

Review

Enantioselective Drug Recognition by Drug Transporters

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Academic Editor: Maria Elizabeth Tiritan

Received: 25 October 2018; Accepted: 22 November 2018; Published: 22 November 2018



Abstract: Drug transporters mediate the absorption, tissue distribution, and excretion of drugs. The cDNAs of P-glycoprotein, multidrug resistance proteins (MRPs/ABCC), breast cancer resistance protein (BCRP/ABCG2), peptide transporters (PEPTs/SLC15), proton-coupled folate transporters (PCFT/SLC46A1), organic anion transporting polypeptides (OATPs/SLCO), organic anion transporters (OATs/SLC22), organic cation transporters (OCTs/SLC22), and multidrug and toxin extrusions (MATEs/SLC47) have been isolated, and their functions have been elucidated. Enantioselectivity has been demonstrated in the pharmacokinetics and efficacy of drugs, and is important for elucidating the relationship with recognition of drugs by drug transporters from a chiral aspect. Enantioselectivity in the transport of drugs by drug transporters and the inhibitory effects of drugs on drug transporters has been summarized in this review.

Keywords: drug transporter; enantioselectivity; transport; inhibition; pharmacokinetics

1. Introduction

Many drugs are chiral, and each enantiomer may exhibit specific therapeutic efficacy. For example, several nonsteroidal antiinflammatory drugs (NSAIDs) have an asymmetric carbon in their chemical structures, and the (*S*)-enantiomers exhibit stronger inhibitory potencies against cyclooxygenases [1]. The (*S*)-enantiomer of naproxen is commercially available. We examined the enantioselective effects of flurbiprofen on the disposition of lithium in rats, and demonstrated that the (*S*)-enantiomer, but not the (*R*)-enantiomer, decreased the renal clearance of lithium with the impairment of renal function [2]. The anticoagulant drug warfarin is also chiral. Warfarin is orally administered as the racemate and exhibits enantioselectivity not only in its pharmacological effects, but also in its pharmacokinetics. (*S*)-Warfarin has greater anticoagulant potency than the (*R*)-enantiomer [3]. (*S*)-Warfarin is metabolized by cytochrome P450 (CYP) 2C9, and the metabolism of the (*R*)-enantiomer is mediated by CYP1A2 and CYP3A4 [4]. The development of drugs with enantioselective pharmacokinetic properties, such as esomeprazole, has recently been accomplished. This proton pump inhibitor is the (*S*)-enantiomer of omeprazole, which is the racemate. Both enantiomers exert identical effects on H⁺, K⁺-ATPase [5], but exhibit different pharmacokinetic characteristics. The clearance of esomeprazole is lower than that of the (*R*)-enantiomer [6]. Furthermore, the metabolism of the (*R*)-enantiomer is mainly mediated by CYP2C19, which exhibits a genetic polymorphism, and the contribution of CYP2C19 to the metabolism of esomeprazole is negligible [6].

In 1988, CYP2D6 was the first cytochrome P450 enzyme whose cDNA was identified [7]. The cDNAs of organic ion transporters have been identified since the 1990s. These findings promoted research on the function and expression of drug transporters. Drug transporters are expressed in the plasma membranes of a number of cells including enterocytes, hepatocytes, brain microvascular endothelial cells, and renal epithelial cells, and facilitate the transport of drugs across the plasma membrane.

Drug transporters are now known to play important roles in the absorption, tissue distribution, and excretion of drugs. Previous studies reported enantioselective drug transport by drug transporters. Furthermore, the enantioselective inhibitory effects of drugs on drug transporters has been demonstrated.

Representative drug transporters functioning in the intestinal absorption, biliary excretion, and renal tubular secretion of drugs have been summarized in this review. The interactions between chiral drugs and drug transporters have also been discussed. Figure 1 shows the chemical structures of the chiral drugs described herein.

