A Novel Human Hepatic Organic Anion Transporting Polypeptide (OATP2)

IDENTIFICATION OF A LIVER-SPECIFIC HUMAN ORGANIC ANION TRANSPORTING POLYPEPTIDE AND IDENTIFICATION OF RAT AND HUMAN HYDROXYMETHYLGLUTARYL-CoA REDUCTASE INHIBITOR TRANSPORTERS

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A novel human organic transporter, OATP2, has been identified that transports taurocholic acid, the adrenal androgen dehydroepiandrosterone sulfate, and thyroid hormone, as well as the hydroxymethylglutaryl-CoA reductase inhibitor, pravastatin. OATP2 is expressed exclusively in liver in contrast to all other known transporter subtypes that are found in both hepatic and nonhepatic tissues. OATP2 is considerably diverged from other family members, sharing only 42% sequence identity with the four other subtypes. Furthermore, unlike other subtypes, OATP2 did not transport digoxin or aldosterone. The rat isoform oatp1 was also shown to transport pravastatin, whereas other members of the OATP family, i.e. rat oatp2, human OATP, and the prostaglandin transporter, did not. Cis-inhibition studies indicate that both OATP2 and oatp1 also transport other statins including lovastatin, simvastatin, and atorvastatin. In summary, OATP2 is a novel organic anion transport protein that has overlapping but not identical substrate specificities with each of the other subtypes and, with its liver-specific expression, represents a functionally distinct OATP isoform. Furthermore, the identification of oatp1 and OATP2 as pravastatin transporters suggests that they are responsible for the hepatic uptake of this liver-specific hydroxymethylglutaryl-CoA reductase inhibitor in rat and man.

The liver functions in the clearance of a large variety of metabolic products, drugs, and other xenobiotics by transporting them across the sinusoidal membrane into the hepatocyte. Several classes of transport systems have been described that mediate these processes including the Na+/taurocholate cotransporter polypeptide, in rat and human liver (1, 2), and a family of organic anion transporting polypeptides (OATPs)† that are principally expressed in liver, kidney, and brain. These transport a broad spectrum of substrates in a sodium-independent manner (3, 4). The distribution of this latter family of transporters in liver, kidney, and choroid plexus in the brain is thought to reflect common physiological requirements of these organs for the clearance of a multitude of organic anions. There are three OATP isoforms identified to date in the rat: roatp1 (5), roatp2 (6), and roatp3 (7). Rat oatp1 and oatp2 are abun-
dantly expressed in liver and kidney and much less in brain, whereas oatp3 is absent in liver but highly expressed in kidney. In addition to bile acids, OATPs are known to transport a variety of other compounds. These include, depending on the transporter, unconjugated and conjugated steroids, such as estrone sulfate, estradiol-17β-glucuronide, and aldosterone, and cardiac glycosides (6, 8–11). Bromosulfophthalain (5), myco
toxin (12), leukotriene C4 (13), and thyroid hormone (7) are additional substrates.

In contrast to the rat, only one transporter of this family, OATP, has been identified in humans (14). It is expressed most abundantly throughout the brain and in much lower amounts in liver, kidney, and lung. In addition to bile acids and the above steroids, human OATP has recently been shown to transport the adrenal androgen dehydroepiandrosterone sulfate (DHEAS) (15).

