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Journal of Pharmacology & Clinical Toxicology

Review Article

OATP Transporters: Potential Targets for Enhancing Organ and Tissue Specific Drug Delivery

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Submitted: 24 October 2014

Accepted: 18 November 2014

Published: 20 November 2014

ISSN: 2333-7079

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Keywords

- Organ-specific drug delivery
- OATP transport
- Drug disposition processes
- Drug efficacy

Abstract

Drug transporters are increasingly recognized for their role in organ-specific drug entry. Among a group of transporters known as uptake transporters which mediate the cellular influx of substrate compounds, members of the Organic Anion Transporting Polypeptide (OATP) family are of particular relevance to targeted drug delivery. Certain members of the OATP transporters have broad substrate specificity. Indeed, structurally divergent compounds ranging from anionic, neutral, zwitter ionic, as well as cationic compounds have been noted to be efficiently transported by OATPs. Moreover, certain members of the OATP transporters such as OATP1B1 and 1B3 are known for their liver-enriched expression pattern. They have already been demonstrated to be of relevance to efficacy and toxicity for the HMG-CoA reductase inhibitor class of lipid lowering drugs. A number of OATPs are expressed in organs such as the brain, kidney, and certain cancer cells.

For this review, a search of the literature regarding past and current concepts in OATP transport was carried out. Herein, a focused discussion of specific OATP isoforms was conducted where the expression, function, and substrate selectivity of OATPs provide the basis for considering how such transporters may be used to facilitate drug delivery. Potential benefits as well as challenges that face OATP-mediated drug targeting and delivery are also outlined.

ABBREVIATIONS

HMG-CoA: 3-hydroxy-3-methylglutaryl coenzyme A

INTRODUCTION

There is increasing recognition of the importance of organ-specific drug delivery as a way for optimizing drug efficacy. Indeed, the ability to more specifically target organs such as the brain, would then allow for enhanced efficacy of drugs designed to modulate central nervous system specific or enriched targets such as neurotransmitter transporters and receptors. The need for targeted drug delivery is further compounded by the often profound inter-subject variation in the expression and activity of drug disposition pathways which manifest as marked variation of the pharmacokinetic profile of such drugs when assessed in a real-world clinical setting. Although drug metabolizing enzymes and transporters are systematically assessed during the drug development process, particularly for predicting the in vivo PK profiles and drug interactions risk, we are now starting to see that drug transporters can also be targeted for drug delivery and efficacy. Although in humans a large number of transporters are expressed, one family of drug transporters known as organic anion transporting polypeptide (OATP) has garnered significant interest for its demonstrated ability for mediating organ-specific drug uptake.

ORGANIC ANION TRANSPORTING POLYPEPTIDES

Organic anion transporting polypeptides (OATP) refer to a super-family of membrane-bound transport proteins that are responsible for the sodium-independent uptake of a variety of endogenous and exogenous compounds into the cell. They are encoded by *SLCO* genes (Table 1). OATPs within the same family share a largely homologous structure, with 12 trans-membrane domains and >40% common amino acid sequence [1]. To date, rat Oatp-mediated substrate uptake appears to occur via anion exchange; substrate uptake appears to be coupled to the export of endogenous intracellular ions such as bicarbonate. For human OATPs, the precise mechanism has not been well-characterized, although there is data from Kobayashi et al [2] that suggests anion exchange may play a role in human OATP2B1 transport.

Further research is needed to better elucidate the physiologic mechanism by which OATP-mediated transport occurs. There are eleven members of the OATP family including OATP1A2, 1B1, 1B3, 1C1, 2A1, 2B1, 3A1, 4A1, 4C1, 5A1, and 6A [3-22] (Table 1). OATPs have broad substrate specificity that include endogenous compounds as well as a wide variety of therapeutic agents such as HMG-CoA reductase inhibitors, chemotherapeutics, ACE-inhibitors and anti-microbials (Table 2) [17, 23]. Expression of OATPs tend to be polarized to specific cell membrane domains, either the apical or basolateral membrane of cells in organs in such as brain, kidney, liver, intestine, testes and heart [24].

More detailed information continues to emerge regarding the transcriptional regulation of the various OATP transporters. As an example, transcriptional regulation of OATP1B1 has been linked to the activity of hepatocyte nuclear factor 1 α (HNF1α). In vitro models have shown that HNF1α increases SLCO1B1 activity significantly and that mutations in HNF1α are linked to complete abolition of SLCO1B1 activity [25,26]. Similarly, HNF1α, HNF3β and HNF4α transcriptionally regulate OATP1B3 while constitutive expression of OATP2B1 in the small intestine is dependent on the Sp1 transcription factor [27-29].