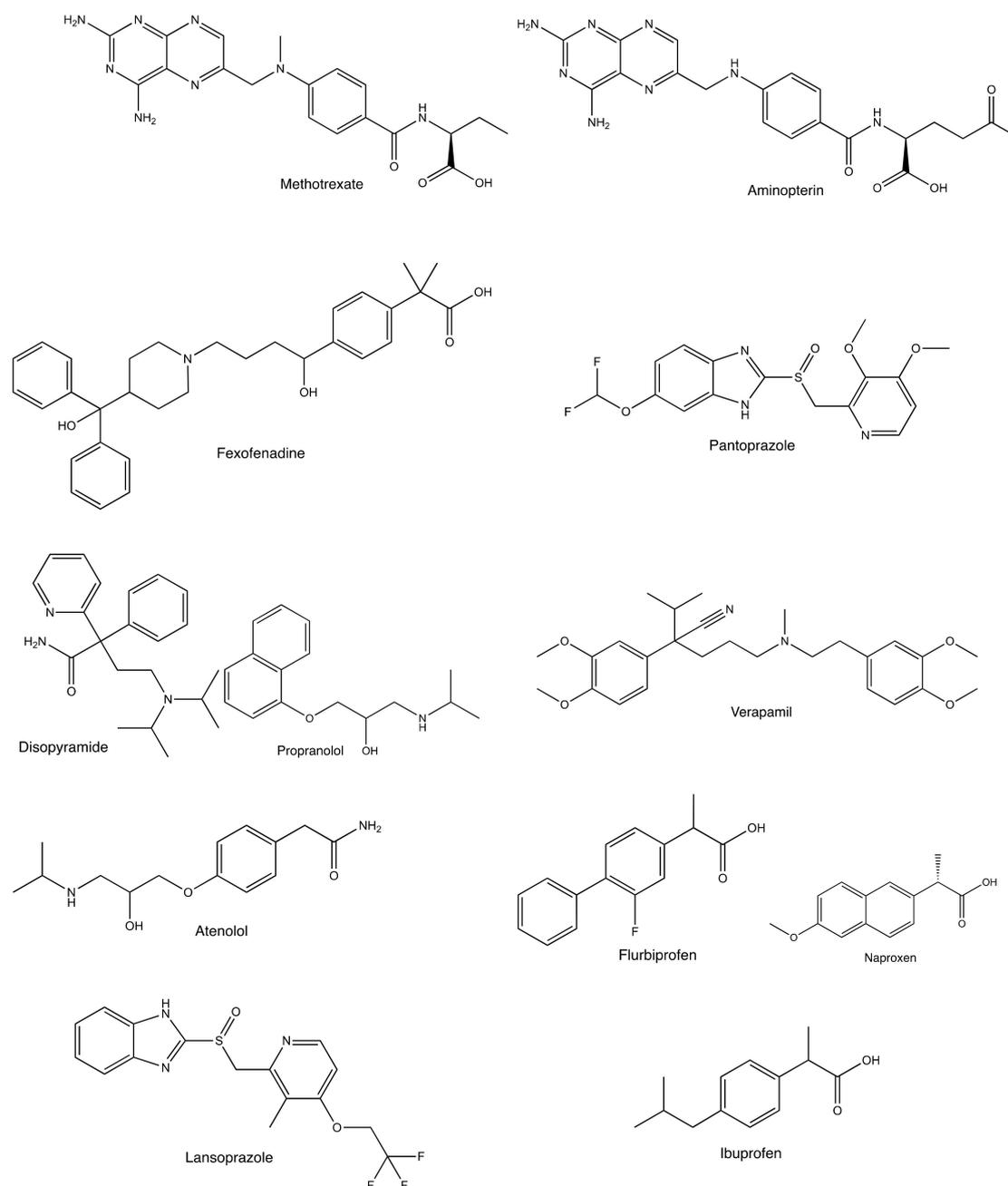


Figure 1. Chemical structures of chiral drugs described in this review.

2. Role of Drug Transporters in the Intestinal Absorption, Biliary Excretion, and Renal Tubular Secretion of Drugs

2.1. Intestinal Drug Absorption by Drug Transporters

Drugs are absorbed by the small intestine after their oral administration. Figure 2 shows drug transporters that are involved in the intestinal absorption of drugs. Peptide transporter PEPT1 (SLC15A1) is one of the most extensively studied drug transporters in the small intestine. It is expressed in the brush-border membrane of intestinal epithelial cells and is responsible for the uptake of dipeptides and tripeptides from the lumen using an inward H^+ -electrochemical gradient [8]. PEPT1 recognizes peptide-like β -lactam antibiotics that are orally administered [8]. PEPT1 is used as a target molecule for improving the absorption of poorly absorbed drugs. Valganciclovir, the valine ester prodrug of ganciclovir, was developed to enhance the low bioavailability of ganciclovir, and the mechanism responsible for improved absorption was identified as drug recognition by PEPT1 [9].

