Modulation of OATP1B-Type Transporter Function Alters Cellular Uptake and Disposition of Platinum Chemotherapeutics

Cynthia S. Lancaster, Jason A. Sprowl, Aisha L. Walker, Shuiying Hu, Alice A. Gibson, and Alex Sparreboom

Abstract

Expression of the human organic anion transporting polypeptides OATP1B1 and OATP1B3 has been previously believed to be restricted to hepatocytes. Here we show that the gene encoding OATP1B3, but not OATP1B1, is abundantly expressed in multiple human solid tumors that include hepatocellular, lung, and ovarian carcinomas. Surprisingly, OATP1B3 gene expression in a panel of 60 human tumor cell lines was linked with sensitivity to multiple cytotoxic agents, including the platinum anticancer drugs cisplatin, carboplatin, and oxaliplatin. In addition, overexpression of OATP1B3 in mammalian cells increased cellular accumulation of platinum agents and decreased cell survival. In mice with a targeted disruption of the ortholog transporter Oatp1b2, the liver-to-plasma ratio of cisplatin was significantly reduced compared with wild-type mice, without concurrent changes in expression profiles of other transporter genes. Our findings indicate an unexpected role for tumoral and host OATP1B-type carriers in the toxicity and disposition of platinum anticancer drugs, and may provide a foundation for understanding the extensive interindividual pharmacodynamic variability seen with these drugs in patients. Mol Cancer Ther; 12(8); 1–8. ©2013 AACR.

Introduction

Membrane-localized transport proteins have evolved to catalyze migration or expulsion of an endogenous or exogenous molecule across biological membranes. Such evolution has been necessary because membrane lipid bilayers would otherwise present virtually impenetrable barriers to many molecules or, alternatively, permit excessive intracellular accumulation. Although most of the currently known transporters have unknown physiologic function, several have gained interest within the scientific community due to the recognition that drugs may “hitchhike” on these proteins that normally act on endogenous substrates (1).

Although the role of ABC transporters in drug resistance has historically been a major focus of research, recent years have seen a greater emphasis on studies devoted to the so-called solute carriers, which comprise approximately 400 proteins organized into 52 distinct families and are involved in the uptake of molecules into cells (http://slc.bioparadigms.org/). One reason contributing to the apparent historic lack of interest in solute carrier research is the long-held belief that most xenobiotics are transported across membranes via passive diffusion at a rate related to their hydrophobicity (2). Not only is this paradigm itself poorly supported by experimental data, but evidence accumulated over the last decade now supports the notion that solute carrier-mediated migration of drugs across the highly organized lipid bilayers of biological membranes is a predominant mechanism of cellular uptake (3).

Among the most widely studied solute carrier family is the SLCO cluster of genes that encode organic anion transporting polypeptides (OATP; ref. 4). Two of these proteins, namely OATP1B1 (formerly OATP2, OATP-C, LST-1; gene symbol, SLCO1B1, SLC21A6) and OATP1B3 (formerly OATP8, LST-2; SLCO1B3, SLC21A8), are highly expressed in hepatocytes, and are of particular importance for hepatic drug elimination. Unlike SLCO1B1, SLCO1B3 is also overexpressed in various human cancer tissues as well as in several cancer cell lines derived from solid tumors (5), and is therefore a potential therapeutic target to enhance drug delivery into cancer cells. Previous studies have identified a number of widely used anticancer drugs as substrates of OATP1B3, including paclitaxel (6), docetaxel (7), lapatinib (8), and methotrexate (9). However, a systematic approach to evaluate the ability of...
anticancer drugs to interact with OATP1B3 and subsequently affect tumor sensitivity and drug disposition is still lacking. In this study, we exploited the NCI60 database (10) to correlate gene expression data with efficacy data for 118 anticancer drugs and unexpectedly identified several platinum chemotherapeutics as OATP1B3 substrates. These findings were validated in vitro using overexpressing cell models and in vivo with OATP-deficient mice.