HMG-CoA reductase inhibitors, or statins, are members of an important class of lipid lowering drugs that have been demonstrated to decrease risk for myocardial infarction (16–18) and stroke (19, 20). This is due, at least in part, to their ability to lower low density lipoprotein cholesterol through the inhibition of cholesterol synthesis in the liver. This results in an induction of hepatic low density lipoprotein receptors, thereby increasing the catabolism of circulating low density lipoprotein. The majority of statins, including lovastatin, simvastatin, and atorvastatin, are lipophilic molecules with high octanol:water partition coefficients, and, as such, they freely diffuse across membranes (21). Consequently, they are potent inhibitors of HMG-CoA reductase in a broad spectrum of tissues. In contrast, the reductase inhibitor pravastatin is hydrophilic in nature, is relatively membrane impermeable, and exhibits much greater tissue selectivity than the other statins. It is taken up, primarily in the liver, by a transport mechanism that is sodium-independent and is competitively inhibited by bile acids and dibromosulfophthaelin in isolated rat hepatocytes (22, 23). It is the presence or absence of this transporter that is likely the basis for the tissue selectivity of pravastatin. However, the protein that is responsible for this pravastatin transport activity has not been identified. Because of their substrate specificities and tissue localization, members of the OATP fam-

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‡ The abbreviations used are: OATP, organic anion transporting polypeptide; DHEAS, dehydroepiandrosterone sulfate; HMG-CoA, hydroxymethylglutaryl-CoA; PCR, polymerase chain reaction; DMEM, Dulbecco’s modified Eagle’s medium; TMD, transmembrane domain; EST, expressed sequence tag.

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ily are good pravastatin transporter candidates. Clearly the OATP transporter class plays a critical role in hepatic organic anion uptake mechanisms. However, only a single human isoform has been identified, and it has very low hepatic expression. Consequently, we sought to identify additional human OATPs that are found in liver. The novel transporter, OATP2, was cloned, and its substrate specificity was examined in expression studies. It transports taurocholate, DHEAS, and pravastatin and is the only known OATP whose expression is confined to liver. Furthermore, we have identified oATP1 as a pravastatin transporter in the rat.

**Experimental Procedures**

**cDNA Cloning and Expression**—Full-length rat oATP1 and oATP2 coding sequences corresponding to nucleotides 75–2077 and 105–2108, respectively, of the published sequences (5, 6) were amplified by PCR from rat liver poly(A)+RNA (CLONTECH). Full-length coding sequence from human OATP corresponding to nucleotides 42–2101 of the published sequence was amplified from human liver poly(A)+RNA (CLONTECH). The following oligonucleotides were used as forward and reverse primers to amplify the indicated cDNAs: rat oATP1, CGGTGACCCAGAGAAGACACCATGGAAGAAACAG (forward) and AGCGGCCGCG-TCTGTTTGGTGTTCT (reverse); rat oATP2, CGGTGACCCAGAGAAGACACCATGGAAGAAACAG (forward) and AGCGGCCGCG-CATACAGCTTCGTTTTCAGTTCTC (reverse); human OATP, GCAGATCTCCTAGGAGCCAACTGGAACATCGA (forward) and AGCGGCCGCG-CATACAGCTTCGTTTTCAGTTCTC (reverse); and human oATP2, GCAGATCTCCTAGGAGCCAACTGGAACATCGA (forward) and AGCGGCCGCG-CATTACAGCTTCGTTTTCAGTTCTC (reverse).

**PCR amplifications** were performed using a GeneAmp Amplification kit (Perkin Elmer, Inc.) according to the following schedule: for hOATP, 94 °C for 0.5 min, 55 °C for 1 min, and 72 °C for 3 min for 40 cycles followed by 72 °C for 7 min; for rat oATP1 and oATP2, 94 °C 1 min, 55 °C for 1 min, and 72 °C for 3 min for 40 cycles followed by 72 °C for 7 min for roATP1 Transports Pravastatin—293c18 cells transfected with pCEP4 expression plasmids containing roATP1, roATP2, and hOATP cDNAs were assayed for the uptake of pravastatin. Specific transport of [3H]pravastatin was observed in roATP1 transfected cells (Fig. 1A). A time course experiment showed pravastatin transport to be linear for approximately 5 min with uptake reaching equilibrium after 10 min (Fig. 1B), whereas uptake was saturable with an apparent Km of 30 μM (Fig. 1C).

