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REVIEW ARTICLE

# Blood–brain barrier transporters and response to CNS-active drugs

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**Abstract**
*Background* The capillary endothelial cells of the blood–brain barrier express an array of uptake and efflux drug transporters. Regulated expression and function of these transporters govern the central nervous system (CNS) penetration of essential nutrients, therapeutic drugs and, in some cases, toxins. Emerging evidence supports the notion of interplay between uptake and efflux drug transport as the determinants that define the extent of exposure of many drugs and their CNS action.
*Objective* In this brief report, we review a number of key drug transporters known to be expressed at the blood–brain barrier and/or choroid plexus and focus on the implications of such transporters to CNS drug activity, side effects, and toxicity. Specifically, this report focuses on the uptake transporters OATP1A2 (organic anion-transporting polypeptide 1A2) and MCT1 (monocarboxylate transporter 1), which are known to have substrates that are either neuroactive or known to result in CNS side effects and/or toxicity. Furthermore, the efflux transporters P-gp (P-gp; MDR1/ABCB1), BCRP (breast-cancer-resistance protein), OAT3 (organic anion transporter 3), and MRP4 (multidrug-resistance-associated protein 4) are also reviewed.
*Conclusions* Drug transporters play a fundamental role in protecting the brain from exposure to drugs and other potential toxicants.

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## Introduction

The tight junctions of capillary endothelial cells of the brain serve to protect the central nervous system (CNS) from exposure to potential toxicants by limiting the paracellular movement of endogenous and exogenous compounds. Consequently, specific uptake transporters are required to carry essential molecules such as glucose and amino acids from the blood to the brain through capillary endothelial cells. Until recently, it was thought that only highly lipophilic drugs were capable of gaining access to the CNS. We now know that in addition to the physicochemical properties of a drug, such as charge, lipophilicity, and molecular weight, uptake and efflux drug transporter expression and their activity at the capillary endothelial cells of the blood–brain barrier are often the rate-limiting determinants of CNS drug entry. For this reason, drug transporters play an important role in determining exposure of the brain to drugs and therefore govern the CNS effects and toxicity of many drugs (Table 1).

Several uptake and efflux drug transporters are expressed at the blood–brain barrier, including organic anion-transporting polypeptide 1A2 (OATP1A2/SLCO1A2) organic anion transporter 3 (OAT3/SLC22A8), monocarboxylate transporter 1 (MCT1/SLC16A1), P-glycoprotein (P-gp; MDR1/ABCB1), breast-cancer-resistance protein (BCRP/ABCG2) and multidrug-resistance-associated protein 4 (MRP4/ABCC4). The objective of this brief report is to review the expression and activity of these drug transporters at the blood–brain barrier and, where appropriate, comment on the implications for response or toxicity observed during drug therapy.

**Table 1** Expression, substrates, and effect of transporters on central nervous system (CNS) exposure to drugs

| Transporter | Expression | Substrates | Effect of transporter on brain substrate exposure |
|---|---|---|---|
| OATP1A2 | BBB-apical | Deltorphin II [5] | ↑ |
| | | Fexofenadine [1] | ↑ |
| | | Levofloxacin [2] | ↑ |
| | | Methotrexate [3] | ↑ |
| | | Microcystins [42] | ↑ |
| | | D-penicillamine(2,5)enkephalin (DPDPE) [5] | ↑ |
| OAT3 | BBB-apical, basolateral | 17β-estradiol-D-17β-glucuronide [43] | ↓ |
| | | Indoxyl sulfate [44] | ↓ |
| | CP- apical | 6-mercaptopurine [15] | ↓ |
| | | Para-aminohippurate (PAH) [13] | ↓ |
| | | 6-Thioguanune [15] | ↓ |
| | BBB & CP expression known in rodent only | Ro 64-0802 [17] | ↓ |
| MCT1 | BBB-apical | Lactate [45] | ↑ |
| | | Pyruvate | ↑ |
| | | GHB [19] | ↑ |
| P-gp | BBB-apical | Abacavir [46] | ↓ |
| | CP-apical | Cerivastatin [47] | ↓ |
| | | Cetirizine [48] | ↓ |
| | | Cyclosporin A [49] | ↓ |
| | | Digoxin [49] | ↓ |
| | | Domperidone [20] | ↓ |
| | | Eletriptan [50] | ↓ |
| | | Fexofenadine [1, 51] | ↓ |
| | | Flesinoxan [52] | ↓ |
| | | Gefitinib [53] | ↓ |
| | | Glabridin [54] | ↓ |
| | | Imatinib mesylate [33] | ↓ |
| | | Indinavir [23] | ↓ |
| | | Ivermectin [49] | ↓ |
| | | Loperamide [20] | ↓ |
| | | Loratadine [55] | ↓ |
| | | Nelfinavir [23] | ↓ |
| | | Ondansetron [20] | ↓ |
| | | Prednisolone | ↓ |
| | | Saquinavir [23] | ↓ |
| | | Salinomycin [56] | ↓ |
| | | Sparfloxacin [57] | ↓ |
| | | Quinacrine [58] | ↓ |
| | | Vinblastine [59] | ↓ |
| BCRP | BBB-apical | Alfuzosin [39] | ↔ |
| | | Cimetidine [39] | ↔ |
| | | Daidzein [37] | ↓ |
| | | Dihyroepiandosterone sulfate [38] | ↔ |
| | | Dipyridamole [39] | ↔ |
| | | Gefitinib [53] | ↓ |
| | | Genistein [37] | ↓ |
| | | Imatinib mesylate [33] | ↓ |