Materials and Methods

Real-time PCR

Tissue plates containing cDNA from 68 normal human tissues and 312 human cancer tissues were obtained from Origene. RNA from the NCI anticancer screening panel (NCI60) was provided by the National Cancer Institute tumor repository. RNA was reverse transcribed using SuperScript III first-strand synthesis supermix for real-time reverse transcriptase PCR (Invitrogen) according to manufacturer’s recommendations. Gene transcripts were quantified using SYBR Green PCR Mastermix (Qiagen) and primers obtained from Origene that were specific to SLCO1B1 (HP209396) and SLCO1B3 (HP213461). Reactions were carried out in triplicate as previously reported (11). Transcripts of each sample were normalized to the housekeeping gene, GAPDH.

Correlation analyses

Growth inhibition data for the compounds of interest were obtained from the Developmental Therapeutics Program at the National Cancer Institute (http://dtp.cancer.gov/). The database comprises information on 60 different human tumor cell lines (NCI60), representing leukemia, melanoma, and cancers of the lung, colon, brain, ovary, breast, prostate, and kidney. The 60 cell line dose–response produced by a given compound results in a biological response pattern that can be used in a pattern recognition algorithm known as COMPARE (see http://dtp.nci.nih.gov/docs/compare/compare.html). Using this algorithm, Pearson correlation coefficients were calculated for assessment of SLCO1B3–drug relationships. For in vivo associations, each cell line was classified as a low expresser if SLCO1B3 expression fell at or below the median expression of all cell lines, whereas cell lines above the median were considered high expressers. The 2 classifications of SLCO1B3 expressers were then correlated with cisplatin sensitivity (at a dose of 2.5 mg/kg) in xenograft mouse models (reported as a ratio of treatment vs. control) that were available from the Invitrogen Summary Data (see http://dtp.nci.nih.gov/dtpstandard/InvivoSummary/index.jsp).

Cellular transport

Xenopus laevis oocytes injected with OATP1B1 or OATP1B3 cRNA along with water-injected controls were obtained from BD Biosciences. OATP1B1 or OATP1B3 overexpressing human embryonal kidney (HEK293) cells were created by stably transfecting the respective cDNA fragments spliced from TrueClone plasmids (Origene Technologies), cloned into a pIRE2-EGFP vector (BD Biosciences). HEK293 cells were obtained from Invitrogen (Aug 2006) and no authentication was conducted by the authors. These cells were functionally characterized with the OATP1B1/OATP1B3 substrate [6,7-3H(6)]estradiol-17β-d-glucuronide (E2-Glu) (radiochemical purity of 99% and specific activity of 45.8 Ci/mmol; obtained from American Radiolabeled Chemicals Inc. (Lot No. 080709)]. Additional uptake experiments were conducted as described previously (12) using 500 μmol/L of cisplatin, carboplatin, or oxaliplatin in X. laevis oocytes or HEK293 cells, with results normalized to uptake values in water-injected controls or cells transfected with an empty vector. The concentration of cisplatin used and the 30-minute time point were selected on the basis of feasibility and sensitivity of currently available analytical methods for the determination of Pt concentrations (12). Previous experiments indicated that Phenol Red, a pH indicator in trypsin used to re-suspend cultured cells, influenced OATP1B-mediated uptake of substrates (7), and therefore these studies were conducted in Phenol Red free conditions.

Animal experiments

Pharmacokinetic studies were conducted in adult male Oatp1b2(−/−) mice (13) and age-matched wild-type mice (Taconic), both on a DBA1/lacJ background, that were housed in a temperature-controlled environment with a 12-hour light cycle, and given a standard diet and water ad libitum. Cisplatin was administered by intraperitoneal (i.p.) injection at a dose of 10 mg/kg, after which plasma and liver from each animal were collected at 5, 10, 15, and 30 minutes. Urine was collected from animals housed in metabolic cages for 72 hours after cisplatin administration. All experiments involving animals were approved by the Institutional Animal Care and Use Committee of St. Jude Children’s Research Hospital.

Determination of platinum concentrations

Total platinum concentration was determined using an AAAnalyst 600 atomic absorption spectrometer with Zee-man background correction (Perkin-Elmer). Concentrations in unknown samples were interpolated on linear calibration curves ranging 0.2 to 3 μg/mL that were constructed fresh daily in the relevant matrix. The percentage deviation from nominal values and the within-run and between-run precision of quality control samples spiked with known amounts of cisplatin were always <15%. Pharmacokinetic parameters were calculated using PK Solutions 2.0 (Summit Research Services).