In contrast, no pravastatin transport was observed in 293c18 cells transfected with roATP2, hOATP, or the empty vector, pCEP4 (Fig. 1A). In control experiments all three transporters transported taurocholate (data not shown), in agreement with earlier studies demonstrating uptake of taurocholate by oATP1 expressing Xenopus laevis oocytes and HeLa cells (5, 10); this verifies that all three transporters are active in this system.

Pravastatin transport in isolated rat hepatocytes is competitively inhibited by taurocholate and the statins lovastatin and simvastatin (22). To further characterize statin interactions with roATP1, the cis-inhibition of pravastatin and taurocholate uptake by statins and other compounds was examined. Both [3H]pravastatin and [3H]taurocholate transport was inhibited by 50 μM (100-fold molar excess over tracer) of pravastatin, taurocholate, and several other HMG-CoA reductase inhibitors including simvastatin, lovastatin, atorvastatin, BMS241423, and BMS243887 (Fig. 2). The latter are two hydroxylated atorvastatin metabolites that are found in plasma from treated subjects. The rank order of statin potency for inhibition of pravastatin uptake was BMS243887 > BMS241423 = lovastatin = simvastatin > atorvastatin > pravastatin. A similar pattern was observed for statin inhibition of taurocholate transport. Taurocholate also blocked pravastatin uptake, consistent with it being a substrate of roATP1 (Fig. 2 and Ref. 5) and its inhibition of pravastatin transport in hepatocytes. DHEAS, a substrate for human OATP, was also an inhibitor of pravastatin and taurocholate transport by roATP1. In contrast, digoxin and prostaglandin Ep, substrates for the OATP family members roATP2 and PG2, respectively, are not roATP1 substrates, and these molecules did not inhibit pravastatin transport.

Identification of a Novel Human Organic Anion Transporter—The lack of pravastatin transport activity by hOATP plus the existence of multiple OATP isoforms in the rat suggested that an additional OATP exists that could account for the hepatic uptake of...
pravastatin in humans. A number of PCR-based approaches utilizing degenerate PCR primers based on conserved sequences within the OATP family failed to identify any novel sequences from human adult and fetal liver or kidney cDNA or from human genomic DNA. However, a search of the GenEMBL EST database revealed a sequence (GenBank accession number T73863) obtained from a human liver library with significant homology to hOATP. The insert of this clone did not contain full-length coding sequence. Thus, an oligonucleotide based on EST T73863 was used to screen for full-length clones using the Gene Trap method. A 2.8-kilobase cDNA was identified containing 134, 2076, and 620 nucleotides of 5'-untranslated, coding, and 3'-untranslated sequences, respectively (Fig. 3). Conceptual translation of the cDNA sequence predicts a 691-amino acid protein with the following putative structural features: (i) 12 transmembrane domains (TMDs) ranging from 18 to 28 amino acids each (Fig. 4) and (ii) 11 potential N-glycosylation sites. Only two of the latter (Asn134 and Asn617) are predicted to be in extracellular loops. No sequence prior to the first TMD that strongly conforms to a signal peptide consensus predicted by the SPScan algorithm (27) could be found. This new transporter will be referred to as OATP2 (organic anion transporting polypeptide 2).