The proton-coupled folate transporter PCFT (SLC46A1) is localized to the brush-border membrane of enterocytes, and mediates the absorption of folate [10]. PCFT recognizes the antifolates, methotrexate and aminopterin, as its substrates [11,12]. Aminopterin has not yet been approved as a medicine, and methotrexate is used in the treatment of neoplasia and rheumatoid arthritis. PCFT is considered to play a role in the intestinal absorption of orally administered methotrexate [13].

The organic anion transporting polypeptide OATP2B1 (SLCO2B1), which is expressed in the brush-border membrane of intestinal epithelial cells, is crucially involved in the uptake of fexofenadine, celiprolol, and montelukast from the lumen [14,15].

P-glycoprotein (P-gp; ABCB1) and the breast cancer resistance protein BCRP (ABCG2) are ATP-binding cassette (ABC) transporter proteins that are expressed in the brush-border membrane of enterocytes. These transporters are efflux pumps. P-gp transports various types of drugs, including anticancer agents, antihypertensive agents, antiarrhythmics, antidepressants, antimicrobial agents, anti-human immunodeficiency virus agents, anticonvulsants, antiemetics, immunosuppressants, neuroleptics, and opioids, and there is a broad range of overlapping substrate specificities for CYP3A4 and P-gp [16]. BCRP has also been shown to transport anticancer agents [17]. The tyrosine kinase inhibitors, imatinib, gefitinib, and nilotinib, have also been identified as substrates of BCRP [18–20]. P-gp and BCRP prevent drug absorption in the intestine.

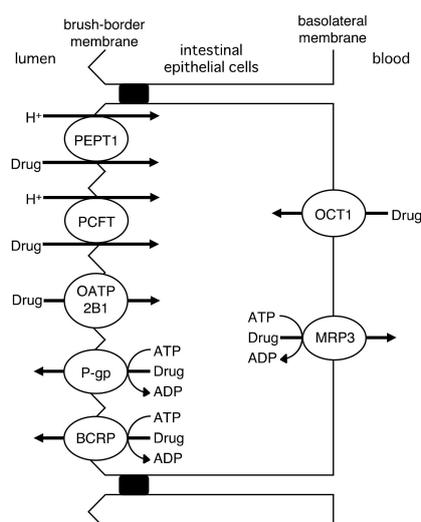


Figure 2. Drug transporters in the small intestine.

In the basolateral membrane, the organic cation transporter OCT1 (SLC22A1) and the multidrug resistance protein MRP3 (ABCC3) mediate drug transport [21]. In OCT1 knockout mice, the intestinal excretion of the typical substrate, tetraethylammonium, was reduced [22]. The serosal efflux of the

glucuronide conjugates of 7-ethyl-10-hydroxycamptothecin (SN-38: the active metabolite of irinotecan) and acetaminophen in the jejunal everted sacs was decreased in Mrp3 knockout mice [23].

2.2. Hepatic Transport of Drugs by Drug Transporters

Drug transporters in the plasma membrane of hepatocytes are shown in Figure 3. The OATP family members OATP1B1 (SLCO1B1) and OATP1B3 (SLCO1B3) mediate the hepatic uptake of various drugs, such as HMG-CoA reductase inhibitors, angiotensin II receptor antagonists, nateglinide, asunaprevir, pemafibrate, and bosentan, from the circulation [14,24]. OCT1 functions in the sinusoidal uptake of organic cations, including metformin, tropisetron, sumatriptan and fenoterol, from the circulation [25–28]. P-gp, MRP2 (ABCC2), BCRP, and multidrug and toxin extrusion MATE1 (SLC47A1), which are expressed in the canalicular membrane, mediate the efflux of drugs into bile [24]. MRP2, a member of the ABC family of transporters, excretes monoglucuronosyl bilirubin and monoglucuronosyl bilirubin into bile, and genetic mutations in MRP2 cause Dubin-Johnson syndrome, an autosomal recessive disease characterized by conjugated hyperbilirubinemia [29]. MRP3 is localized to the sinusoidal membrane of hepatocytes [30]. Kitamura et al. reported decreased plasma levels and increased clearance for the biliary excretion of methotrexate in MRP3 knockout mice, suggesting that MRP3 transports methotrexate from hepatocytes into plasma [31].