**Table 1** (continued)

| Transporter | Expression | Substrates | Effect of transporter on brain substrate exposure |
|---|---|---|---|
| | | LY2228820 [39] | ↔ |
| | | Mitoxantrone [38] | ↔ |
| | | Topotecan [30] | ↓ |
| MRP4 | BBB-apical | 9-(2-phosphonylmethoxyethyl)adenine (PMEA) [60] | ↓ |
| | CP-basolateral | Ro 64-0802 [17] | ↓ |
| | | Topotecan [40] | ↓ |

*OATP1A2* organic anion-transporting polypeptide, *OAT3* organic anion transporter 3, *MCT1* monocarboxylate transporter 1, *P-gp* P-glycoprotein, *BCRP* breast cancer resistance protein, *MRP4* multi-drug resistance associated protein 4, *BBB* blood–brain barrier, *CP* choroid plexus

## Organic anion transporting polypeptide 1A2 (OATP1A2/SLCO1A2)

OATP drug transporters mediate the sodium-independent uptake of a broad range of substrates, including the drugs fexofenadine [1], levofloxacin [2], methotrexate [3], and ouabain [4], along with bile acids and the synthetic peptides deltorphin II and D-penicillamine (2,5)- enkephalin (DPDPE) [5]. Recent studies suggest that in addition to its importance to intestinal drug absorption [6], OATP1A2 plays a role in the transfer of drugs from the blood to the brain, as this transporter is highly expressed on the luminal membrane of capillary endothelial cells of the blood–brain barrier [5, 7]. Given the broad substrate spectrum associated with OATP1A2, this transporter is likely one of the reasons why certain drugs attain greater than expected CNS drug levels and, in some cases, CNS toxicity profile of a number of compounds (Fig. 1).

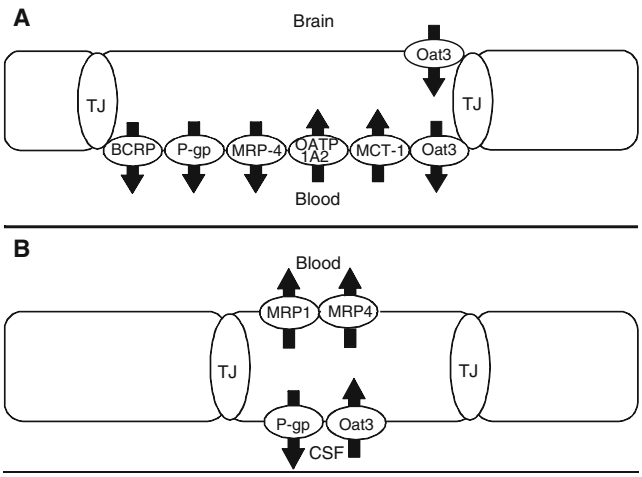


**Fig. 1** Drug transporter expression at the blood brain barrier (**A**) and choroid plexus (**B**). TJ represents tight junctions typical of these regions of the brain