Gene expression analysis of mouse liver and kidney

RNA was extracted using the RNeasy Mini Kit (Qiagen), and samples were amplified from 3 animals per group and then analyzed using the Mouse 430v2 GeneChip array (Affymetrix). Volcano plots were constructed using all
probe sets or using select genes, including those that encode enzymes (N = 27 probe sets), nuclear receptors (N = 27), ABC transporters (N = 56), and solute carriers (N = 293). The data were summarized and normalized by the RMA algorithm. Then t tests were conducted using the Partek Genomics Suite 6.4 software. A Bonferroni correction method was applied to the resulting P values.

**Statistical calculations**

All graphed data are presented as mean values (symbols or bars) with standard error (error bars). Two-tailed P values of less than 0.05 were considered as statistically significant. All statistical calculations were conducted using the software package NCSS version 2004 (Number Cruncher Statistical System).

**Results**

**SLCO1B1/SLCO1B3 expression in normal and human tumor tissue**

To provide insight into the tumor-specific expression profile of the OATP1B1 and OATP1B3 genes, real-time PCR analysis was conducted on a panel of normal human tissues and corresponding tumor specimens. *SLCO1B1* was only detectable in normal and tumor tissue of the liver (Fig. 1A). In contrast, *SLCO1B3* was expressed in various normal and tumor tissues with the exception of the adrenal gland, breast, or kidney (Fig. 1B). Interestingly, the expression of *SLCO1B3* was higher in colon, endometrium, esophagus, lung, ovary, prostate, stomach, tests, and bladder tumors, when compared with the baseline expression in the corresponding normal tissue (Fig. 1B). These findings are consistent with recent expression data for these transporters that were reported by Pressler and colleagues (5) in a similar set of human samples.

**Association of SLCO1B3 expression with anticancer drug sensitivity**

Because expression of the OATP1B3 gene was detectable in all cell lines of the NCI60 panel (Fig. 2A), a COMPARE analysis was conducted on the growth-inhibitory potential of 118 well-characterized anticancer drugs (14). Using a cut-off correlation coefficient of 0.3, corresponding to a P value of 0.025, we found that the cytotoxicity of 9 anticancer drugs of different classes was statistically significantly associated with *SLCO1B3* expression (Table 1 and Supplementary Table S1). Among the top-ranking compounds were 3 platinum-based chemotherapeutics (Fig. 2B), including cisplatin, carboplatin, and (trans-1,2-diaminocyclo-hexane)platinum-II (DACH-Pt), which is structurally related to the anticancer agent oxaliplatin (15). Using the DTP in vivo screen summary data obtained from xenograft studies, we found that OATP1B3 may contribute in vivo to the tumor sensitivity of cisplatin, because cells lines with low *SLCO1B3* expression are less sensitive to treatment than cells with high *SLCO1B3* expression (Fig. 2C).

**Characterization of platinum transport by OATP1B3**

We next evaluated the in vitro transport of cisplatin by OATP1B3 in *Xenopus laevis* oocytes injected with OATP1B3 cRNA. Compared with water-injected control oocytes, the presence of OATP1B3 was associated with increased uptake of E2-Glu, a known OATP1B3 substrate, and increased uptake of cisplatin (Fig. 3A), as determined by atomic absorption spectrometry. The uptake of cisplatin was also facilitated in HEK293 cells transfected with OATP1B1 or OATP1B3 (Fig. 3B and C). Similar observations were made for OATP1B3 in the case of carboplatin and oxaliplatin, but not for tetraplatin, a platinum analog that was not identified to be of significance in the COMPARE analysis (Fig. 3D). In agreement with above findings, enhanced accumulation was also observed in OATP1B3-overexpressing HEK293 cells for 14C-carboplatin and 14C-oxaliplatin (Supplementary Fig. S1), as determined by liquid scintillation counting.
Influence of OATP1B-deficiency on cisplatin pharmacokinetics

