diodothyronine (3,3′-T2) (Visser et al. 1996). However, the proteins expressed from the cDNAs that were used also had amino acid changes at positions 282 (Glu→Lys) and 290 (Ser→Thr) for the Arg213 variant and at positions 146 (Ala→Thr) and 181 (Glu→Gly) for the His213 variant (Wilborn et al. 1993, Jones et al. 1995, Visser et al. 1996; see Table 1).

We were interested in determining whether there were differences in apparent K_m values, biochemical properties and activities of the two most common SULT1A1 allozymes when iodothyronines were used as the substrates. Identification of differences might make it possible to predict individual responses to iodothyronines based upon the presence of distinct SULT1A1 allozymes. In this report, we demonstrated that the common polymorphisms of human liver SULT1A1*1 and SULT1A1*2 expressed in COS-1 cells catalyzed the sulfation of T3 and other iodothyronines. We also characterized common biochemical properties of these allozymes with T3 as the substrate, and determined their preferences for T3, 3,3′,5,5′-tetraiodothyronine (T4), 3,3′,3′-triiodothyronine (rT3), 3,3′,3′,3′,5,5′-pentaiodothyronine (3,3′-T2) and 3,5-diodothyronine (3,5′-T2).

### Materials and Methods

#### Materials

COS-1 cells were obtained from the American Type Culture Collection (ATCC), Rockville, MD, USA. [35S]-Phosphoadenosine-5′-phosphosulfate ([35S]PAPS, specific activity from 1-52 to 2-50 Ci/mmol) was purchased from New England Nuclear (NEN) Dupont, Boston, MA, USA. 3,3′,5-Triodothyronine (T3), 3,3′,5′,3′-triiodothyronine (rT3), 3,5-diodothyronine (3,5′-T2) was a gift from Dr S-Y Wu (Long Beach, CA, USA). 3,3′,5-Triodothyronine (T3), 3,3′,5′,3′-triiodothyronine (rT3), 3,3′,5,5′-tetraiodothyronine (T4), 3,5-diodothyronine (3,5′-T2), 2,6-dichloro-4-nitrophenol (DCNP), p-nitrophenol, o-nitrophenol-β-D-galactopyranoside (ONPG) and ecteola cellulose (fine mesh) were purchased from Sigma, St Louis, MO, USA. Dithiothreitol (DTT) was purchased from CalBiochem, La Jolla, CA, USA. Lipofectamine was obtained from Gibco, Grand Island,

## Table 1 Comparison of amino acids among SULT1A1 allozymes

<table>
<thead>
<tr>
<th>Allozyme</th>
<th>AA37</th>
<th>AA213</th>
<th>AA223</th>
<th>AA90</th>
<th>AA243</th>
<th>AA282</th>
<th>AA290</th>
<th>AA146</th>
<th>AA181</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>SULT1A1*1</td>
<td>Arg</td>
<td>Arg</td>
<td>Met</td>
<td>Pro</td>
<td>Val</td>
<td>Glu</td>
<td>Ser</td>
<td>Ala</td>
<td>Glu</td>
<td>Ozawa et al. (1995); Clemens et al. (1996)</td>
</tr>
<tr>
<td>SULT1A1*2</td>
<td>Arg</td>
<td>His</td>
<td>Met</td>
<td>Pro</td>
<td>Val</td>
<td>Glu</td>
<td>Ser</td>
<td>Ala</td>
<td>Glu</td>
<td>Zhu et al. (1993)</td>
</tr>
<tr>
<td>SULT1A1*3</td>
<td>Arg</td>
<td>Arg</td>
<td>Val</td>
<td>Pro</td>
<td>Val</td>
<td>Glu</td>
<td>Ser</td>
<td>Ala</td>
<td>Glu</td>
<td>Raftogianis et al. (1997, 1999)</td>
</tr>
<tr>
<td>SULT1A1*4</td>
<td>Gln</td>
<td>Arg</td>
<td>Met</td>
<td>Pro</td>
<td>Val</td>
<td>Glu</td>
<td>Ser</td>
<td>Ala</td>
<td>Glu</td>
<td>Raftogianis et al. (1997, 1999)</td>
</tr>
<tr>
<td>SULT1A1*5</td>
<td>Arg</td>
<td>Met</td>
<td>Leu</td>
<td>Ala</td>
<td>Glu</td>
<td>Ser</td>
<td>Ala</td>
<td>Glu</td>
<td>Hwang et al. (1995)</td>
<td></td>
</tr>
<tr>
<td>SULT1A1*6</td>
<td>Arg</td>
<td>Arg</td>
<td>Met</td>
<td>Pro</td>
<td>Val</td>
<td>Lys</td>
<td>Thr</td>
<td>Ala</td>
<td>Glu</td>
<td>Wilborn et al. (1993)</td>
</tr>
<tr>
<td>SULT1A1*7</td>
<td>Arg</td>
<td>His</td>
<td>Met</td>
<td>Pro</td>
<td>Val</td>
<td>Glu</td>
<td>Ser</td>
<td>Thr</td>
<td>Gly</td>
<td>Jones et al. (1995)</td>
</tr>
</tbody>
</table>