Methotrexate is a dihydrofolate reductase inhibitor used to treat several clinical conditions including rheumatoid arthritis, Crohn's disease, and several types of cancer. Recently, methotrexate has been shown to be a substrate for OATP1A2 [3]. Interestingly, a common OATP1A2 polymorphism (Ile13Thr) present in 16% of European Americans was shown to confer a two-fold increase in OATP1A2-mediated methotrexate uptake. High-dose methotrexate is used to treat several cancers, and the resulting CNS side effects range from mild white-matter changes to severe CNS demyelination and encephalopathy [8]. Given the role of OATP1A2 in mediating methotrexate uptake and the high allele frequency of this gain of function polymorphism Ile13Thr, OATP1A2 should be considered as a factor in the observed CNS toxicity of methotrexate, although this remains to be confirmed in clinical studies.

Levofloxacin is a fluoroquinolone antibacterial agent used to treat respiratory tract infections and in the treatment and prevention of traveler's diarrhea. Several CNS side effects have been associated with levofloxacin use, including seizures, toxic psychoses, increased intracranial pressure, and CNS stimulation. These side effects may even occur following a single dose of levofloxacin. Although the efflux of quinolone antibiotics by MRP, BCRP and P-gp drug transporters has been well established [9, 10], it was only recently that OATP1A2 was implicated in the uptake of levofloxacin [2]. Although P-gp effectively limits the CNS penetration of levofloxacin [10], it is possible that under conditions of reduced P-gp expression or activity (i.e., drug interactions), OATP1A2-mediated increases in brain accumulation of levofloxacin may be at least partly accountable for the adverse CNS side effects.

## Organic anion transporter 3 (OAT3/SLC22A8)

Oat3 was originally isolated from rat brain and shown to mediate the transport of cimetidine, estrone sulfate, para-

aminohippurate (PAH), and ochratoxin A [11]. Oat3 has been detected on the apical membrane of the choroid plexus [12, 13] and the luminal and abluminal membranes of rat brain endothelial cells [14]. The function of Oat3 in the choroid plexus appears to mediate the transport of organic anions from the cerebrospinal fluid (CSF) to the blood, whereas at the blood–brain barrier, it transfers substrate drugs from the brain to the blood. In terms of drug action, rOat3 has been implicated in the brain to blood transport of the thiopurines 6-mercaptopurine and 6-thioguanine [15]. Thiopurines are used to treat acute lymphoblastic leukemia (ALL). During treatment of ALL, patients often have relapse due to the entry of leukemic cells into the brain. It has been proposed that Oat3-mediated transport of thiopurines out of the brain allows the proliferation of these cells in the CNS, and thereby result in the observed leukemia relapse during chemotherapy [15].

Oseltamivir (Tamiflu) is a prodrug of Ro 64-0802, which is used for the symptomatic treatment of illnesses caused by the influenza virus. It is a potent inhibitor of the enzyme neuraminidase and such functional effects results in decreased release of viral particles from infected cells. The use of this drug has been implicated with CNS side effects in animals and more recently in humans [16, 17]. A recent study investigated the impact of Oat3 on the CNS penetration of the active metabolite Ro 64-0802 using Oat3 knockout mice [17]. Ro 64-0802 accumulation in the brain was significantly greater in knockout animals at 1 and 2 h following administration compared with wild-type control. Interestingly, there was no difference in the brain to plasma ratio in the Oat3 knockout animals, and therefore other transporters may also contribute to the CNS exposure of oseltamivir. Accordingly, Oat3 likely plays a significant role in the clearance of Ro 64-0802 from the brain, and modulation of Oat3 activity may result in CNS toxicity associated with oseltamivir. Although the results implicating Oat3-mediated drug transport in rodent brain are intriguing, at this time, experimental evidence demonstrating OAT3 expression and/or activity in the human brain is lacking.