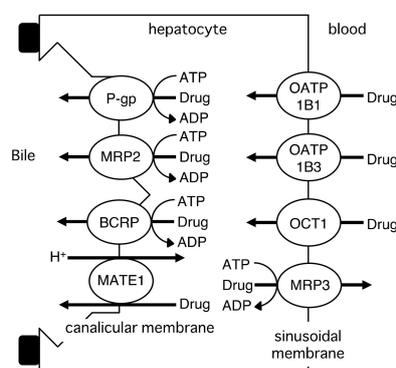


Figure 3. Drug transporters in the liver.

2.3. Renal Tubular Secretion of Drugs

The renal tubular secretion of drugs is mediated by drug transporters, as shown in Figure 4. Organic anion and cation transport systems are present in renal proximal epithelial cells. The organic anion transporter system is involved in the tubular secretion of anionic drugs, including anticancer agents, β -lactam antibiotics, antivirals, and diuretics [24,32]. The organic anion transporters OAT1 (SLC22A6) and OAT3 (SLC22A8) are responsible for the basolateral uptake of anionic drugs from the circulation via an exchange with intracellular α -ketoglutarate, an intermediate in the Krebs cycle. Information on the drug transporters responsible for mediating the efflux of drugs via the brush-border membrane of proximal epithelial cells is more limited than that on basolateral transporters. Studies using rat renal brush-border membrane vesicles indicated that a potential-sensitive organic anion transporter and an anion/organic anion exchange transporter function [33–35]. However, their genes have not yet been identified. Previous studies reported reductions in the urinary excretion of adefovir, tenofovir, hydrochlorothiazide, furosemide, ceftizoxime, and cefazolin in MRP4 knockout mice [36–38]. Based on these findings, MRP4 has been suggested to play an important role in drug transport in the brush-border membrane. MRP2 and OAT4 are known to be expressed in the brush-border membrane of proximal epithelial cells [39,40]. Although their interactions with drugs have been investigated in *in vitro* experiments, the roles of MRP2 and OAT4 in the tubular transport of drugs currently remain unclear.

The organic cation transport system consists of the uptake type of OCT2 (SLC22A2) and the efflux modes of MATE1 and MATE2-K (SLC47A2) [24,32,41]. Drug transport by OCT2 is electrogenic,

and is driven by an internal negative membrane potential. The efflux of drugs by MATE1 and MATE2-K is dominated by a H^+ /organic cation antiport, which involves electroneutral transport [41]. Cationic drugs, including cimetidine, metformin, procainamide, memantine, and amantadine, are secreted into urine by the organic cation transport system [32].

P-gp functions in the renal tubular secretion of the cardiac glycoside, digoxin [42]. Although a wide variety of drugs are transported by P-gp [16], most are not recovered into urine. The substrate drugs of P-gp may be reabsorbed by the distal tubules via simple diffusion after tubular secretion.

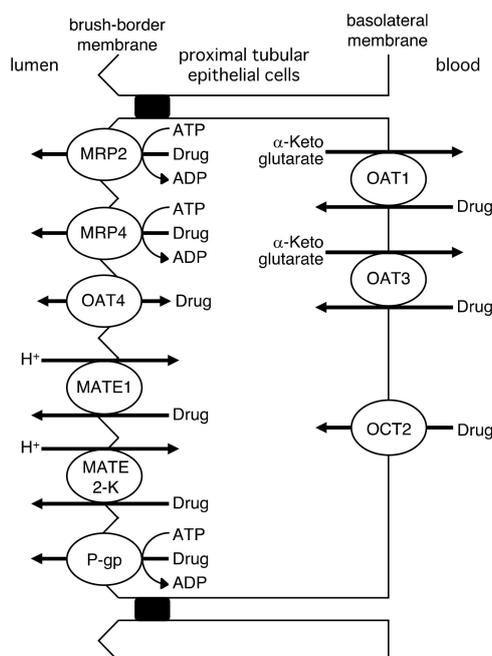


Figure 4. Drug transporters mediating renal tubular secretion drugs.