To assess the role of OATP1B transporters in the disposition properties of cisplatin in vivo, we used mice deficient for the ortholog transporter Oatp1b2 [Oatp1b2(−/−) mice]. These animals were phenotypically normal compared with wild-type mice as determined from a serum chemistry screen with the exception of slightly altered amylase and bilirubin levels (Supplementary Fig. S2), as reported previously (13, 16). Transcriptional profiling of liver samples of wild-type mice did not reveal aberrant gene expression patterns in males versus females beyond a number of genes with known sex-dependent expression (Supplementary Fig. S3A). Furthermore, liver and kidney
samples from Oatp1b2(−/−) mice did not have altered expression of genes of putative relevance to the anticancer drugs of interest (Supplementary Figs. S3B and S3C). Preliminary examination revealed the absence of a sex dependence in Oatp1b2-mediated cisplatin distribution in the liver (Supplementary Fig. S4), and therefore only male mice were used in subsequent experiments.

Following the administration of cisplatin at a dose of 10 mg/kg (i.p.), hepatic levels of cisplatin were higher in wild-type mice compared with Oatp1b2(−/−) mice, indicating that platinum transport into the livers of these mice is compromised (Fig. 4A). This phenomenon occurred without a substantial influence on circulating concentrations of cisplatin (Fig. 4B). In line with the altered hepatobiliary handling of cisplatin, urinary excretion of platinum was significantly increased in the Oatp1b2(−/−) mice (Fig. 4C).

Analysis of kidneys from Oatp1b2(−/−) mice revealed that the expression of common drug-metabolizing enzymes, nuclear receptors, ATP-binding cassette transporters, and solute carrier genes were not substantially changed compared with kidneys obtained from wild-type animals, with the exception of an upregulation of Slc14a2 in Oatp1b2(−/−) mice (Supplementary Figs. S5A and S5B). The Slc14a2 gene encodes the urea transporter UT-B1 that has been implicated in the transport of molecules into urine (17). However, the overexpression of Slc14a2 in the kidney of the Oatp1b2(−/−) mice is unlikely to affect the renal handling of cisplatin because overexpression of UT-B1 or the related transporter UT-A1 (SLC14A1) expressed in HEK293 cells (Supplementary Fig. S5C) did not alter intracellular transport of cisplatin (Supplementary Fig. S5D), which suggests that the drug is not a transported substrate of urea transporters.

Discussion

This study provides support for a growing body of knowledge that solute carriers belonging to the family of OATPs can have a dramatic impact on cancer cell sensitivity and hepatic accumulation of multiple xenobiotics. Using an array of in vitro transport assays, including intracellular accumulation studies in multiple transfected model systems, the platinum chemotherapeutics cisplatin, carboplatin, and oxaliplatin were identified as substrates for the human OATP1B1 and OATP1B3 transporters.

Using quantitative real-time PCR, we measured the mRNA expression of SLCO1B3 in the NCI60 cancer cell line panel. By correlating the mRNA expression pattern with the growth inhibitory potential of 118 drugs for which the mechanism of action is largely understood (14), we identified multiple putative compounds for which OATP1B3 is likely to play a dominant role in tumor sensitivity, including several platinum chemotherapeutics. To substantiate some of the OATP1B3–drug pairs for which the transporter was predicted to be sensitizing, follow-up experiments were conducted using engineered and characterized models overexpressing OATP1B3. As predicted by the statistical correlations, expression of OATP1B3 in a human cell model resulted in increased cellular uptake of cisplatin, carboplatin, and oxaliplatin. It is important to note that the platinum complexes transported by OATP transporters are unknown. However, Di Pasqua and colleagues have shown that cisplatin and carboplatin can react with carbonate to form negatively charged complexes that are more cytotoxic than parent cisplatin and carboplatin (18). Interestingly, tetrataplatin is a platinum (IV) complex and is therefore less reactive, providing support for the concept that these transporters seem to regulate accumulation of selective platinum agents.