## Monocarboxylate transporter 1 (MCT1/SLC16A1)

MCT1 is expressed on the luminal membrane of endothelial cells at the blood–brain barrier [18]. Its primary role is in the transport of monocarboxylate solutes, such as lactate and pyruvate, into the brain, although more recently, drug substrates of MCT1 and other members of the MCT family have been studied. The most widely studied drug associated with MCT1 is γ-hydroxy butyrate (GHB), a controlled substance that has been used clinically to treat insomnia, cataplexy, and narcolepsy. CNS-related side effects of GHB include respiratory depression, seizure, and loss of consciousness and may even result in coma or death. Recent studies using an in situ rat brain perfusion model show saturable GHB transport at the blood–brain barrier [19]. Further, transport is inhibited by the MCT1 substrates lactate and pyruvate, suggesting that blood–brain barrier GHB transport is predominantly mediated by MCT1. The direct role of MCT1 in mediating CNS activity and side effects of GHB remain to be elucidated.

## P-glycoprotein (MDR1/ABCB1)

P-gp is a member of the adenosine triphosphate (ATP)-binding cassette family of efflux drug transporters and is the most widely studied of all efflux drug transporters. P-gp is known for is critical role in mediating cellular resistance to many chemotherapeutic agents and in limiting the tissue penetration of a broad range of chemically diverse substrate drugs at many blood–tissue barriers. In the brain, P-gp is expressed on the luminal membrane of capillary endothelial cells as well as the epithelium of the choroid plexus, therefore functioning to limit the brain and CSF distribution of drugs.

One of the best examples describing the prominent role P-gp plays in limiting CNS penetration of drugs is the antidiarrheal agent loperamide [20]. Loperamide is a potent opiate. However, due to its high affinity for P-gp as a substrate, it is unable to cross the blood–brain barrier. For this reason, loperamide is available over the counter to reduce gut motility and does not result in the central effects of euphoria and respiratory depression typical of opiates, even when ingested at high doses. A similar example exists with the dopaminergic antagonist domperidone. Unlike other dopaminergic receptor blockers that are used as neuroleptic agents, domperidone does not penetrate the brain and is therefore ineffective as an antipsychotic [21]. Elegant studies have shown that domperidone is actively extruded by P-gp and that its lack of CNS activity is a result of P-gp-mediated extrusion from the brain [20]. In contrast, the neuroleptic agent haloperidol, a non-P-gp substrate, displays significant CNS penetration and is an effective antipsychotic.

Aside from being a substrate for OATP1A2-mediated cellular uptake, fexofenadine is also efficiently extruded from cells by P-gp [1]. The colocalization of these transporters in many tissues, including the brain, suggests that disposition of dual substrates such as fexofenadine will be greatly influenced by transporter expression. Indeed, it has been shown that mice with disruption of the *mdr1a* gene have a nine-fold increase in the brain level of fexofenadine compared with wild-type controls [1]. As fexofenadine is relatively impermeable by passive diffusion, P-gp is essential in limiting the brain distribution of this non-sedating antihistamine despite its high affinity for OATP1A2-mediated uptake. Importantly, even at supra-

clinical doses (360 mg), fexofenadine is devoid of CNS side effects [22], likely owing to its low brain penetration.

The late stage of HIV infection is often characterized by neurological complications such as confusion, forgetfulness, and behavioral changes. HIV protease inhibitors are one of the mainstay treatments of HIV infection. Several HIV protease inhibitor drugs have been shown to be substrates of P-gp. Studies using mdr1a(-/-) mice show that the brain concentration and brain to plasma ratio of indinavir, nelfinavir, and saquinavir are significantly increased compared with wild-type control [23]. It is clear from these studies that P-gp plays a fundamental role in limiting the CNS penetration of HIV protease inhibitors and therefore may limit the action of these drugs in treating some of the neurological complications of disease.

## Breast-cancer-resistance protein (BCRP/ABCG2)

BCRP was originally identified in a breast cancer cell line that exhibited resistance to anthracyclines [24]. Subsequent studies have clearly shown that BCRP is expressed on the luminal membrane of endothelial cells lining the brain [25], and BCRP is now a widely appreciated component of the blood−brain barrier. Not surprisingly, much effort has gone into defining the role of this transporter as a mediator of drug resistance to chemotherapeutic agents.