Four OATPs expressed in liver have been previously reported; three isoforms have been identified in the rat (oatp1, 2, and 3) and one in human liver (OATP) (5–7, 14). The alignment of OATP2 with these other transporters is shown in Fig. 4. 32% of the amino acids are conserved, and twelve TMDs are found in all five proteins predicted by the algorithm TMPred. The sequence identities of all pairwise comparisons are shown in Table I. There is high homology among human OATP and the three rat oatp isoforms, ranging from 67 to 82% identical residues. However, OATP2 is substantially diverged in sequence; its sequence is only 42% identical to each of the four other proteins. Furthermore, the lengths of all of the inter-TMD loops are identical among the transporters shown in Fig. 4 with the exception of OATP2. Loops between TMDs 3 and 4, TMDs 6 and 7, and TMDs 9 and 10 are all four to six residues longer in OATP2 compared with the others. In addition, OATP2 is considerably more basic than the other proteins, in particular hOATP; the predicted pI of OATP2 is 8.51 compared with 7.75, 7.74, 7.70, and 5.80 for oatp1, oatp2, oatp3, and hOATP, respectively. OATP2 has overlapping but not identical sub-
The nucleotide sequence of the longest OATP2 cDNA clone is shown with the predicted amino acid sequence underneath. Nucleotide numbering are indicated on the left and right sides, respectively. Potential N-linked glycosylation sites are indicated by an asterisk below the residue. Underlined letters indicate a putative polyadenylation signal utilized in a shorter cDNA that was isolated (Fig. 3), which could account for the smaller 2.4-kilobase mRNA species seen in the Northern blot.

**FIG. 3.** Nucleotide and amino acid sequence of human OATP2.

The ability of unlabeled compounds to inhibit OATP2 mediated [3H]pravastatin and [3H]taurocholate uptake was also determined. Specific uptake was inhibited 36 and 89% by 50 and 500 μM unlabeled pravastatin, respectively (Fig. 8). All other statins tested were much more potent than pravastatin in this regard: 50 μM each of simvastatin, atorvastatin, and its metabolites, with lovastatin being the most potent inhibitors, similar pattern with simvastatin, atorvastatin, and its metabolites, with lovastatin being the most potent inhibitors, whereas taurocholate and DHEAS showed more modest effects. In contrast, the expression OATP2 is very hepatocyte-specific; a major 3.2-kilobase band and several minor hybridizing bands were observed only in RNA from liver and no other tissue (Fig. 5). A potential alternative polyadenylation signal was likely utilized in one of the OATP2 cDNA clones that was isolated (Fig. 3), which could account for the smaller 2.4-kilobase mRNA species seen in the Northern blot. In situ hybridization of OATP2 probe to human liver showed signal in hepatocytes throughout the liver lobule, whereas no signal was observed in bile ducts, Kupffer cells, or vessels.

**OATP2 Is a Human Pravastatin Transporter**—The transport of pravastatin by OATP2 was investigated in transfected 293c18 cells. Specific uptake of [3H]pravastatin was observed in cells transfected with OATP2 but not with empty vector (pCEP4) (Fig. 6A). Transport was linear for approximately 5 min (Fig. 6B) and was saturable with an apparent $K_m$ of 35 μM (Fig. 6C), similar to that of roatp1 for pravastatin. Thus, OATP2 is a liver-specific human pravastatin transporter.

**Other Substrates of OATP2**—The ability of OATP2 to transport other molecules was examined using additional radiolabeled compounds in addition to assaying the cis-inhibition of [3H]pravastatin uptake by unlabeled substrates. Known substrates of other transporters in this family include taurocholate (all OATPs), DHEAS (human OATP), and thyroid hormone (T3/T4) (roatp2 and roatp3). Of these, taurocholate, DHEAS, and T4, were shown to be transported by OATP2 (Fig. 7A). Uptake of T4 was only modestly higher in OATP2 compared with mock transfected cells (2.38 ± 0.58 and 1.3 ± 0.18 pmol/min/mg, respectively; $p < 0.05$) because of a high endogenous uptake by 293 cells. However, this uptake was repeatable and statistically significant. The apparent $K_m$ of OATP2 for taurocholate uptake was 33.8 μM (Fig. 7B), compared with 60, 50, 34, and 18 μM for uptake by human OATP (14), roatp1 (28), roatp2 (6), and roatp3 (7), respectively. Additional substrates tested but not transported include aldosterone and digoxin.

