COMPARISON OF “TYPE I” AND “TYPE II” ORGANIC CATION TRANSPORT BY ORGANIC CATION TRANSPORTERS AND ORGANIC ANION TRANSPORTING POLYPEPTIDES

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ABSTRACT

Previous inhibition studies with taurocholate and cardiac glycosides suggested the presence of separate uptake systems for small “type I” (system1) and for bulky “type II” (system2) organic cations in rat hepatocytes. To identify the transport systems involved in type I and type II organic cation uptake, we compared the organic cation transport properties of the rat and human organic cation transporter 1 (rOCT1; hOCT1) and of the organic anion transporting polypeptides 2 and A (rat Oatp2; human OATP-A) in cRNA-injected Xenopus laevis oocytes. Based on characteristic cis-inhibition patterns of rOCT1-mediated tributylmethylammonium and Oatp2-mediated rocuronium uptake, rOCT1 and Oatp2 could be identified as the organic cation uptake systems1 and 2, respectively, in rat liver. While hOCT1 exhibited similar transport properties as rOCT1, OATP-A- but not Oatp2-mediated rocuronium uptake was inhibited by the OATP-A substrate N-methyl-quinidine. The latter substrate was also transported by rOCT1 and hOCT1, demonstrating distinct organic cation transport activities for rOCT1 and Oatp2 and overlapping organic cation transport activities for hOCT1 and OATP-A. Finally, the data demonstrate that unmethylated quinidine is transported by rOCT1, hOCT1, and OATP-A at pH 6.0, but not at pH 7.5, indicating that quinidine requires a positive charge for carrier-mediated uptake into hepatocytes. In conclusion, the studies demonstrate that in rat liver the suggested organic cation uptake systems1 and 2 correspond to rOCT1 and Oatp2, respectively. However, the rat based type I and II organic cation transporter classification cannot be extended without modification from rat to man.

INTRODUCTION

Hepatic clearance of organic cations is a major pathway of xenobiotic elimination from the systemic circulation. It has been estimated that at least 50% of the presently available therapeutic agents have a (partly) cationic character (Groothuis and Meijer, 1996). The positive charge is either due to quaternary ammonium groups in the molecule or to tertiary amine groups, which are protonated to a large extent at physiological pH (Meijer et al., 1990). In isolated rat hepatocytes and in isolated perfused rat liver, two uptake systems for organic cations have been proposed (Steen et al., 1992; Groothuis and Meijer, 1996). Uptake system1 transports relatively small “type I” organic cations such as tetraethylammonium (TEA) (Moseley et al., 1992), tributylmethylammonium (TBuMA) (Steen et al., 1991; 1992; Moseley et al., 1996), procainamide ethobromide (PAEB) and its azido analogue azidoprocainamide methiiodide (APM) (Mol et al., 1992). Uptake system2 transports more bulky “type II” organic cations, including d-tubocurarine, metocurine as well as the steroidal muscle relaxants vecuronium (Mol et al., 1988) and rocuronium (ORG 9426) (Steen et al., 1992; Proost et al., 1997). While the rat liver organic cation uptake system1 can be inhibited by type II organic cations, it is not sensitive to cardiac glycosides and taurocholate (Steen et al., 1992; Oude Elferink et al., 1995). In contrast, the rat liver organic cation uptake system2 is insensitive to type I substrates, but it is inhibited by cardiac glycosides and taurocholate (Steen et al., 1992; Oude Elferink et al., 1995). Hence, uptake system2 seems to represent a multispecific organic solute uptake system that recognizes bulky amphipathic compounds independent of their charge (Groothuis and Meijer, 1996).
Rat hepatocytes express the organic cation transporter 1 (rOCT1; gene symbol Slc22a1) (Grundemann et al., 1994; Meyer-Wentrup et al., 1998) and the organic anion transporting polypeptide 2 (Oatp2; Slc21a5) (Reichel et al., 1999) at their blood faced basolateral (sinusoidal) plasma membrane domain. rOCT1 mediates charge-selective transport of relatively water-soluble small organic cations such as TEA, 1-methyl-4-phenylpyridinium, and choline (Koepsell, 1998) and, thus, could qualify for the organic cation uptake system1 in rat liver. Oatp2 exhibits a wide substrate preference and can mediate uptake of anionic bile salts, uncharged cardiac glycosides (e.g. digoxin) and type II organic cations such as $N$-(4,4-azo-n-pentyl)-21-deoxyajmalinium (APDA) and rocuronium (Reichel et al., 1999; van Montfoort et al., 1999), indicating that Oatp2 might represent the multispecific organic cation uptake system2 in rat liver (van Montfoort et al., 1999).