Topotecan is a camptothecin derivative that is used primarily to treat recurrent small-cell lung and ovarian cancer, although some studies suggest it may be moderately effective in treating brain metastases [26, 27] and malignant gliomas [28, 29]. Topotecan is an excellent substrate of BCRP and a moderate substrate of P-gp. As BCRP and P-gp often have overlapping substrates and are both highly expressed at tissues, such as the brain, that represent barriers to drug entry, it is important to evaluate the effect that both of these transporters have to the CNS penetration of drugs such as topotecan. Through the use of Bcrp1(-/-), Mdr1a/b(-/-), and Bcrp1(-/-)Mdr1a/b(-/-) mouse models, de Vries et al. clearly demonstrate the important role that Bcrp plays in limiting the brain penetration of topotecan [30]. In Bcrp1 (-/-) Mdr1 (a/b) (-/-) mice, the brain to plasma area under the curve (AUC) ratio of topotecan was 3.2-fold higher than wild-type control. Importantly, the authors point out that when investigating drugs such as topotecan, it is important to perform experiments in a P-gp-deficient background, as P-gp clearly plays a role in limiting the entry of shared substrates.

Imatinib mesylate is indicated for the treatment of chronic myelogenous leukemia and gastrointestinal stromal tumors and functions as a potent inhibitor of Bcr-Abl, platelet-derived growth-factor receptor (PDGFR)-α, PDGFR-β c-Fms, and C-Kit tyrosine kinases. In vitro evidence suggests that imatinib mesylate may also be effective in the treatment of malignant gliomas owing to its potent ($IC_{50}$=0.1 μmol/L) inhibition of PDGFR [31]. However a recent clinical study suggests that imatinib mesylate has minimal activity in the treatment of malignant gliomas in humans [32]. Studies by Breedveld et al. not only show that imatinib mesylate is a substrate of BCRP but also that Bcrp1 knockout mice have a 2.5-fold increased imatinib brain penetration compared with wild-type controls [33]. Similarly, pretreatment with the BCRP inhibitor pantoprazole increases the brain exposure of imatinib by approximately five fold. Taken together, these results suggest that BCRP limits the brain penetration of imatinib and at least in part explains its minimal efficacy in the treatment of malignant gliomas.

Aside from its role in mediating drug efflux, BCRP is also noted for its protective role in limiting the exposure of plant-derived compounds [34]. Phytoestrogens such as genistein and daidzein are obtained in the diet predominantly from soy beans. Recently, they were shown to inhibit the proliferation of neuroblastoma cells in vitro [35] and therefore may be effective agents in the treatment of certain brain tumors. These compounds are known to have low brain penetration [36]. Studies using mouse and human BCRP overexpressing Madin-Darby canine kidney (MDCK) cell lines clearly demonstrate that genistein and daidzein are substrates for BCRP [37]. In a Bcrp knockout mouse model, the brain penetration of genistein and daidzein was significantly increased in knockout animals compared with wild-type controls, suggesting that the low brain penetration of these compounds is mediated by efflux drug transport by BCRP. Should these compounds be further evaluated for treatment of neuroblastoma, strategies to overcome their low brain penetration need to be addressed.

Nevertheless, it should be noted that the role BCRP plays in mediating drug exposure in the brain remains controversial. Brain penetration of known BCRP substrates mitoxantrone and dehydroepiandrosterone sulfate were shown to be minimally affected in a Bcrp knockout mouse model [38]. Similarly, a recent study showed a minor role of BCRP in the brain distribution of cimetidine, alfuzosin, dipyridamole, and LY22288220 despite strong in vitro evidence in Bcrp transfected cell lines [39]. This may be in part related to the overlap in the substrate specificity between BCRP and P-gp. Accordingly, caution is warranted when interpreting results from in vitro experiments and extrapolating them to in vivo human situation.

## Multidrug-resistance-associated protein 4 (MRP4/ABCC4)

MRP4 is an efflux transporter known to play a role in the extrusion of organic anions and antiretroviral drugs and has also been implicated in multidrug resistance during chemo-

therapy. In the brain, MRP4 is expressed on the luminal membrane of capillary endothelial cells and the basolateral membrane of the choroid plexus [40, 41]. In an Mrp4 knockout mouse model, the chemotherapeutic drug topotecan was not only elevated in the brain but also in the CSF, emphasizing the important role that Mrp4 plays in determining the CNS distribution of this drug [40]. It is likely that multiple efflux drug transporters including MRP4 govern the brain penetration and activity of this anticancer agent.