3. Enantioselective Drug Transport by Drug Transporters

3.1. Enantioselective Transport of Antifolates by PCFT

Previous studies reported enantioselectivity in drug transport by drug transporters, with PCFT as a representative. The antifolates methotrexate and aminopterin have an asymmetric carbon in their structures (Figure 1), and their enantioselective transport was examined. Narawa et al. constructed stably transfected human embryonic kidney cells 293 (HEK293 cells) expressing PCFT, and conducted a methotrexate uptake experiment using these cells [43]. Menter et al. examined aminopterin transport using Chinese hamster ovary (CHO) cells expressing PCFT [12]. The transport of both antifolates showed enantioselectivity, and kinetic parameters were summarized in Table 1. The (S)-enantiomers were found to have greater affinity to PCFT than each (R)-enantiomer. Menter et al. performed a pharmacokinetic study on aminopterin in dogs and patients with psoriasis, and the findings obtained revealed a correlation with enantioselective absorption and in vitro findings [12].

Table 1. Kinetic parameters of the PCFT-mediated transport of methotrexate and aminopterin.

Drug	K_m or K_t (R)-enantiomer	K_m or K_t (S)-enantiomer	K_m or K_t (R)/(S)	V_{max} (R)-enantiomer	V_{max} (S)-enantiomer	V_{max} (R)/(S)	Ref.
Methotrexate	211 μ M	4.98 μ M	42.4	909 pmol/mg/min	891 pmol/mg/min	1.02	[43]
Aminopterin	15.0 μ M	0.69 μ M	21.7	42.9 pmol/mg/2 min	68.8 pmol/mg/2 min	0.624	[12]

3.2. Enantioselectivity in the Pharmacokinetics of Fexofenadine and Its Transport by OATP2B1

Fexofenadine, a histamine H_1 -receptor antagonist, has non-sedative properties that have been attributed to the restriction of its brain penetration by P-gp [44]. Enantioselectivity has been reported

in its pharmacokinetics. Miura et al. demonstrated that the maximum plasma concentration and area under the plasma concentration-time curve of (*R*)-fexofenadine were higher than those of the (*S*)-enantiomer after the single oral administration of racemic fexofenadine to healthy volunteers [45]. Sakugawa et al. examined effect of verapamil, an inhibitor of P-gp, on the disposition of each enantiomer of fexofenadine in healthy volunteers, and suggested that the other mechanisms in addition to P-gp contribute to the stereoselective pharmacokinetics of fexofenadine [46]. To my knowledge, there is no reports representative of enantioselective transport of fexofenadine by P-gp from in vitro experiments. Most of the dosage of fexofenadine administered is excreted into urine in its unmetabolized form, and various drug transporters have been shown to contribute to its pharmacokinetics. The OATP family members, OATP1A2, OATP1B1, OATP1B3, and OATP2B1, were proposed to be responsible for the intestinal uptake of fexofenadine or its distribution into the liver [47–52]. MRP2 and the bile salt export pump BSEP (ABCB11) mediate the efflux of fexofenadine from hepatocytes into bile, while MRP3 transports it into plasma [52,53]. OAT3 plays a role in the renal tubular uptake of fexofenadine, and MATE1 contributes to its efflux into urine [54,55]. At least one of the drug transporters described above may be responsible for the enantioselective pharmacokinetics of fexofenadine. The enantioselective transport of fexofenadine has only been reported to occur by OATP2B1. Akamine et al. found greater uptake amounts of (*R*)-fexofenadine in *Xenopus* oocytes injected with OATP2B1 cRNA than that of the (*S*)-enantiomer [56]. They also demonstrated that apple juice decreased the absorption of fexofenadine orally administered to healthy volunteers, and that the juice inhibited its transport by OATP2B1 [56]. Accordingly, OATP2B1 appears to mediate the enantioselective absorption of fexofenadine by the small intestine. Akamine et al. did not describe the kinetic parameters of the transport of enantiomers by OATP2B1. The renal clearance of (*S*)-fexofenadine was higher than that of the (*R*)-enantiomer [45,56], whereas Kusuhara et al. reported no enantioselective transport of fexofenadine by OAT3 and MATE1 [57]. In addition, they showed the similar transport of both enantiomers by OATP1B3 [57]. Unidentified drug transporter(s) may be responsible for the enantioselective disposition of fexofenadine.