The goals of the current study were 2-fold: 1) to definitely investigate the suggested correspondence of the rat liver organic cation uptake systems1 and 2 with rOCT1 and Oatp2, respectively, using the same model compounds as originally used to establish the type I and II classification of organic cations (Steen et al., 1992); and 2) to compare the organic cation transport specificities of the rOCT1 and Oatp2 with the human transporters hOCT1 (SLC22A1) and OATP-A (previously called OATP; SLC21A3), the latter having the broadest transport activity for type II organic cations of all Oatps/OATPs so far characterized (van Montfoort et al., 1999; Kullak-Ublick et al., 2001). The results support the hypothesis that rOCT1 corresponds to the organic cation uptake system1 and Oatp2 to the organic cation uptake system2 in rat liver. Some cationic drugs such as APDA can be transported both by Oatp2 and rOCT1, indicating at least some overlapping substrate specificity between the two families of membrane transporters. The data also demonstrate differences in the substrate preferences between rat (rOCT1; Oatp2) and human (hOCT1; OATP-A) carriers, indicating that the type I and II classification can not be extended without modification from rat to man.

**EXPERIMENTAL PROCEDURES**

**Materials**

$[^{14}\text{C}]}$Tetraethylammonium (TEA; 5 mCi/mmol) was obtained from PerkinElmer Life Science Products (Boston, MA). $[^{3}\text{H}]}$Quinidine (QD; 20 Ci/mmol) was purchased from American Radiolabeled Chemicals (St. Louis, MO). $[^{14}\text{C}]}$Rocuronium (54 mCi/mmol) and unlabeled rocuronium were kind gifts of Organon International BV (Oss, The Netherlands). $N$-(4,4-azo-n-pentyl)-21-deoxy[21-$^{3}\text{H}]}$ajmalinium (APDA; 1.2 Ci/mmol), $N$-(4,4-azo-n-pentyl)-quinuclidine (APQ; 2.5 Ci/mmol), and unlabeled APQ were synthesized as described (Müller et al., 1994). $[^{3}\text{H}]}$Tributylmethylammonium (TBuMA; 85 Ci/mmol) was synthesized according to Neef et al. (1984). Unlabeled TBuMA was obtained from Fluka (Buchs, Switzerland). $[^{3}\text{H}]}$N-methyl-quinine (NMQ; 85 Ci/mmol) and $[^{3}\text{H}]}$N-methyl-quinidine (NMQD; 85 Ci/mmol) were synthesized and characterized as described (van Montfoort et al., 1999). $[^{3}\text{H}]}$Azidoprocainamide methiodide (APM; 85 Ci/mmol) and unlabeled APM were synthesized according to Mol et al. (1992). Radiochemical purity of the not commercially available substrates was determined by thin-layer chromatography and
exceeded 99%. All other chemicals were of analytical grade and readily available from commercial sources.

**Uptake studies in Xenopus laevis oocytes**

\[ v = \frac{V_{\text{max}} \times [S]}{K_m + [S]} \]

Statistical analysis

Uptake results are given as means ± S.D. Statistical significance of transport differences between the various oocyte groups was determined by the Student’s t test (Systat 8.0, SPSS Inc., Chicago, IL).