OATPs FOR DRUG DELIVERY

The efficacy of an oral drug is influenced by its physicochemical properties which determines the extent of its absorption, distribution, metabolism, and excretion [30]. We now recognize that the true extent of drug absorption, distribution and excretion is highly affected by carrier mediated processes, broadly referred to as drug transporters. Drug transporters facilitate the movement of substrate drugs across physiologic membranes, such as from the gut lumen into enterocytes then subsequently into the portal circulation. This is followed by transporter-mediated uptake into hepatocytes and subsequent excretion into bile. Drug transporters including the members of the OATP family may facilitate or prevent the movement of substances to a degree that rivals the effect of metabolizing enzymes on drug efficacy [31]. Among the various OATP isoforms, OATP1A2, 1B1, 1B3 and 2B1 display the largest range of exogenous substrate specificity and thus appear to play an important role in the overall drug disposition process.

OATPs for enhancing drug delivery to liver: Liver-specific OATPs

OATP1B1 and 1B3 are two of the best characterized OATPs. They are considered to be liver-specific in their expression, although low levels of these transporters, particularly OATP1B3 can be detected in normal intestine (Table 1) as well as in colon cancer [32] and more recently in pancreatic β-islet cells [33]. OATP1B1 and 1B3 exist at the sinusoidal membrane of the hepatocyte, en face with the central veins, allowing substrates access from the portal circulation. OATP 2B1 is also expressed on the basolateral domain of hepatocytes; however, it has much more limited drug substrate specificity. Other OATPs including 3A1, 1A2, and 4A1 also exist in the liver in descending degrees of expression (Table 1) [34]. However, the in vivo relevance of such OATPs to hepatic drug disposition remains to be clarified.

OATP1B1 and 1B3 have been widely studied particularly in relation to the disposition of the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, also known as statins [35-38] (Figure1). These OATP transporters allow HMG-CoA reductase inhibitors to gain access to the hepatocyte and subsequently target liver HMG-CoA reductase, competitively inhibiting cholesterol synthesis and effectively reducing the progression of vascular disease [35,39]. Changes in the degree of expression or activity of these uptake transporters may alter the efficacy as well as the potential toxicity of HMG-CoA reductase inhibitors [26], though this has not been demonstrated for all statins. Thus, HMG-CoA reductase inhibitors have become a model for targeted drug delivery via OATP transporters in the hepatocytes.

The co-administration of OATP inhibitors or loss of function *SLCO* genetic variants are known to play an important role in the transport of OATP substrates. A number of commonly occurring single nucleotide polymorphisms (SNPs) in OATP1B1 and 1B3 are associated with loss of transport activity for various HMG-CoA reductase inhibitor lipid-lowering medications [37,38]. Not surprisingly, reduced activity of these hepatic OATPs have been linked to alterations in substrate drug disposition and efficacy [40]. In vitro as well as in vivo, OATP1B1 has been the most extensively studied. For OATP1B1, multiple SNPs are associated

Table 1: OATP Family (11 members with tissue distribution and reference).

Transporter	Gene Symbol	Tissue	References
OATP1A2	*SLCO1A2*	Brain, cholangiocytes, kidney	[4-6]
OATP1B1	*SLCO1B1*	Liver, intestine	[6,7]
OATP1B3	*SLCO1B3*	Liver, pancreas, intestine	[6,8,22]
OATP1C1	*SLCO1C1*	Brain, testis, ciliary body	[9,10]
OATP2A1	*SLCO2A1*	Ubiquitous	[11-13]
OATP2B1	*SLCO2B1*	Liver, heart, intestine, ovary, testis, spleen, ciliary body	[6,14,15]
OATP3A1	*SLCO3A1*	Ubiquitous	[16-18]
OATP4A1	*SLCO4A1*	Ubiquitous	[9]
OATP4C1	*SLCO4C1*	Kidney	[19]
OATP5A1	*SLCO5A1*	Lactiferous ducts in breast	[20]
OATP6A1	*SLCO6A1*	Testis	[21]

Abbreviations: OATP: organic anion transporting polypeptide; *SLCO*: solute carrier gene family

Table 2: Substrates of OATP.