Residues in bold and italic are different amino acids (AA) when compared with SULT1A1*1.
The SULT1A1*2 cDNA was a gift from Dr M E McManus (Queensland, Australia) (Zhu et al. 1993).

Isolation of SULT1A1*1 cDNAs

Human SULT1A1*1 cDNAs were isolated from a λUni-ZAP XR human liver cDNA library (Stratagene, La Jolla, CA, USA). Briefly, phage were plated at 25 000 pfu/plate on Escherichia coli XL1-Blue. Plaques were transferred to Hybond-N (Amersham, Arlington Heights, IL, USA) membranes and hybridized to a 32P-labeled fragment of a SULT1A1 cDNA (Zhu et al. 1993). Twenty positive plaques were identified and subjected to two additional rounds of plaque purification. Bluescript phagemids were rescued from the λUni-ZAP vector by coinfection of infected cultures with ExAssit helper phage and propagated as double stranded phagemids in E. coli SOLR. The recombinant Bluescript phagemids were isolated by alkaline lysis (Ish-Horowicz & Burke 1981) and initially analyzed by digestion with EcoRI and XhoI to determine the size of the inserts. Three different sizes of inserts were observed and one representative clone from each size class was subcloned into pSP72 (Promega, Madison, WI, USA), transformed into E. coli DH5α and further analyzed by restriction and sequence analysis. Sequence analysis was performed on both strands by the dideoxy method (Sanger et al. 1977) using the Sequenase version 2 kit (USB, Cleveland, OH, USA).

Construction of expression vectors

In order to express the SULT1A1*1 in eukaryotic cells, SULT1A1*1 cDNA was inserted into the EcoRI and EcoRV sites of the eukaryotic expression vector pcDNA3 (Invitrogen, Carlsbad, CA, USA). The SULT1A1*2 cDNA was also inserted into the pcDNA3 vector.

Expression of SULT1A1*1 and SULT1A1*2

Human SULT1A1*1 and SULT1A1*2 were expressed in COS-1 cells by transfection using lipofectamine as previously described (Li & Anderson 1999), and the cells were harvested three days later. The high speed supernatants were prepared as described previously (Li & Anderson 1999). Protein was determined by the method of Bradford (1976) with BSA as the standard. In order to normalize for the transfection efficiency, 2-25 µg DNA of pCH110 (Pharmacia, Piscataway, NJ, USA) were co-transfected with 22-5 µg plasmid containing SULT1A1 allozyme/75 cm² flask.

Sulfotransferase assays

SULT activity was measured by the method of Young et al. (1988) as modified by Li and Anderson (1999). The enzyme assay was performed at optimal conditions with T3 as the substrate and 0-4 µM 35S-PAPS as the co-substrate. SULT1A1*1 preparations of 23-25 µg and SULT1A1*2 preparations of 19-4 µg of high speed supernatant protein were used in all assays. Samples were incubated for 15 min, and 60 mM potassium phosphate buffer, pH 7-0 was used. The SULT assay with p-nitrophenol as the substrate was carried out by the method of Anderson and Liebentritt (1990). Mock transfected COS-1 cells (no cDNA) served as controls for each assay. Net activities were calculated by subtraction of the activities/mg protein in mock transfected cells from the activities/mg protein detected in the transfected cells. This accounted for the potential effect of endogenous SULT activities. Net SULT activities were expressed as Units/mg protein. One Unit of enzyme activity represents one nmol of sulfated product formed per hour at 37 °C. Thermal stability was tested by the methods of Reiter et al. (1983) as modified by Anderson et al. (1988).