The ability of unlabeled compounds to inhibit OATP2 mediated [3H]pravastatin and [3H]taurocholate uptake was also determined. Specific uptake was inhibited 36 and 89% by 50 and 500 μM unlabeled pravastatin, respectively (Fig. 8). All other statins tested were much more potent than pravastatin in this regard: 50 μM each of simvastatin, atorvastatin, the two hydroxylated atorvastatin metabolites BMS241423 and BMS243887, and lovastatin inhibited [3H]pravastatin transport by greater than 95%. Taurocholate and DHEAS also inhibited pravastatin transport, consistent with these two compounds being substrates of OATP2 (Fig. 8A). The cis-inhibition of [3H]taurocholate uptake by the same compounds showed a similar pattern with simvastatin, atorvastatin, and its metabolites, withLovastatin being the most potent inhibitors, whereas taurocholate and DHEAS showed more modest effects.

**DISCUSSION**

The present work describes a new member of the organic anion transporter polypeptide family, OATP2. It was obtained during efforts to uncover additional hepatic transporters and to define the molecular mechanism that mediates the transport of HMG-CoA reductase inhibitors. In addition to the novel human OATP2, oatp1 was also shown to transport pravastatin in the rat.

OATP2 is unique among OATPs in several ways. It is substantially diverged in sequence from the other family members; it is only 42% identical to each of the other OATPs, compared with 67–92% identity seen among the other transporters. Furthermore, although all of the loops between TMDs are strictly conserved among the other transporters, OATP2 has additional amino acids in three of eleven loops. Our inability to clone the other family members, all of which are found in multiple liver, kidney, and brain. In contrast, the expression OATP2 is very hepatocyte-specific; a major 3.2-kilobase band and several minor hybridizing bands were observed only in RNA from liver and no other tissue (Fig. 5). A potential alternative polyadenylation signal was likely utilized in one of the OATP2 cDNA clones that was isolated (Fig. 3), which could account for the smaller 2.4-kilobase mRNA species seen in the Northern blot. In situ hybridization of OATP2 probe to human liver showed signal in hepatocytes throughout the liver lobule, whereas no signal was observed in bile ducts, Kupffer cells, or vessels.

3 V. Sasseville and T. Kirchgessner, unpublished work.
tissues in addition to liver. This includes kidney, skeletal muscle and colon for roatp1 (5), and kidney brain and retina for roatp2 and roatp3 (6, 7). Human OATP mRNA, although found in liver, kidney, and lung, is expressed much more in brain than in these other tissues (14).

Although there is evidence for a single multivalent hepato-cellular uptake site for amphipathic compounds (29, 30), the discovery of a second OATP isoform in human suggests that, as in the rat, such uptake is in fact mediated by more than one carrier with partially overlapping substrate specificities. A comparison of OATP2 with human OATP reveals that the two proteins are functionally distinct with respect to the types of substrates transported by each. Both OATP2 and OATP transport taurocholate and DHEAS. However, only OATP2 transports HMG-CoA reductase inhibitors. Furthermore, OATP2 transports HMG-CoA reductase inhibitors. This suggests that OATP2 may be the predominant sodium-independent transporter of bile acids in human liver, whereas OATP might be a relatively minor hepatic carrier. DHEAS along with the nonsulfated DHEA are the major

![Fig. 4. Amino acid sequence alignment of OATP2 with other OATP family members.](image)

![Fig. 5. Tissue-specific expression of OATP2.](image)
circulating adrenal steroids, serving as precursors for endogenous sex steroid synthesis (31). Furthermore, they have been suggested to have positive neuropsychiatric, immune, and metabolic effects (32). OATP2 is the second DHEAS transporter described to date and the only hepato-specific carrier. The majority of DHEAS is formed in the liver from the sulfation of DHEA, after which it is effluxed back into the circulation across the sinusoidal surface of the hepatocyte (33). Furthermore, taurocholate inhibitable DHEAS uptake into isolated rat hepatocytes is also known to occur (34). Because members of this family are bi-directional transporters, OATP2 along with OATP are candidates for either of these transport processes in humans.