Transporter	Endogenous Substrate	Exogenous Substrates^
OATP1A2	Bile acids*; conjugated steroids[¥]; thyroid hormones[Φ]	Erythromycin; fexofenadine; imantinib; levofloxacin; methotrexate; ouabain; pitavastatin; rocuronium; rosuvastatin; saquinavir; unaprostone
OATP1B1	Bile acids; conjugated steroids[¥]; eicosanoids; thyroid hormones[Φ]	Atorvastatin; atrasentan; benzylpenicillin; bosentan; caspofungin; cerivastatin; enalapril; ezetimibe; fexofenadine; fluvastatin; methotrexate; olmesartan; pitavastatin; pravastatin; rifampicin; rosuvastatin; SN-38; temocapril; troglitazone; valsartan
OATP1B3	Bile acids*; bilirubin; cholecystokinin; conjugated steroids[¥]; eicosanoids[o]; thyroid hormones[Φ]	Atrasentan; bosentan; digoxin; docetaxel; enalapril; erythromycin; fexofenadine; fluvastatin, imantinib; methotrexate; olmesartan; ouabain; paclitaxel; pitavastatin; pravastatin; rifampicin; rosuvastatin; telmisartan; SN-38; thyroxine, valsartan
OATP1C1	Thyroid hormones[Φ]	Unknown
OATP2A1	Prostaglandin	Unknown
OATP2B1	Conjugated steroids[¥]; prostaglandin E2	Atorvastatin; benzylpenicillin; bosentan; fexofenadine; fluvastatin; glibenclamide; pravastatin; rosuvastatin; unaprostone
Transporter	**Endogenous Substrate**	**Exogenous Substrates^**
OATP4A1	Conjugated steroid[¥]; prostaglandin; thyroid hormones[Φ]	Benzylpenicillin
OATP4C1	thyroid hormones[Φ]	Digoxin; methotrexate
OATP5A1	Unknown	Unknown
OATP6A1	Unknown	Unknown

*Bile acids include cholate and taurocholate; [¥]conjugated steroids include estradiol-17β-glucoronide, estrone-3-sulfate, dehydroepiandrosterone-3-sulfate; [o]eicosanoids include leukotrienes C4 and E4, prostaglandin E2, thromboxane B2; [Φ]thyroid hormones include thyroxine and triiodothyronine (Kalliokoski and Niemi 2009). ^Exogenous substrates adapted from Shitara, Maeda et al. (2013)[23] and Kalliokoski and Niemi (2009).
Abbreviations: OATP: organic anion transporting polypeptide