β-Galactosidase quantitation

β-Galactosidase activity was determined as described by Clemens and Carlson (1989). Briefly, high speed supernatant (50 µl) was added to 350 µl Z buffer (60 mM Na2HPO4, 40 mM NaH2PO4.H2O, 10 mM KCl, 1 mM MgSO4, 50 mM 2-mercaptoethanol), pH 7-0 and 80 µl ONPG (4 mg/ml) in 0·1 M potassium phosphate buffer, pH 7-5. The reaction was incubated at 30 °C for 10 min. The reaction was stopped by addition of 200 µl of 1 M Na2CO3 at pH 11. β-Galactosidase activity was determined spectrophotometrically at 420 nm.

Data analysis

Apparent K_m and V_max values were calculated by the direct linear plot method (Eisenthal & Cornish-Bowden 1974) using the Enzpack 3 program by Williams (Elsevier-Biosoft, Cambridge, UK). Kinetic data were presented in double reciprocal plots using the K_m values obtained by the direct linear plot method. The 50% inactivation temperatures (T50) and 50% inhibitory concentrations (IC50) with DCNP and NaCl were determined using a curve-fitting program (GraphPad Software, San Diego, CA, USA). Statistical significance was analyzed by Student’s t-test.

Results and Discussion

Isolation and molecular characterization of SULT1A1*1 clones

Initially 250 000 plaques were screened; 10 of these were positive. The positive isolates were plaque purified twice more prior to the rescue of phagemids. The phagemids rescued from the positive bacteriophage were digested with EcoRI and XhoI to determine the size of the inserts.

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All of the isolates appeared to contain inserts of approximately 1200 bp, which was in close agreement with previously isolated clones (Wilborn et al. 1993, Zhu et al. 1993, Hwang et al. 1995, Jones et al. 1995). Further restriction enzyme analysis indicated variations in the inserts, which fell into three classes. One representative of each class was chosen for further detailed analysis. Sequence analysis of these three clones revealed that the only differences were located outside of the putative coding regions in the 3’ and 5’ untranslated regions. Each of the clones contained an identical open reading frame of 885 bp (Fig. 1). This open reading frame was predicted to encode a protein of 295 amino acids with a molecular mass of approximately 34 kDa, which is in close agreement with the previously reported apparent molecular mass of SULT1A1 (Wilborn et al. 1993).

At least 7 allozymes from 18 allelic variants of SULT1A1 have previously been reported (Wilborn et al. 1993, Zhu et al. 1993, Hwang et al. 1995, Jones et al. 1995, Ozawa et al. 1995, raftogianis et al. 1997, 1999). A comparison of these with the predicted amino acid sequence of our isolate showed that they were all very similar, and that our isolated cDNA was identical to that reported by Ozawa et al. (1995; Genbank accession no.: X...).
The diﬀerences from the predicted amino acid sequences reported by others are listed in Table 1. Allozyme designations 1*5, 1*6 and 1*7 have been adopted for ease of identiﬁcation.

Expressed SULT1A1 allozyme biochemical properties

**K**ₘ and **V**ₘₐₓ Initially, sulftotransferase assays for the two allozymes were performed with 150 µM T₃ and diﬀerent concentrations of [³⁵S]PAPS. The apparent Kₘ values with [³⁵S]PAPS were 1·06 µM for SULT1A1*1 and 0·70 µM for SULT1A1*2 (Fig. 2a). The values with PAPS were similar to the results obtained by other groups: 0·65 µM with T₃ from Kester et al. (1999a), and 1·21 µM with p-nitrophenol from Raftogianis et al. (1999) for SULT1A1*1, and 0·98 µM from Raftogianis et al. (1999) for SULT1A1*2. Apparent Kₘ values were determined by using T₃ in concentrations ranging from 1 to 256 µM. No activity was detected consistently below 8 µM T₃. Apparent Kₘ values were 84·4 ± 5·5 µM for SULT1A1*1 and 101·3 ± 5·7 µM for SULT1A1*2 (mean ± s.e.m., n=3 experiments, P=0·10; Fig. 2b). These values were similar to each other and to the results obtained by other groups using partially puriﬁed SULT1A1 from pooled cytosol preparations of human liver (Young et al. 1988, Kester et al. 1999a). The data supported the conclusion that SULT1A1 expressed in COS-1 cells was similar to the endogenous human liver SULT1A1.

We next investigated the ability of these allozymes to use other iodothyronines as substrates. Apparent Kₘ values for SULT1A1*1 with iodothyronines were: 3,3′-T₂, 0·63 µM; rT₃, 36·1 µM; and T₄, 126 µM. Apparent Kₘ values for SULT1A1*2 with iodothyronines were: 3,3′-T₂, 0·51 µM; rT₃, 49·8 µM; and T₄, 208 µM (Table 2). The Kₘ values with each substrate were similar for the two allozymes.