**RESULTS**

To identify rOCT1 as the type I organic cation uptake system (system1) and Oatp2 as the type II organic cation uptake system (system2) of rat liver, we first performed a series of cis-inhibition studies in rOCT1- and Oatp2-expressing X. laevis oocytes using TBuMA as a type I and rocuronium as a type II substrate. As illustrated in Fig. 1A, rOCT1-mediated TBuMA uptake was inhibited by APM (a type I compound) and rocuronium (a type II compound), but not by taurocholate, ouabain, and K-strophantoside. This cis-inhibition pattern is characteristic for the rat liver organic cation uptake system1 (Steen et al., 1992), which therefore corresponds to rOCT1. The latter was also inhibited by QD as previously described (Koepsell et al.,
Figure 1. cis-Inhibition pattern of TBuMA and rocuronium uptake mediated by rOCT1 (A) and Oatp2 (B), respectively. *X. laevis oocytes were injected with 10 ng of rOCT1 or 5 ng of Oatp2 cRNA. After 3 days in culture, uptakes of [3H]-TBuMA (35 µM) by rOCT1 (A) and of [14C]-rocuronium (25 µM) by Oatp2 (B) were measured at 30 min (under Experimental Procedures) in the absence (control) and presence of the indicated compounds (all 200 µM, except ouabain 2 mM). Uptake rates of water-injected oocytes were subtracted from cRNA-injected oocytes for each substrate. Data are expressed as means ± S.D. of uptake measurements into 10 oocytes. *, significant uptake inhibition (Student’s t test, p < 0.01) compared with controls.

Next we evaluated whether the characteristic cis-inhibition pattern of rOCT1 and Oatp2 is also valid for the human transporters hOCT1 and OATP-A. As
Figure 2. cis-Inhibition pattern of TBuMA and rocuronium uptake mediated by hOCT1 (A) and OATP-A (B), respectively. X. laevis oocytes were injected with 10 ng of hOCT1 or 2.5 ng of OATP-A cRNA. After 3 days in culture, uptakes of [3H]-TBuMA (35 µM) by hOCT1 (A) and of [14C]-rocuronium (25 µM) by OATP-A (B) were measured at 30 min (under Experimental Procedures) in the absence (control) and presence of the indicated compounds (all 200 µM, except ouabain 2 mM). Uptake rates of water-injected oocytes were subtracted from cRNA-injected oocytes for each substrate. Data are expressed as means ± S.D. of uptake measurements into 10 oocytes. *, significant uptake inhibition (Student’s t test, p < 0.01) as compared with controls.

Illustrated in Fig. 2A, hOCT1-mediated TBuMA uptake showed qualitatively a similar cis-inhibition pattern as rOCT1-mediated TBuMA uptake (Fig. 1A), indicating that hOCT1 and rOCT1 represent orthologous gene products with similar type I organic cation transport properties in rat and human liver. In contrast, OATP-A-mediated rocuronium uptake was inhibited by APM, taurocholate, K-strophantoside, QD, and NMQD, but not by TBuMA and ouabain (Fig. 2B). This cis-inhibition pattern is clearly different compared to Oatp2 (Fig. 1B). While part of these differences can be explained by distinct transport activities [e.g., NMQD is a transport substrate of OATP-A, but not of Oatp2 (van Montfoort et al., 1999)] and/or substrate affinities [e.g., $K_m$ values for ouabain transport: OATP-A, ~ 5.5 mM; Oatp2, ~ 470 uM (Bossuyt...
**Figure 3.** Comparison of rOCT1- and hOCT1-mediated uptake of [³H]NMQ, [³H]NMQD, [³H]APDA, [¹⁴C]rocuronium, [³H]TBuMA, [³H]APM and [³H]APQ. *X. laevis* oocytes were injected with 10 ng of rOCT1 (A) or 10 ng of hOCT1 cRNA (B). After 3 days in culture, uptakes of the indicated substrates were measured at 2 µM (except rocuronium at 14 µM) for 30 min in Na⁺ buffer (under Experimental Procedures). The standard substrate TEA was used as positive control to test the expression of rOCT1 and hOCT1 in the cRNA-injected oocytes. The uptake rates of the water-injected control oocytes were subtracted from the cRNA-injected oocytes for each substrate. Data represent the mean ± S.D. from 11 to 15 oocyte uptake measurements. *, significantly different from water-injected control oocytes (Student’s t test, p < 0.001).

et al., 1996; Noe et al., 1997]) of OATP-A and Oatp2, the inhibitory effect of the type I organic cation APM on OATP-A-mediated rocuronium uptake is surprising since APM has been shown to be not transported by OATP-A (van Montfoort et al., 1999). Hence, the data indicate that the rat based classification of type I and type II organic cations and its association with distinct organic cation carriers cannot be applied to the human situation without modification.