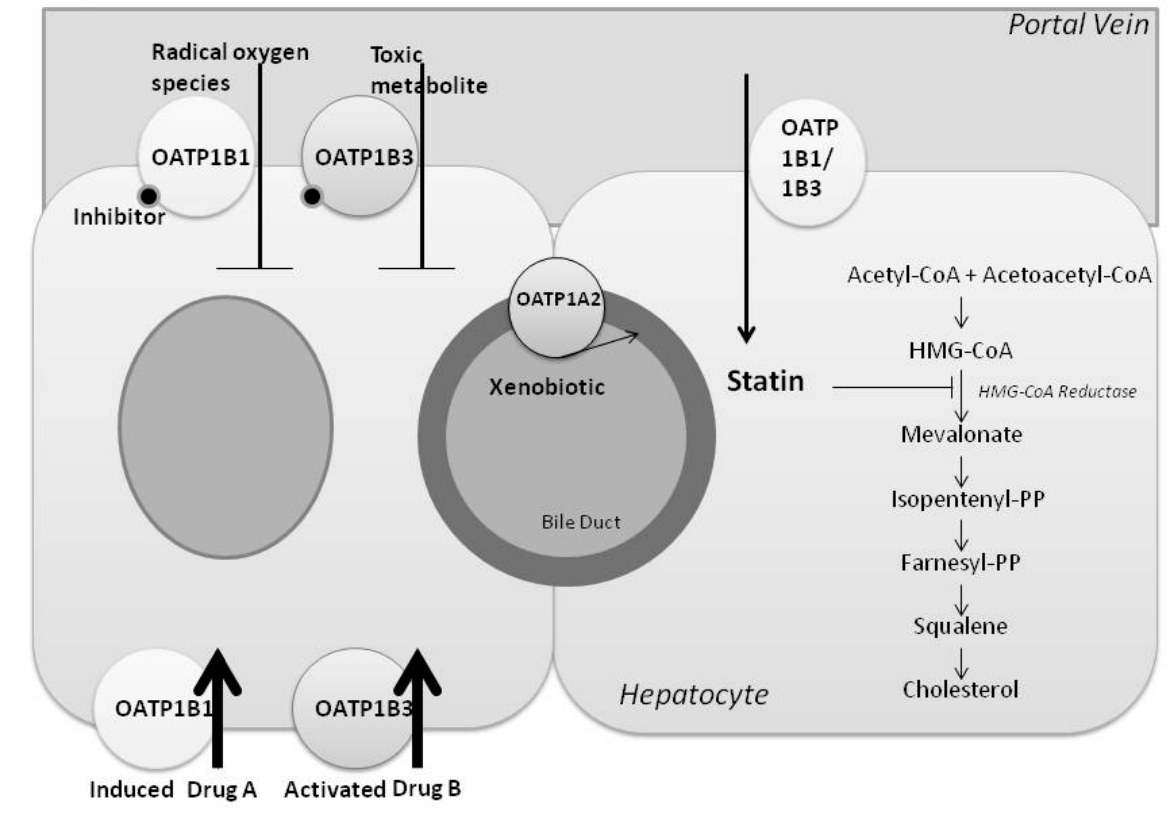

Figure 1 Possible mechanisms of OATP-mediated, liver-targeted therapy. OATP1B1 or 1B3-specific drugs would allow for hepatocyte-targeted therapy. OATP1B1 or 1B3 inducers or activators could enhance delivery of hepatic OATP-specific drugs to the hepatocyte. Inhibitors of OATP1B1 or 1B3 could reduce or prevent hepatocyte-specific injury mediated by bile acids or other toxic metabolites. OATP1A2 mediates the transport of xenobiotics excreted in the bile to be taken up by the cholangiocytes lining the bile ducts. HMG-CoA reductase inhibitors provide a real-life example of OATP-mediated liver targeted therapy.

with decreased substrate uptake resulting in lower hepatic concentrations of drugs such as HMG-CoA reductase inhibitors and methotrexate [41-44]

The frequencies of SNPs vary by population with 40% of Europeans, 80% of sub-Saharan Africans and 80% of East Asians expressing the variant C388A>G allele. Similarly, 10-20% of Europeans, 10-20% of Asians and 2% of sub-Saharan Africans express the variant C521T>C allele [17,45]. In combination, these create four functionally distinct haplotypes, with 3 of the 4 haplotypes displaying reduced activity [17,40].

This concept extends beyond HMG-CoA reductase inhibitors to include alterations in the disposition of other medications. In Oatp1a-/1b2- knockout mice exposed to methotrexate and fexofenadine, there was a dramatic reduction in hepatic uptake of and a subsequent increase in systemic exposure to both medications [46]. Conversely, induction of OATP1B1 and 1B3 may allow enhanced hepatic drug uptake. This was shown in a recent study by van de Steeg e*t al* [47] where humanized OATP1B1 and 1B3 transgenic mice could "rescue the [hepatic] uptake" of bilirubin glucoronides as well as anti-cancer medications such as methotrexate and paclitaxel.

Liver-targeted drug delivery could play a significant role in the treatment of liver disease (Figure 1). Liver disease is a major cause of morbidity and mortality in North America. One of the limiting factors in the treatment of liver disease is the myriad of diseases that exist and the difficulty of targeting and accumulating drug within the appropriate liver cell. Hepatic OATP-targeted therapy could allow the accumulation of the appropriate substrate within the hepatocyte.

This is relevant to disease affecting the hepatocyte such as the viral hepatitides, alcoholic and non-alcoholic fatty liver diseases as well as other rarer diseases. Studies of the asialoglycoprotein receptor (ASGP-R), another hepatocyte membrane bound target receptor for liver-targeted drug delivery, have successfully demonstrated its use for delivering therapeutic substances such as anti-viral medications and cancer therapies to the isolated hepatocyte [48].

Furthermore, in primary biliary cirrhosis (PBC), an autoimmune disease of the intrahepatic bile ducts, bile acid uptake and retention has been defined as a key mediator of immune system activation as well as hepatocyte "foamy" degeneration and hepatoxocity [49]. Theoretically, one may hypothesize that inhibition of OATP1B1 and 1B3 would decrease the uptake of naturally-occurring bile acids that are mediating this toxic event. OATP1B1 and 1B3 are known to be key transporters for sodium-independent uptake of bile acids into liver. This could be a potential therapeutic target.