To compare the Vₘₐₓ values of expressed SULT1A1*1 and SULT1A1*2 activities, we normalized transfection eﬃciency by β-galactosidase quantitation. The Vₘₐₓ values for SULT1A1*1 and SULT1A1*2 with T₃ as

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Concentration range (µM)</th>
<th>SULT1A1*1</th>
<th>SULT1A1*2</th>
</tr>
</thead>
<tbody>
<tr>
<td>T₃</td>
<td>1–256</td>
<td>84·4</td>
<td>101·3</td>
</tr>
<tr>
<td>T₄</td>
<td>30–600</td>
<td>126</td>
<td>208</td>
</tr>
<tr>
<td>rT₃</td>
<td>0·1–100</td>
<td>36·1</td>
<td>49·8</td>
</tr>
<tr>
<td>3,3′-T₂</td>
<td>0·03–30</td>
<td>0·63</td>
<td>0·51</td>
</tr>
<tr>
<td>3,5-T₂</td>
<td>3–300</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

ND=not detected.
Characterization of human SULTs (Reiter et al. 1999). SULT1A1 activity was more sensitive to inhibition by NaCl than SULT1A1*2 when assayed with T3 (Fig. 3). Both were more resistant to NaCl inhibition when compared with the data obtained using p-nitrophenol (Clemens et al. 1996) and minoxidil (Kudlacek et al. 1999) as the substrates.

**SULT1A1*1 and SULT1A1*2 preferences for iodothyronines**

The relative abilities of SULT1A1*1 and SULT1A1*2 to use other iodothyronines as substrates were estimated by
Sulfation of T3 by human SULT1A1 allozymes

K_m (Table 2). Assays were carried out under the optimal conditions established with T3 as the substrate. The preferences for the two allozymes were the same when estimated from the apparent K_m values. Both SULT1A1*1 and SULT1A1*2 were most active toward 3,3'-T2, followed by rT3, T3, T4, and 3,5-T2 in order of decreasing specificity and activity.

Conclusions

There are at least six known human cytosolic SULTs (SULT1A1, SULT1A3, SULT1B1, SULT1C1, SULT1E1, SULT2A1) that contribute to the sulfation of thyroid hormones. We have demonstrated that human SULT1A1 allozymes (SULT1A1*1 and SULT1A1*2) catalyze the sulfation of T3 and three other iodothyronines. T3 enhances the resting metabolism of tissues through interaction with nuclear receptors. Sulfation and subsequent inactivation of T3 by SULT1A1 allozymes might block the availability of T3 to bind the nuclear receptors. Thyroid hormones including T4, rT3, and 3,5-T2 mediate several extranuclear (nongenomic) actions at the cell membrane and cytoskeleton, such as the regulation of actin polymerization in glial cells to control cell surface availability of the type II 5'-deiodinase (Davis & Davis 1996, Leonard & Farwell 1997). In addition, 3,3'-T2 and 3,5-T2 have been reported to act through nonnuclear pathways to enhance mitochondrial respiration and thus resting metabolism (Lanni et al. 1996, Moreno et al. 1997, Pillar & Seitz 1997). Both SULT1A1*1 and SULT1A1*2 preferentially sulfotransfer 3,3'-T2. Whether sulfation of 3,3'-T2 might be a pathway for regulation of these nonnuclear actions is not clear. Exogenous thyroid hormone preparations are among the most commonly prescribed medicines. Our results indicate that SULT1A1*1 and SULT1A1*2 present in the liver and gut may contribute to metabolism of thyroid hormones taken orally. Recombinant SULT1A1*1 and SULT1A1*2 had essentially the same substrate specificities and preferences for iodothyronines. However, their thermal stabilities and sensitivities to NaCl were different. It is not known whether the differences in biochemical properties of the SULT1A1 allozymes might alter individual response to exogenous or endogenous thyroid hormones. Potential differences in thyroid hormone sulfation between individuals with predominant SULT1A1*1 versus SULT1A1*2 allozymes would be expected to be due to differences in catalytic activity rather than substrate specificity.

There are at least 7 allozymes of SULT1A1 and, undoubtedly, additional allozymes that have not yet been identified. We have tested the two most common SULT1A1 allozymes. Our work with COS-1 cell expressed SULT enzymes has demonstrated that these preparations reliably reflect the biochemical properties of the native human enzyme. Further studies of other SULT1A1 allozymes will be required to clarify potential differences in activity and specificity for thyroid hormones and their subsequent effects on thyroid hormone metabolism.

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