Similar to OAT3, MRP4 has been implicated in CNS exposure to the active metabolite of oseltamivir, Ro 64-0802. Both brain exposure and brain to plasma ratio of Ro 64-0802 are significantly increased in Mrp4 knockout mice compared with wild-type control [17]. As there are several known polymorphisms in MRP4 that are known to affect transport activity, it would be interesting to evaluate their impact on the CNS side effects of Ro 64-0802 in humans. It is likely that the interplay of OAT3 and MRP4 activity in the brain determines the brain exposure of oseltamivir and Ro 64-0802, and their expression or function may predict the risk for CNS toxicity associated with this drug.

## Summary

The endothelial cells that line the brain limit the CNS entry of many drugs in clinical use today. Although this barrier is beneficial in terms of its role in preventing xenobiotic-associated CNS toxicity, it can often block the delivery of drugs needed for optimal treatment of CNS diseases. It is clear that for many drugs, their CNS entry is determined by the interplay of certain uptake and efflux transport proteins expressed at the blood−brain barrier. This will allow us to optimize therapy and prevent the toxicity commonly associated with some pharmacological interventions. Indeed, although the efflux transporter P-gp appears to be the master gatekeeper with respect to limiting drug penetration in the brain, recent evidence also suggests important and emerging roles for BCRP and MRP4, as well as uptake transporters such as OATP1A2. Clearly, additional studies are needed to further our understanding of the clinical relevance of drug transporters expressed at the level of the blood−brain barrier to CNS exposure and efficacy of drug substrates.

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## References

1. Cvetkovic M, Leake B, Fromm MF et al (1999) OATP and P-glycoprotein transporters mediate the cellular uptake and excretion of fexofenadine. Drug Metab Dispos 27:866–871
2. Maeda T, Takahashi K, Ohtsu N et al (2007) Identification of influx transporter for the quinolone antibacterial agent levofloxacin. Mol Pharm 4:85–94
3. Badagnani I, Castro RA, Taylor TR et al (2006) Interaction of methotrexate with organic-anion transporting polypeptide 1A2 and its genetic variants. J Pharmacol Exp Ther 318:521–529
4. Bossuyt X, Muller M, Meier PJ (1996) Multispecific amphipathic substrate transport by an organic anion transporter of human liver. J Hepatol 25:733–738
5. Gao B, Hagenbuch B, Kullak-Ublick GA et al (2000) Organic anion-transporting polypeptides mediate transport of opioid peptides across blood-brain barrier. J Pharmacol Exp Ther 294:73–79
6. Glaeser H, Bailey DG, Dresser GK et al (2007) Intestinal drug transporter expression and the impact of grapefruit juice in humans. Clin Pharmacol Ther 81:362–370
7. Lee W, Glaeser H, Smith LH et al (2005) Polymorphisms in human organic anion-transporting polypeptide 1A2 (OATP1A2): implications for altered drug disposition and central nervous system drug entry. J Biol Chem 280:9610–9617
8. Sioka C, Kyritsis AP (2009) Central and peripheral nervous system toxicity of common chemotherapeutic agents. Cancer Chemother Pharmacol 63:761–767
9. Merino G, Alvarez AI, Pulido MM et al (2006) Breast cancer resistance protein (BCRP/ABCG2) transports fluoroquinolone antibiotics and affects their oral availability, pharmacokinetics, and milk secretion. Drug Metab Dispos 34:690–695
10. Tamai I, Yamashita J, Kido Y et al (2000) Limited distribution of new quinolone antibacterial agents into brain caused by multiple efflux transporters at the blood-brain barrier. J Pharmacol Exp Ther 295:146–152
11. Kusuhara H, Sekine T, Utsunomiya-Tate N et al (1999) Molecular cloning and characterization of a new multispecific organic anion transporter from rat brain. J Biol Chem 274:13675–13680
12. Sweet DH, Miller DS, Pritchard JB et al (2002) Impaired organic anion transport in kidney and choroid plexus of organic anion transporter 3 (Oat3 (Slc22a8)) knockout mice. J Biol Chem 277:26934–26943
13. Sykes D, Sweet DH, Lowes S et al (2004) Organic anion transport in choroid plexus from wild-type and organic anion transporter 3 (Slc22a8)-null mice. Am J Physiol Renal Physiol 286:F972–F978
14. Mori S, Takanaga H, Ohtsuki S et al (2003) Rat organic anion transporter 3 (rOAT3) is responsible for brain-to-blood efflux of homovanillic acid at the abluminal membrane of brain capillary endothelial cells. J Cereb Blood Flow Metab 23:432–440
15. Mori S, Ohtsuki S, Takanaga H et al (2004) Organic anion transporter 3 is involved in the brain-to-blood efflux transport of thiopurine nucleobase analogs. J Neurochem 90:931–941
16. Izumi Y, Tokuda K, O'dell KA et al (2007) Neuroexcitatory actions of Tamiflu and its carboxylate metabolite. Neurosci Lett 426:54–58
17. Ose A, Ito M, Kusuhara H et al (2009) Limited brain distribution of [3R, 4R, 5 S]-4-acetamido-5-amino-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxyl ate phosphate (Ro 64–0802), a pharmacologically active form of oseltamivir, by active efflux across the blood-brain barrier mediated by organic anion transporter 3 (Oat3/Slc22a8) and multidrug resistance-associated protein 4 (Mrp4/Abcc4). Drug Metab Dispos 37:315–321
18. Gerhart DZ, Enerson BE, Zhdankina OY et al (1997) Expression of monocarboxylate transporter MCT1 by brain endothelium and glia in adult and suckling rats. Am J Physiol 273:E207–E213
19. Bhattacharya I, Boje KM (2004) GHB (gamma-hydroxybutyrate) carrier-mediated transport across the blood-brain barrier. J Pharmacol Exp Ther 311:92–98