However, this has not been supported in the literature thus far. Unfortunately, OATP1B1 and 1B3 expression in various liver diseases has not been well characterized. There is data from small patient cohorts to suggest that OATP expression is altered in the setting of liver disease. Ogasawara *et al* found that OATP1B1and 1B3 mRNA expression was decreased in the setting of hepatitis C infection with or without cirrhosis [50]. Furthermore, Oswald *et al* found that OATP1B1 mRNA expression was reduced in four patients with primary sclerosing cholangitis (PSC) [51]. Kojima *et al* found that OATP1B1 mRNA and protein expression were significantly reduced in advanced primary biliary cirrhosis (PBC) [52]. Furthermore, cirrhosis in rats has been linked to reduced hepatic Oatp expression [53]; however, this has not been shown in cirrhosis in humans across all causes. From this, it can be concluded that larger studies are needed to characterize OATP expression by type and severity of liver disease before evaluating its effectiveness as a drug target.

OATPs for delivery of anticancer drugs

OATPs appear to play an important role in anti-cancer therapy. They mediate the uptake of many clinically important hormones as well as anti-cancer drugs such as methotrexate, SN-38, paclitaxel and imatinib (Table 2). Therefore, for cancer cells which express OATPs, utilization of OATP anti-cancer drug substrates may result in better prediction of response to such agents due to the enhanced accumulation of such therapeutic agents in those cancer tissues.

However, it should be noted that the pattern of OATP expression in malignant tumours does not emulate the expression of OATPs in normal tissue. As an example, the presence of OATP1A2 has been confirmed in the brain, kidney and bile ducts of the liver; however, it is absent in neoplasms of the brain and colon and yet detected in high concentrations in neoplasms of the breast and prostate [22,54-56]Furthermore, OATP1B1 and 1B3, which are relatively specific to hepatic tissue, tend to be down-regulated in hepatocellular carcinoma (HCC) [57,58]. They also tend to be expressed in a wide variety of neoplastic tissues in which they would not normally be found such as breast, prostate and a number of gastrointestinal tract tumours such as pancreas, stomach and colon [59-61]

Certain OATPs have been shown to be up- or down-regulated in many cancers such as testicular, prostate, and colon cancer, leading to potentially important biomarkers of malignancy presence and stage [62]. Lee *et al* demonstrated in vivo that cells derived from colorectal adenocarcinomas over-express OATP1B3 mRNA and protein in comparison to normal enterocytes from the same subject [32]. Similarly, Wlcek *et al* demonstrated increased expression of OATP2B1 in breast cancer in comparison with non-cancerous breast tissue [63]. In vitro studies have demonstrated that OATP2B1 as well as other OATPs are high affinity transporters of conjugated estrogens that are important for the growth of hormone-dependent breast cancers; thus over-expression of OATP2B1 and others could lead to excessive proliferation of cancer cells [64].

Furthermore, *in vitro*, the activity of certain OATP transporters has been shown to be influenced by the pH of their environment. OATP2B1 is capable of HMG-CoA reductase inhibitor transport at a neutral pH; however, it demonstrates increased substrate specificity as well as activity at an acidic pH [65]. Another study using *in vitro* models, showed that the activity of OATP1B1 and 1B3 are significantly altered by changes in pH, with 1B1 showing a decrease in activity with decreasing pH and 1B3 showing increasing activity with decreasing pH [66,67]

This has important implications for drug delivery in malignancy. The microenvironment in which tumours exist, made up of a complex of blood vessels, immune cells, cytokines

and other molecular structures is often acidic [68]. This is the result of tumour tissue hypoxia as it outgrows its blood supply leading to anaerobic glycolysis and the production of lactate.

In a review by Obaidat *et al*, the authors hypothesized a variety of ways in which treatment of certain cancers could be mediated through alteration of OATP expression and activity [69]. This includes the prevention of OATP-mediated hormone uptake in malignant tissues by OATP inhibitors, the designing of anti-cancer OATP-selective substrates with resultant enhanced uptake in cancerous tissue that over-express OATPs as well as the enhanced OATP-mediated anti-cancer drug uptake through drugs which further stimulates the activity of this transporter. It should be noted however, modulation of OATP substrate transport has not yet been validated in a clinical setting, particularly in terms of outcomes for oncology patients. Clearly additional research is needed.