Based on their physicochemical properties as permanently charged bulky quaternary ammonium compounds it has been suggested that NMQ and NMQD represent new type II organic cations (van Montfoort et al., 1999). However, the
overall structure of these compounds shows a spatial separation of the single
cationic group (surrounded by aliphatic moieties as in TBuMA and PAEB) from an
aromatic structure as has been considered as being typical for type I compounds
(Meijer et al., 1990; Groothuis and Meijer, 1996). Even APDA exhibits these
structural features to some extent. The latter consideration is supported by the
findings that NMQD inhibits rOCT1- and hOCT1-mediated TBuMA uptake rather than
Oatp2-mediated rocuronium uptake (Figs. 1 and 2). Therefore, we tested next
organic cation transport in rOCT1- and hOCT1-expressing oocytes. As illustrated in
Fig. 3, and consistent with the cis-inhibition data, rOCT1 and hOCT1 mediated not
only transport of the type I compounds TBuMA, APM, and APQ but also of the
previously supposed type II substrates NMQ, NMQD and also but to a lesser extent,
ADPA. The only type II organic cation not significantly transported by rOCT1 and
hOCT1 was rocuronium.

Time course experiments showed linear uptake rates for NMQ, NMQD,
TBuMA, and APM for at least 30 min (data not shown). Therefore, kinetic uptake
measurements were performed at 15 min. They showed saturation kinetics as
indicated in Fig. 4 for hOCT1. Similar kinetic features were also obtained for rOCT1
with all apparent $K_m$ values given in Table 1. These data confirm the affinity of rOCT1
and hOCT1 for the established type I organic cations TBuMA, APM and APQ. However, since rOCT1 and hOCT1 also transport the rather bulky organic cations
NMQ, NMQD, and APDA, the data indicate that this physicochemical property alone
should not be used to predict the types of carrier involved in hepatic organic cation
uptake. In this study, only rocuronium showed entirely the expected behaviour as a
type II organic cation, i.e., exclusive and taurocholate/cardiac glycoside inhibitable
transport by Oatp2 and OATP-A, respectively. Other examples of type II compounds
are d-tubocurarine, metocurine, hexafluoruronium and vecuronium. A general feature of
these agents is that a) the cationic groups are not clearly separated from the
aromatic moieties or other bulky ring structures and b) that they contain a second
quaternary or tertiary amine structure and consequently can form bivalent cationic
molecules.

The quaternary ammonium compounds used in this study are permanently
positively charged model compounds and with the exception of rocuronium not used
as drugs. Therefore we also investigated transport of the drug quinidine, which is a
tertiary amine and shown to inhibit rOCT1, hOCT1 and OATP-A (Figs. 1 and 2)
Quinidine is a base with a $pK_a$ of 8.5 (Notterman et al., 1986) which means that at pH
7.5 about 10% of the quinidine molecules are protonated, while at pH 6.0 almost all
molecules are positively charged. It can be seen in Fig. 5 that there is no significant
quinidine transport by OATP-A-, rOCT1- or hOCT1-cRNA injected $X$. laevis oocytes
at pH 7.5. At pH 6.0, however, transport of quinidine becomes detectable since the
unspecific uptake into water injected oocytes is markedly reduced. These findings
suggest that quinidine molecules need a positive charge to be transported by OATP-
A, rOCT1, and hOCT1. In the unprotonated form, quinidine most probably enters the
oocytes by passive diffusion as can be seen by the large unspecific uptake into
water-injected oocytes at pH 7.5 (Fig. 5).

**DISCUSSION**

The present study identifies rOCT1 as the type I organic cation uptake system
Figure 4. Saturation kinetics of NMQ, NMQD, TBuMA and APM in hOCT1-cRNA injected X. laevis oocytes. *X. laevis* oocytes were injected with 10 ng of hOCT1-cRNA. After 3 days in culture, uptakes of [*H]*NMQ (A), [*H]*NMQD (B), [*H]*TBuMA (C) and [*H]*APM (D) were measured at 15 min in Na+ buffer (under Experimental Procedures) containing increasing substrate concentrations. The dotted lines represent fitted uptake differences between hOCT1-cRNA (λ) and water-injected oocytes (Ο). Data are expressed as mean ± S.D. of 10 to 12 oocyte uptake measurements.