3.3. Enantioselective Secretion of Pantoprazole into Milk by BCRP

Enantioselective drug transport was demonstrated with the combination of pantoprazole and BCRP. BCRP affects the absorption, distribution, and excretion of drugs, and BCRP actively secretes xenobiotics, including drugs and carcinogens, and riboflavin into milk [58–60]. Wang et al. showed the greater accumulation of (–)-pantoprazole in the milk of lactating rats infused with racemic pantoprazole than that of (+)-pantoprazole [61], and the higher affinity of the (–)-enantiomer with BCRP [62].

4. Enantioselective Inhibitory Effects of Drugs on Drug Transporters

4.1. Enantioselectivity in Inhibitory Effects of Drugs on OCT1, and Binding Affinities

Enantioselectivity was shown in the inhibitory effect of disopyramide and propranolol on OCT1. The (*R*)-disopyramide inhibited the uptake of tetraethylammonium by HeLa cells expressing OCT1 more strongly than the (*S*)-enantiomer [63], and also for propranolol the inhibitory effect of (*S*)-enantiomer is stronger than for the (*R*)-enantiomer [64]. The IC₅₀ values of each enantiomer were described in Table 2.

Table 2. IC₅₀ values of each enantiomer of disopyramide and propranolol for OCT1.

Drug	IC ₅₀ Value (μM) (<i>R</i>)-enantiomer	IC ₅₀ Value (μM) (<i>S</i>)-enantiomer	(<i>R</i>)/(<i>S</i>)	Ref.
Disopyramide	15.4	29.9	0.515	[63]
Propranolol	41.7	15.1	2.76	[64]

Moaddel et al. studied the binding of drugs to OCT1 with a liquid chromatography stationary phase containing immobilized membranes obtained from a cell line that expresses OCT1, and estimated

their binding affinities using frontal displacement chromatography with [^3H]1-methyl 4-phenyl pyridinium as the marker ligand. The significant enantioselectivity on the binding to OCT1 was recognized in verapamil, atenolol, and propranolol [64,65]. (*R*)-Verapamil, (*S*)-atenolol, and (*S*)-propranolol showed the higher affinities than each enantiomer. In Table 3, their K_d values are summarized.

Table 3. K_d values of each enantiomer of verapamil, atenolol, and propranolol for OCT1.

Drug	K_d Value (μM) (<i>R</i>)-enantiomer	K_d Value (μM) (<i>S</i>)-enantiomer	(<i>R</i>)/(<i>S</i>)	Ref.
Verapamil	0.05	3.46	0.0145	[65]
Atenolol	0.98	0.46	2.13	[64]
Propranolol	2.85	0.95	3.00	[64]

4.2. Enantioselective Inhibitory Effects of NSAIDs and Lansoprazole on OAT1 and OAT3

The inhibition of renal organic anion transporters leads to the delayed elimination of their substrates from the circulation. NSAIDs interfere with the renal excretion of methotrexate, and this combination is a representative among drug interactions via OAT1 and OAT3. The interaction is fatal when high-dose methotrexate therapy is given to a patient [66,67]. Previous studies demonstrated the inhibitory effects of NSAIDs, including cyclooxygenase-2 inhibitors, on methotrexate uptake by OAT1 and OAT3 [68–72]. Some NSAIDs are chiral (Figure 1). We conducted a drug transport experiment using the *Xenopus* oocyte expression system in order to examine enantioselectivity in the inhibition of OAT1 and OAT3 by NSAIDs [73]. The findings obtained showed the stronger inhibitory effects of the (*S*)-enantiomers of flurbiprofen, ibuprofen, and naproxen on the transport of *p*-aminohippurate and methotrexate by OAT1 than that of each (*R*)-enantiomer. The inhibitory mechanisms of flurbiprofen were investigated, and both enantiomers were found to competitively inhibit OAT1. Enantioselective differences were not observed in the inhibition of OAT3.

Proton pump inhibitors also interact with methotrexate [74,75]; OAT1 and OAT3 were found to be inhibited by omeprazole, lansoprazole, pantoprazole, rabeprazole, and esomeprazole [76,77]. Chirality exists in the structures of proton pump inhibitors (Figure 1), and enantioselectivity was examined in the inhibition of OAT1 and OAT3 by lansoprazole [78]. The inhibitory effects of (*S*)-lansoprazole on the transport of estrone sulfate, methotrexate, and pemetrexed by OAT3 were stronger than those of the (*R*)-enantiomer. Furthermore, enantioselectivity was not recognized against OAT1. Enantioselectivity has been demonstrated in the pharmacokinetics of lansoprazole. The slower elimination of the (*R*)-enantiomer from plasma has been reported in healthy subjects [79]. The faster metabolism of (*S*)-lansoprazole by human liver microsomes was also shown [80]. This information is useful when considering drug interactions between lansoprazole and the substrate drugs of OAT3.