Furthermore, possible limitations should be noted with respect to targeting OATPs that are co-expressed in cancerous cells as well as in normal tissues. Theoretically, in the case of OATP1B3, the use of anti-cancer OATP-targeted substrates in OATP1B3-expressing colon cancers, the simultaneous expression of hepatic OATP1B3 may lead to early removal of the treatment drug from the circulation and ineffective cancer treatment. Also, in the case of OATP2B1, targeting this OATP in breast cancer may lead to toxic accumulation of anti-cancer drug in the enterocyte and subsequent patient morbidity.

OATPs for enhancing gut drug absorption

OATP2B1 likely plays a role in the absorption of substrates from the GI tract [15,70] OATP2B1 is concentrated at the apical membrane of the enterocytes near the villous tip [2]. In the past, another transporter known as OATP1A2, was suspected to be similarly distributed along the apical membranes of the intestinal epithelial cells, though expressed in negligible amounts [15,71]. More recently, however, proteomic analysis by Groer *et al* has shown that while OATP2B1 is observed at similar concentrations in the small intestine as what has been seen in past studies, OATP1A2 protein was not detectable using mass spectrometry [72]

Thus, the impact of OATP2B1 may have clinical relevance with respect to drug disposition. Given its locations, OATP2B1 likely acts in concert with other membrane transporters such as the efflux protein, P-glycoprotein, the breast cancer resistance protein (BCRP), the peptide transporter, PEPT1 as well as several other efflux and influx transporters and influence the intestinal absorption of shared substrates [70]. Although inhibition of OATP2B1 could lead to marked changes in systemic exposure to exogenous substances that are substrates of this transporter, the clinical relevance of inhibitors of OATPs to intestinal substrate drug absorption needs additional research.

As noted previously, OATP2B1 transport activity is pH-dependent, with increased activity at lower pHs [73]. This observation has been duplicated in vitro, whereby HMG-CoA reductase inhibitors had enhanced OATP2B1 activity in the intestine at acidic pHs [65]. In healthy small bowel, the luminal pH is weakly acidic proximally with values ranging between 5.5-7 and increasing distally to 7.5 near the terminal ileum. In healthy colon, luminal pH is again weakly acidic on the right side (pH 5.5-7.5) and increasing to 6.5-7.5 at the rectum [74]. In most reports on pH values in diseased bowel, such as in active Crohn's disease or ulcerative colitis, colonic luminal pH is reduced from as low as 3 up to values of 6 as a result of many factors including decreased mucosal secretion of bicarbonate, increased mucosal and bacterial production of lactate and altered short chain fatty acid absorption [74]. Luminal pH affects net intestinal OATP2B1-mediated drug transport may be clinical significance, particularly in the setting of intestinal diseases; however, its clinical relevance has yet to be elucidated. One could speculate by optimizing a weakly acidic intraluminal environment, one could enhance the uptake of OATP substrates from the gut. Moreover, the presence of luminal disease could significantly impact an individual's systemic exposure to a drug; therefore, data assessing the pharmacokinetics of a drug in a healthy volunteer population should not be extrapolated to this patient population.

Genetic variation also exists in OATP2B1, though not as extensively as is seen with OATP1B1 or 1B3. Only a few variants have been identified and currently, conflicting data have been presented between *in vivo* and *in vitro* studies. Mougey *et al* demonstrated that montelukast is an *in vitro* substrate of OATP2B1 and that the single nucleotide polymorphism (SNP) c935G>A is associated with decreased drug plasma levels as well as reduced clinical response [75]. The same group later affirmed that montelukast is a substrate of OATP2B1 and that SNP c935G>A plays a role in montelukast plasma levels; however, they could not demonstrate any clinical relevance with respect to patient outcomes [76]. Conversely, other groups have failed to show that variants of OATP2B1 including c935G>A alter the plasma levels of other known OATP2B1 substrates such as aliskren [77]. Thus, while such SNPs may play a role in inter-individual variability in intestinal drug absorption, more research in this area is needed [40].