(system1) and Oatp2 as the type 2 organic cation uptake system (system2) in rat liver. This conclusion is based on the typical cis-inhibition of rOCT1-mediated TBuMA uptake by type I and type II cations, but not by taurocholate and cardiac glycosides (Fig. 1A) (Steen et al., 1992), and of Oatp2-mediated rocuronium uptake by taurocholate and cardiac glycosides, but not by type I cations (Fig. 1B) (Steen et al., 1992). While the transport properties of hOCT1 were similar to rOCT1 (Fig. 2A), the cis-inhibition patterns of Oatp2- and OATP-A-mediated rocuronium uptake were different in part in that OATP-A, but not Oatp2, was inhibited by the type I organic cation APM, QD and NMQD (Fig. 2B). Thus, the clear-cut associations between transport of type I and type II organic cations by rOCT1 and Oatp2, respectively, is not entirely valid for hOCT1 and OATP-A, which supports the concept that the human OATP-A is not the orthologous gene product of the rat Oatp2 (Kullak-Ublick et al., 2001). Furthermore, studies in isolated human hepatocytes showed that rocuronium uptake could be inhibited by K-strophantoside and by the type I organic cation PAEB, but not by taurocholate (Olinga et al., 1998). These findings are an additional indication for species differences between organic cation uptake systems of rat and human liver. Since none of the so far identified human hepatic OATPs [i.e., OATP-B (SLC21A9), OATP-C (SLC21A6) and OATP8 (SLC2A8)] was able to transport organic cations, a human orthologue of rat Oatp2 remains to be identified (Kullak-Ublick et al., 2001). It might also be possible that the transport functions of rat and
human OATPs have evolved differently since in contrast to rat Oatp2 no human OATP can transport both rocuronium and digoxin. In man, rocuronium is transported by OATP-A (van Montfoort et al., 1999), while digoxin is transported by OATP8 (Kullak-Ublick et al., 2001).

The concept of rOCT1 corresponding to uptake system1 and Oatp2 to uptake system2 is valid for the same substrates and inhibitors that were used originally in rat hepatocytes (Steen et al., 1992). Other substrates have to be classified with caution. NMQ, NMQD and APDA could, at first sight, be viewed upon as type II organic cations because of their bulky structure (van Montfoort et al., 1999). According to the proposed concept their uptake into rat liver is supposed to be mediated by Oatp2 rather than by rOCT1. However, while Oatp2 solely mediates the transport of the real type II organic cation rocuronium, APDA is only to some extent accommodated by OATP-A and Oatp2, respectively, whereas NMQ and NMQD even seem pure rOCT1-mediated type I compounds (van Montfoort et al., 1999). Therefore, a positive charge and a bulky structure alone are not sufficient to predict the putative uptake system. As NMQ and NMQD are mainly taken up by rOCT1 which corresponds to uptake system1, they should be reclassified as type I organic cations despite their bulky structure. It is possible that rOCT1 and hOCT1 recognize a single cationic group spatially separated from a flat (aromatic) ring structure that can be recognized in APDA, NMQ, NMQD, and PAEB. The type I agents TBuMA and APQ also have a single cationic group but lack an aromatic moiety. The only true type II substrate used in this study that is consistently transported only by Oatps is the steroidal muscle relaxant rocuronium. It shares a potential dicationic nature with previously categorized type II compounds (Meijer et al., 1990) in combination with a sufficient lipophilicity. The latter aspect and the presence of a permanently charged ammonium group as well as a second tertiary amine function may render APDA a mixed type I/type II substrate.
Table 1: Comparison of apparent \( K_m \) values between OATP-A, rOCT1, and hOCT1. X. laevis oocytes were injected with 2.5 ng of OATP-A-cRNA, 10 ng of rOCT1-cRNA, and 10 ng of hOCT1-cRNA. After 3 days in culture, uptakes of the indicated substrates were measured at 15 min in Na\(^+\) buffer under Experimental Procedures containing increasing substrate concentrations. Data are expressed as mean ± S.D. of 10 to 12 oocyte uptake measurements. nt, not transported. \(^a\) Taken from van Montfoort et al., 1999.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>OATP-A</th>
<th>hOCT1</th>
<th>rOCT1</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-methyl-quinine</td>
<td>5.1 ± 2.1(^a)</td>
<td>19.5 ± 7.3</td>
<td>17.3 ± 4.9</td>
</tr>
<tr>
<td>N-methyl-quinidine</td>
<td>25.6 ± 4.1(^a)</td>
<td>11.5 ± 2.1</td>
<td>7.4 ± 2.1</td>
</tr>
<tr>
<td>TBuMA</td>
<td>nt</td>
<td>53.0 ± 13.9</td>
<td>34.0 ± 7.7</td>
</tr>
<tr>
<td>APM</td>
<td>nt</td>
<td>100.9 ± 43.0</td>
<td>54.0 ± 15.2</td>
</tr>
</tbody>
</table>