20. Schinkel AH, Wagenaar E, Mol CA et al (1996) P-glycoprotein in the blood-brain barrier of mice influences the brain penetration and pharmacological activity of many drugs. J Clin Invest 97:2517–2524
21. Laduron PM, Leysen JE (1979) Domperidone, a specific in vitro dopamine antagonist, devoid of in vivo central dopaminergic activity. Biochem Pharmacol 28:2161–2165
22. Hindmarch I, Shamsi Z, Kimber S (2002) An evaluation of the effects of high-dose fexofenadine on the central nervous system: a double-blind, placebo-controlled study in healthy volunteers. Clin Exp Allergy 32:133–139
23. Kim RB, Fromm MF, Wandel C et al (1998) The drug transporter P-glycoprotein limits oral absorption and brain entry of HIV-1 protease inhibitors. J Clin Invest 101:289–294
24. Doyle LA, Yang W, Abruzzo LV et al (1998) A multidrug resistance transporter from human MCF-7 breast cancer cells. Proc Natl Acad Sci U S A 95:15665–15670
25. Cooray HC, Blackmore CG, Maskell L et al (2002) Localisation of breast cancer resistance protein in microvessel endothelium of human brain. Neuroreport 13:2059–2063
26. Korfel A, Oehm C, Pawel J von (2002) Response to topotecan of symptomatic brain metastases of small-cell lung cancer also after whole-brain irradiation. a multicentre phase II study. Eur J Cancer 38:1724–1729
27. Wong ET, Berkenblit A (2004) The role of topotecan in the treatment of brain metastases. Oncologist 9:68–79
28. Friedman HS, Kerby T, Fields S et al (1999) Topotecan treatment of adults with primary malignant glioma. The Brain Tumor Center at Duke. Cancer 85:1160–1165
29. Pipas JM, Meyer LP, Rhodes CH et al (2005) A Phase II trial of paclitaxel and topotecan with filgrastim in patients with recurrent or refractory glioblastoma multiforme or anaplastic astrocytoma. J Neurooncol 71:301–305
30. de Vries NA, Zhao J, Kroon E et al (2007) P-glycoprotein and breast cancer resistance protein: two dominant transporters working together in limiting the brain penetration of topotecan. Clin Cancer Res 13:6440–6449
31. Kilic T, Alberta JA, Zdunek PR et al (2000) Intracranial inhibition of platelet-derived growth factor-mediated glioblastoma cell growth by an orally active kinase inhibitor of the 2-phenylaminopyrimidine class. Cancer Res 60:5143–5150
32. Wen PY, Yung WK, Lamborn KR et al (2006) Phase I/II study of imatinib mesylate for recurrent malignant gliomas: North American Brain Tumor Consortium Study 99–08. Clin Cancer Res 12:4899–4907
33. Breedveld P, Pluim D, Cipriani G et al (2005) The effect of Bcrp1 (Abcg2) on the in vivo pharmacokinetics and brain penetration of imatinib mesylate (Gleevec): implications for the use of breast cancer resistance protein and P-glycoprotein inhibitors to enable the brain penetration of imatinib in patients. Cancer Res 65:2577–2582
34. Jonker JW, Buitelaar M, Wagenaar E et al (2002) The breast cancer resistance protein protects against a major chlorophyll-derived dietary phototoxin and protoporphyria. Proc Natl Acad Sci U S A 99:15649–15654