Huang and colleagues previously exploited the NCI60 database to correlate transporter expression data from an oligonucleotide array with the cytotoxicity of the same panel of agents (19). In both these authors’ analyses as in our own, the agent ranked with the highest positive correlation in the SLCO1B3 analysis was Asaley (NSC167780), an L-leucine derivative of melphalan with DNA alkylating activity. Moreover, both cisplatin ($R = 0.33; P = 0.0092$) and carboplatin ($R = 0.37; P = 0.0039$) were top-10 ranking compounds in this earlier analysis [see Supplementary data to Huang and colleagues (19)].

Table 1. Association of SLCO1B3 expression with cytotoxicity of anticancer drugs

<table>
<thead>
<tr>
<th>Rank</th>
<th>NSC number</th>
<th>Drug name</th>
<th>$R$ value</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>167780</td>
<td>Asaley</td>
<td>0.4567</td>
<td>0.0004</td>
</tr>
<tr>
<td>2</td>
<td>606172</td>
<td>Camptothecin,11 formyl (RS)</td>
<td>0.4251</td>
<td>0.0010</td>
</tr>
<tr>
<td>3</td>
<td>95441</td>
<td>Semustine (MeCCNU)</td>
<td>0.3772</td>
<td>0.0038</td>
</tr>
<tr>
<td>4</td>
<td>102816</td>
<td>Azacytidine</td>
<td>0.3712</td>
<td>0.0045</td>
</tr>
<tr>
<td>5</td>
<td>142982</td>
<td>Hyacanthone</td>
<td>0.3490</td>
<td>0.0188</td>
</tr>
<tr>
<td>6</td>
<td>119875</td>
<td>Cisplatin</td>
<td>0.3175</td>
<td>0.0161</td>
</tr>
<tr>
<td>7</td>
<td>95466</td>
<td>PCNU</td>
<td>0.3101</td>
<td>0.0189</td>
</tr>
<tr>
<td>8</td>
<td>291240</td>
<td>Carboplatin</td>
<td>0.3047</td>
<td>0.0212</td>
</tr>
<tr>
<td>9</td>
<td>271674</td>
<td>Diaminocyclohexyl-Pt-II</td>
<td>0.3042</td>
<td>0.0214</td>
</tr>
</tbody>
</table>

Abbreviation: $R$, Pearson correlation coefficient.
but these findings were not experimentally confirmed. It should be pointed out that several previous investigations failed to show indirect (20) or direct transport of cisplatin by OATP1B1 (21), as well as indirect interaction of carboplatin with OATP1B3 (22), or oxaliplatin with OATP1B1 or OATP1B3 (23). The reasons for these discrepant findings are not entirely clear, but may relate to differences in the experimental models and specific conditions applied.

Cisplatin is among the most widely used cytotoxic anticancer agents and has a broad spectrum of activity against various diseases, including endometrial, esophageal, lung, ovarian, gastric, bladder, testicular, and bladder cancers, and we found that the expression of the OATP1B3 gene was particularly high in these tumors, relative to the corresponding healthy tissue. In fact, although expression of SLC01B3 was detectable in colon, endometrium, esophagus, lymph node, ovarian, and bladder tumors, its expression was completely absent in normal tissue. In this context, it is of note that the effectiveness of platinum-based chemotherapy is directly linked with accumulation into target cells where DNA-mediated damage can then occur. Originally, movement of these agents across the cellular lipid bilayer was thought to occur predominantly by passive diffusion (24, 25). Instead, emerging evidence in the literature indicates that carrier-mediated uptake is likely the major determinant of uptake of these drugs into cancer cells (26).

The mechanism of cellular uptake of cisplatin in tumor cells is not entirely clear and may vary from one cell type to another (27). Nonetheless, the current knowledge as to the role of carrier-mediated platinum transport has been reviewed in great detail (28, 29). Preclinical studies have showed that a high-affinity transporter known as copper transporter 1 (CTR1, encoded by the SLC31A1 gene) plays a role in the uptake of cisplatin in yeast as well as several murine and human tumor cell lines (30). However, the accumulation of cisplatin in human cancer cells expressing this transporter is limited by the fact that cisplatin itself can trigger the downregulation and proteasomal degradation of CTR1, thereby limiting its own uptake (31). Our current findings support the possibility that the OATP1B3 transporter is another important uptake mechanism for platinum chemotherapeutics in multiple distinct tumors.