While there were considerable differences in the substrate specificity of Oatp2 and OATP-A in this study, rOCT1 and hOCT1 showed similar substrate specificities and inhibition patterns (Figs. 1-3), although some quantitative differences were observed in the inhibition of TBuMA by APM (rOCT1 > hOCT1) and NMQD (rOCT1 < hOCT1). In addition, the apparent \( K_m \) values for NMQ, NMQD, TBuMA, and APM were comparable (Table 1). hOCT1 showed slightly higher \( K_m \) values, which is in agreement with previous findings where hOCT1 exhibited a lower affinity than rOCT1 for several other ligands (Koepsell et al., 1999). Furthermore, it has been shown that hOCT1 transports larger \( n \)-tetraalkylammonium compounds such as tetrapropylammonium and tetrabutylammonium at higher rates than rOCT1 (Dresser et al., 2000). The kinetics of TBuMA and APM have also been determined in isolated rat hepatocytes (Steen et al., 1991; Mol et al., 1992) where for both substrates the presence of high- and low- affinity uptake systems has been suggested with apparent \( K_m \) values of ∼1.2 and ∼107 µM for TBuMA (Steen et al., 1991) and of ∼3 and ∼100 µM for APM, respectively (Mol et al., 1992). In the present study, rOCT1 showed apparent \( K_m \) values of 34 µM for TBuMA and of 54 µM for APM. If these values, as obtained in the oocyte system, can be extrapolated to the hepatocyte, they could correspond to the low-affinity system found in isolated rat hepatocytes. In that case, candidate carriers for the supposed high affinity systems should be identified in the future.

rOCT1, hOCT1, and OATP-A are not only inhibited by the permanently positively charged NMQD, but also by the base quinidine (Figs. 1 and 2). However, at pH 7.5 where only about 10% of the quinidine molecules are protonated no carrier-mediated transport of quinidine could be detected (Fig. 5). In contrast, at pH 6.0, where almost all quinidine molecules are positively charged, unspecific diffusion into the oocytes was markedly reduced and uptake of the protonated quinidine by rOCT1, hOCT1, and OATP-A became evident (Fig. 5). This finding is an indication that quinidine is only transported by rOCT1, hOCT1, and OATP-A, when it carries a positive charge. The mechanism of quinidine inhibition of rOCT1, hOCT1, and OATP-A at pH 7.5 is not clear. It has been shown that quinine, which is a diastereomer of quinidine, is a noncompetitive inhibitor of rOCT1 when added at the extracellular site, suggesting an allosteric binding site (Koepsell, 1998). Recent experiments with macropatches of rOCT2 cRNA-injected X. laevis oocytes in which quinine could also be added from the cytoplasmic site showed competitive inhibition, suggesting that
quinine inhibits rOCT2 from the intracellular site after crossing the lipid bilayer in its uncharged form (Budimann et al., 2000)

In conclusion, the present study demonstrates that rOCT1 corresponds to the predicted uptake system1 for type I organic cations in rat liver, whereas Oatp2 corresponds to uptake system2 for type II organic cations. However, the results cannot be transferred to human liver without modifications. While the transport properties of rOCT1 and hOCT1 are similar, considerable differences exist between Oatp2 and OATP-A, indicating further that rat Oatps and human OATPs have different transport properties and do not represent orthologous gene products.

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REFERENCES


HEPATIC CATION UPTAKE BY OCTS AND OATPS