OATPs for enhancing CNS drug delivery

OATP1A2 and 1C1 have been localized to the brain among other tissues (Figure 2, Table 1). OATP2A1, 3A1 and 4A1 are ubiquitously expressed (Table 1). OATP transporters are found in the endothelial cells of the blood-brain barrier as well as in the epithelial cells of the blood-cerebrospinal fluid (CSF) barrier [13,78,79]. The role of OATP transporters in concert with efflux transporters such as P-gp at these sites likely mediate the CNS uptake of hormones such as thyroxine (T4 and T3) as well as limit the entry of xenobiotic with potential risk for CNS toxicity [80,81]. The idea that the modulation of OATP transport may be a viable option for brain-targeted therapy has been considered by several groups though has not been consistently demonstrated *in vivo* or *in vitro* and results remain conflicting. Tournier *et al* conducted an in vivo study in baboons where the tissue distribution was assessed using positron emission tomography [82]. Glyburide is an *in vitro* substrate of OATP1A2, 2B1 and 1B1. They found that cerebral uptake of glyburide was not influenced by OATP inhibition in baboons. Thompson *et al* who set out to address the need for improved CNS delivery of brain protective drugs across the blood-brain barrier, used a mouse model to demonstrate that the mouse Oatp1a4 transporter, equivalent to human OATP1A2 [83], is upregulated in the setting of a hypoxic

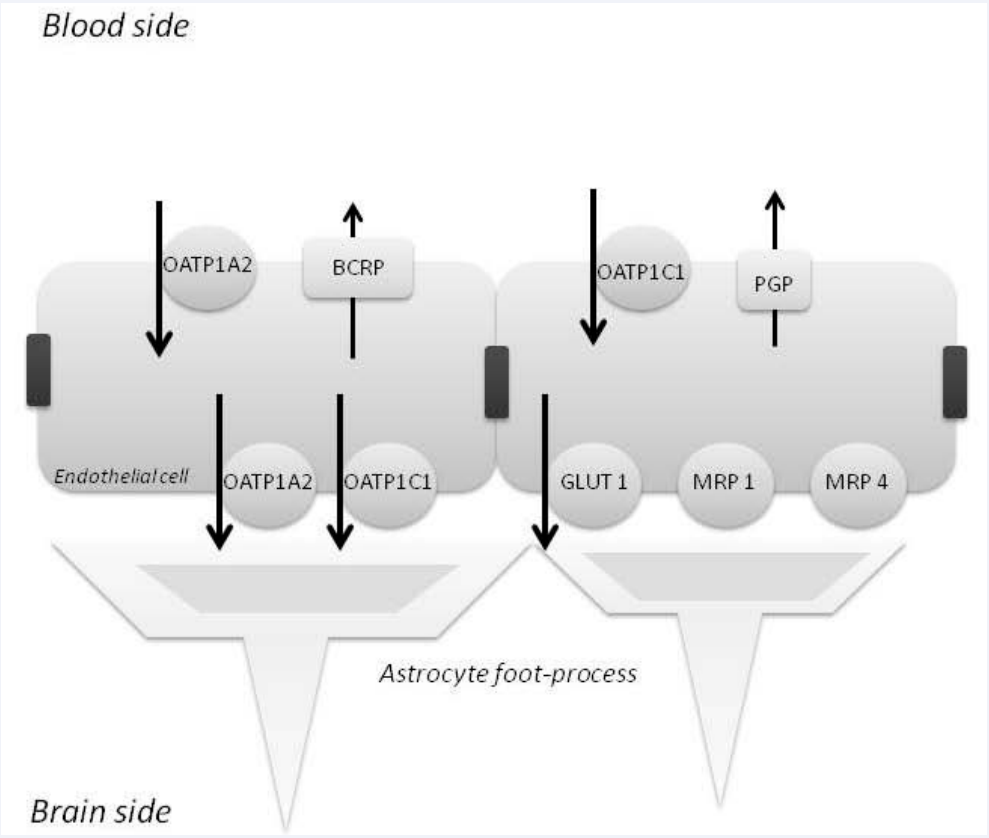

Figure 2 OATP-mediated regulation of the blood-brain barrier. OATP and other transporters such as P-glycoprotein (P-gp) likely function together facilitate or limit the CNS entry of endogenous substrates as well xenobiotic compounds. Note that the role of OATP in drug delivery to the brain remains controversial.

brain and reperfusion injury and that atorvastatin [84], an HMG CoA reductase inhibitor with brain protective effects seen in mouse models of ischemic or hemorrhagic brain injury [84,85] exhibited enhanced CNS entry.