4.3. Enantioselective Inhibitory Effects of NSAIDs on MRP2 and MRP4

The enantioselective inhibitory effects of NSAIDs on MRP2 and MRP4 have been examined. Kawase et al. performed uptake experiments on methotrexate using MRP2- and MRP4-expressing inside-out vesicles, and showed the stronger inhibition of MRP2 by the (*S*)-enantiomers of flurbiprofen, ibuprofen, and naproxen than by each (*R*)-enantiomer [81]. In the case of MRP4, the (*R*)-enantiomers exerted strong inhibitory effects.

Table 4 summarizes the IC_{50} values of each enantiomer of flurbiprofen, ibuprofen, naproxen, and lansoprazole described above. The most prominent enantioselective difference was noted in the inhibition of MRP2 by naproxen.

Table 4. IC₅₀ values of each enantiomer of NSAIDs and lansoprazole for OAT1, OAT3, MRP2, and MRP4.

Drug	Transporter	Substrate	IC ₅₀ Value (μM) (R)-Enantiomer	IC ₅₀ Value (μM) (S)-Enantiomer	(R)/(S)	Ref.
Flurbiprofen	OAT1	<i>p</i> -aminohippurate	2.35	0.615	3.82	[73]
	OAT3	estrone sulfate	2.13	1.80	1.18	[73]
	MRP2	methotrexate	133	58.4	2.28	[81]
	MRP4	methotrexate	10.6	37.2	0.285	[81]
Ibuprofen	OAT1	<i>p</i> -aminohippurate	6.14	2.84	2.16	[73]
	OAT3	estrone sulfate	2.04	1.20	1.70	[73]
	MRP2	methotrexate	303	139	2.18	[81]
	MRP4	methotrexate	129	267	0.483	[81]
Naproxen	OAT1	<i>p</i> -aminohippurate	5.26	1.93	2.73	[73]
	OAT3	estrone sulfate	8.09	6.79	1.19	[73]
	MRP2	methotrexate	510	7.11	71.7	[81]
	MRP4	methotrexate	8.06	49.8	0.162	[81]
Lansoprazole	OAT1	<i>p</i> -aminohippurate	43.8	33.6	1.30	[78]
	OAT3	estrone sulfate	1.75	0.61	2.87	[78]

5. Conclusions

Enantioselectivity has been demonstrated in the transport of methotrexate and aminopterin by PCFT, pantoprazole by BCRP, and fexofenadine by OATP2B1. Enantioselective differences were reported in the inhibitory effects of flurbiprofen, ibuprofen, and naproxen on OAT1, MRP2, and MRP4, and of lansoprazole on OAT3. The number of studies on enantioselective drug recognition by drug transporters is markedly smaller than those on drug metabolism enzymes. In research on enantioselectivity, data on drug metabolism accumulate, and Niwa et al. performed meta-analysis based on the reported values regarding the Michaelis-Menten constant, maximal velocity, intrinsic clearance, and inhibition constants [82]. They considered that there is a limited number of reports regarding stereoselective inhibition and induction in vitro [82]. Because drug transporters are also involved in drug interactions, it is desired to pay attention to enantioselectivity in inhibition as well as in substrate recognition of drug transporters.

Computational methods such as quantitative structure-activity relationship (QSAR) and pharmacophore approaches have become more widely applied to assess interactions between drugs and drug transporters and predictions for substrates and inhibitors for several transporters were described [83]. Because ignoring stereoselectivity reduces the accuracy of the QSAR and modelling analysis, stereoselectivity should become a key aspect of the modelling of interactions between drugs and drug transporters [84].

In the future, research on drug transporters from the chiral aspect of drugs will provide important insights into pharmacokinetics, pharmacodynamics, and drug toxicity.

Author Contributions: Y.U. conceived the study, reviewed the literature, and wrote the manuscript.

Funding: This work was supported by a grant from the Japan Society for the Promotion of Science through a Grant-in-Aid for Scientific Research (KAKENHI, 16K08419 to Y.U.).

Conflicts of Interest: The author states that there are no conflicts of interest.

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