A search for pravastatin transport activity in the rat revealed that rat oatp1 but not oatp2 mediates pravastatin uptake in vivo. In addition to this transport activity in transfected cells, several other lines of evidence suggest that this is the protein responsible for pravastatin uptake observed in rat hepatocytes. Yamazaki et al. (22) demonstrated that uptake in

**Fig. 6. Human OATP2 transports pravastatin.** A, transport of pravastatin in 293c18 cells transfected with the OATP2 expression plasmid, or the empty vector (pCEP4). Cells were incubated for 5 min with 0.5 μM [3H]pravastatin alone (total) or in the presence of 500 μM unlabeled pravastatin (non-specific) and cellular uptake of radiolabel was determined. B, time course of pravastatin transport. Cells were incubated with 0.5 μM [3H]pravastatin for the indicated times, and uptake was subsequently determined. Non-specific uptake was determined as in A and subtracted from each value. Values are the means ± S.E. of triplicate determinations. C, dose dependence of [3H]pravastatin uptake into OATP2 transfected cells for 5 min at room temperature. The inset shows a double reciprocal plot from which the indicated apparent K_m was calculated.

**Fig. 7. Substrate specificity of OATP2.** A, 293c18 cells transfected with OATP2 plasmid or empty vector (MOCK) were incubated for 5 min with 0.5 μM each of the indicated [3H]-labeled substrates, and uptake in the absence (Total) and presence (non-specific) of 500 μM (pravastatin, DHEAS, and taurocholate) or 150 μM (T4) unlabeled substrate was determined. B, dose dependence of taurocholate uptake. OATP2 transfected cells were incubated for 6 min with the indicated concentrations of [3H]taurocholate. Non-specific incorporation was determined by incubation in the presence of 1000-fold molar excess of unlabeled substrate and was subtracted from each value. The apparent K_m calculated from the double reciprocal plot is indicated. Values are the means ± S.E. of triplicate determinations.
liver cells was sodium-independent, appeared to be a single component, and was competitively inhibited by taurocholate and other cholphilics as well as the lipophilic statins, lovastatin, and simvastatin. The order of potency for inhibition of radiolabeled pravastatin transport into rat hepatocytes was lovastatin = simvastatin > taurocholate > pravastatin. The above characteristics of hepatic pravastatin uptake mechanisms are consistent with the known properties of oatp1 and its behavior in mediating pravastatin transport in this study: (i) oatp1 expression is relatively restricted, being expressed in relatively few organs, including liver, consistent with the relative hepatoslectivity of pravastatin; (ii) oatp1 is a sodium-independent transporter of bile acid; and (iii) in the present studies, [3H]pravastatin transport was inhibited byLovastatin, simvastatin, taurocholate, and pravastatin in the same rank order as in isolated hepatocytes. Furthermore, pravastatin inhibits the sodium-independent uptake of taurocholate in rat hepatocytes (22, 23) and in oatp1-transfected 293c18 cells.

Liver and kidney are the two principle organs of distribution when pravastatin is administered intravenously to rats. This clearance occurs by uptake on the sinusoidal or basolateral side of the liver cell followed by biliary excretion across the canicular membrane. Rat oatp1 has been localized to the basolateral surface of the hepatocyte (34), consistent with a role in hepatic pravastatin clearance (35), whereas the unrelated organic anion transport protein family in humans that mediates the transport of bile acid, the adrenal androgen DHEAS, and HMG-CoA reductase inhibitors, a clinically important class of hypolipidemic agents. The divergent sequence of OATP2, its substrate specificity, and its unique tissue distribution indicate that it is not the human orthologue of any previously described OATP, and thus, it represents a new functional entity. This should further facilitate the understanding of hepatic transport and clearance mechanisms for the molecules described as well as additional substrates.

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Addendum—Similar results were recently reported by Abe et al. (42) following the submission of this manuscript.

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