Furthermore, Bronger *et al* focused on the role of OATP transporters in the treatment of brain tumours such as gliomas [54]. They noted expression of 6 OATPs (OATP1A2, OATP1B1, OATP1B3, OATP1C1, OATP2B1, and OATP4A1) in the blood-brain barrier, the blood-tumour barrier and human gliomas. They found that only the protein products of OATP1A2 and 2B1 were localized to the blood-tumour and blood-brain barrier, while none of the 6 listed OATP proteins were found in the glioma cells. This suggests a different mechanism by which xenobiotics are taken up by gliomas and highlights why OATP targeting is an unlikely therapeutic option in glioma management.

Overall, the role of OATP transporters in the brain has not been well defined and further studies are needed to elucidate their potential as drug targets in efforts to enhancing drug uptake at the level of the blood-brain barrier.

Inhibition of OATPs in reducing toxicity: Example from mushroom poisoning

Of the thousands of mushroom species that exist across the globe, less than 0.5% are toxic upon ingestion and very rarely do they cause death in North America [86]. Amatoxin, a substance present in 35 species of mushrooms across 3 different genera, is responsible for the deleterious mushroom poisoning effects [87]. Individuals often present with a biphasic illness characterized by an early and severe gastroenteritis with eventual culmination to fulminant hepatic failure requiring orthotopic liver transplantation if left untreated [86].

After oral ingestion, amatoxins are absorbed through the wall of the gastrointestinal tract and are transported to the liver. Uptake into individual hepatocytes from the portal system is mediated through OATP1B3 and the sodium taurocholate co-transporter (NTCP). Amatoxin-mediated toxicity then results via inhibition of RNA polymerase II which interrupts protein synthesis within the hepatocyte and causes early cell death [88,89]. The high affinity and capacity uptake of amatoxin by these liver-specific transporters provide the mechanism by which mushroom poisoning result in severe liver injury while sparing other organs such as the brain and kidney.

In addition to the standard measures of care in the setting of acute poisoning, several therapies have been examined in vitro and in vivo with success seen with inhibitors of OATP1B3 transport. Silibinin and penicillin G are known inhibitors of OATP1B3 and inhibit uptake of amatoxin into the hepatocyte. These substances show the most success in improving mortality in patients with amatoxin-poisoning [90,91]. In vitro studies also exist demonstrating that other OATP1B3 inhibitors such as cyclosporin A, rifampin and paclitaxel prevent the uptake

of amatoxin by OATP1B3 [88]. Thus the spectrum of potential medications for treatment of this condition may expand in the future.

DISCUSSION AND CONCLUSION

It is now becoming clear that transporters that mediate the uptake and efflux of substrate compounds, including many drugs in clinical use have the potential to be therapeutic targets. This is of particular relevance to organs such as the brain, where the blood-brain-barrier limits the CNS entry of a large number of structurally divergent drugs. Through targeting drug uptake transporters, particularly OATPs, which have broad substrate specificity, it is conceivable that a more CNS selective drug delivery may be feasible. However, the notion of OATP transporters as targets for drug delivery is relatively new. Although drugs such as statins clearly demonstrate the feasibility as well as clinical benefit, such drugs were not initially designed with OATPs in mind. A more systematic inclusion of OATPs earlier in the drug development process is needed, if the goal is organ or tissue specific targeted delivery.

A number of hurdles and challenges remain. OATP transporters appear to have significant species-dependent differences in expression as well as substrate specificity. Therefore in vitro assessment that includes multiple OATPs from various species including humans will be important to gain an understanding of the potential for human OATP isoforms that may be suitable targets for drug delivery. In addition, although various Oatp knockout mice are becoming available, models which lack murine Oatps but transduced to express human isoforms are needed to better understand the in vivo relevance of potential OATP targeting compounds in development. Additional caveats which must be kept in mind relate to the role of genetic variation in OATP transporters as well as the relative impact of OATP-associated drug interactions.

Overall, the importance of OATP transporters continues to increase over time. Targeting specific OATP(s) has the potential to pay off in terms of in vivo drug response. Therefore, OATPs should be considered earlier in the drug discovery process particularly in the design of drugs which need access to organs such as liver and brain or relevant cancer cells.

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Cite this article

Wilson A and Kim RB (2014) OATP Transporters: Potential Targets for Enhancing Organ and Tissue Specific Drug Delivery. J Pharmacol Clin Toxicol 2(3):1037.