Although cisplatin elimination is dependent, in part, on tubular secretion mediated by the organic cation transporter OCT2 (11), in dogs initial levels of platinum are highest in liver and remain significantly elevated over time (32). Similarly, platinum levels are highest in liver in rats (33), mice (34), and are consistently higher than those observed in other organs in humans (35). The high liver uptake of platinum in humans has been confirmed using gamma camera imaging in patients with cancer following a dose of $^{195}$Pt-cisplatin (36).

Cisplatin uptake by the liver is not well understood, although our current finding that platinum chemotherapeutics are substrates of OATP1B1 and OATP1B3 sheds new light on the mechanistic basis for the liver uptake process. It should be pointed out that, using rat hepatocytes in primary culture, the kinetics of platinum uptake process of platinum uptake in the liver. For example, a carrier system with low affinity and high capacity, such as the drug efflux pump P-glycoprotein, may be involved in the transfer of cisplatin into the intracellular compartment of hepatocytes.

The rodent Oatp1b2 transporters share approximately 64% amino acid sequence homology to human OATP1B1 and OATP1B3, and on the basis of their shared basolateral localization in hepatocytes and overlapping substrate specificity (38), it is possible that in rodents Oatp1b2...
fulfills the same function in the liver as OATP1B1 and OATP1B3 in humans. Based on this premise, we evaluated the pharmacokinetic properties of cisplatin in a mouse model with a genetic deletion of Oatp1b2. One possible limitation of this model is the fact that, unlike in humans, mouse hepatocytes express multiple members of Oatp1a, a related subfamily of transporters that can potentially provide compensatory restoration of function when Oatp1b2 is lost (39). Despite this limitation, compared with wild-type mice, the liver uptake of cisplatin in the Oatp1b2(−/−) mice was significantly decreased. Gene expression profiling in liver samples excluded alterations in alternate transport mechanisms or metabolic pathways as a possible cause of this phenotype in Oatp1b2(−/−) mice. These findings suggest that Oatp1b2-mediated transport of cisplatin is an important rate-limiting process in the elimination of this drug in mice. Nonetheless, considering the relatively low amino acid homology between OATP1B1 or OATP1B3 and Oatp1b2, additional investigation is required using humanized models for these proteins to provide direct evidence for involvement of OATP1B-type carriers in the hepatic uptake of cisplatin.

Interestingly, the altered liver distribution of cisplatin in the Oatp1b2(−/−) mice was associated with a shunting of drug into urine. A similar phenomenon has been reported previously for the anticancer and antirheumatic drug methotrexate, where deficiency of Abcc2 (Mrp2), a transporter regulating biliary secretion of this agent, is associated with increases in the extent of urinary excretion compared with wild-type mice (40). Although additional investigation will be required to assess the pharmacodynamic implications of this phenomenon, the observations made in the mice provide further evidence that hepatic OATP1B-type transporters can affect the pharmacokinetic properties of a remarkably broad range of substrates that include charged organic anions (e.g., methotrexate), charged organic cations (e.g., lapatinib), polar zwitterions (e.g., fexofenadine), uncharged hydrophobic agents (e.g., taxanes), and chemically diverse platinum chemotherapeutics.

Collectively, our demonstration that OATP1B-type transporters play an important role in the cellular uptake of platinum chemotherapeutics reveals new tumor and host factors that potentially contribute to enhanced inter-individual variation in the efficacy and tolerability to this class of drugs.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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Conception and design: C.S. Lancaster, A. Sparreboom
Development of methodology: A.L. Walker, S. Hu
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): C.S. Lancaster, J.A. Sprowl, A.L. Walker, S. Hu, A.A. Gibson
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): C.S. Lancaster, J.A. Sprowl, A.A. Gibson, A. Sparreboom
Writing, review, and/or revision of the manuscript: C.S. Lancaster, J.A. Sprowl, S. Hu, A. Sparreboom
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): A.A. Gibson
Study supervision: A. Sparreboom

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References

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