35. Lo FH, Mak NK, Leung KN (2007) Studies on the anti-tumor activities of the soy isoflavone daidzein on murine neuroblastoma cells. Biomed Pharmacother 61:591–595
36. Chang HC, Churchwell MI, Delclos KB et al (2000) Mass spectrometric determination of Genistein tissue distribution in diet-exposed Sprague-Dawley rats. J Nutr 130:1963–1970
37. Enokizono J, Kusuhara H, Sugiyama Y (2007) Effect of breast cancer resistance protein (Bcrp/Abcg2) on the disposition of phytoestrogens. Mol Pharmacol 72:967–975
38. Lee YJ, Kusuhara H, Jonker JW et al (2005) Investigation of efflux transport of dehydroepiandrosterone sulfate and mitoxantrone at the mouse blood-brain barrier: a minor role of breast cancer resistance protein. J Pharmacol Exp Ther 312:44–52
39. Zhao R, Raub TJ, Sawada GA et al. (2009) Breast cancer resistance protein interacts with various compounds in vitro, but plays a minor role in substrate efflux at the blood-brain barrier. Drug Metab Dispos.
40. Leggas M, Adachi M, Scheffer GL et al (2004) Mrp4 confers resistance to topotecan and protects the brain from chemotherapy. Mol Cell Biol 24:7612–7621
41. Zhang Y, Schuetz JD, Elmquist WF et al (2004) Plasma membrane localization of multidrug resistance-associated protein homologs in brain capillary endothelial cells. J Pharmacol Exp Ther 311:449–455
42. Fischer WJ, Altheimer S, Cattori V et al (2005) Organic anion transporting polypeptides expressed in liver and brain mediate uptake of microcystin. Toxicol Appl Pharmacol 203:257–263
43. Sugiyama D, Kusuhara H, Shitara Y et al (2001) Characterization of the efflux transport of 17beta-estradiol-D-17beta-glucuronide from the brain across the blood-brain barrier. J Pharmacol Exp Ther 298:316–322
44. Ohtsuki S, Asaba H, Takanaga H et al (2002) Role of blood-brain barrier organic anion transporter 3 (OAT3) in the efflux of indoxyl sulfate, a uremic toxin: its involvement in neurotransmitter metabolite clearance from the brain. J Neurochem 83:57–66
45. Kido Y, Tamai I, Okamoto M et al (2000) Functional clarification of MCT1-mediated transport of monocarboxylic acids at the blood-brain barrier using in vitro cultured cells and in vivo BUI studies. Pharm Res 17:55–62
46. Shaik N, Giri N, Pan G et al (2007) P-glycoprotein-mediated active efflux of the anti-HIV1 nucleoside abacavir limits cellular accumulation and brain distribution. Drug Metab Dispos 35:2076–2085
47. Kivisto KT, Zukunft J, Hofmann U et al (2004) Characterisation of cerivastatin as a P-glycoprotein substrate: studies in P-glycoprotein-expressing cell monolayers and mdr1a/b knock-out mice. Naunyn Schmiedebergs Arch Pharmacol 370:124–130
48. Polli JW, Baughman TM, Humphreys JE et al (2003) P-glycoprotein influences the brain concentrations of cetirizine (Zyrtec), a second-generation non-sedating antihistamine. J Pharm Sci 92:2082–2089
49. Schinkel AH, Wagenaar E, van Deemter L et al (1995) Absence of the mdr1a P-Glycoprotein in mice affects tissue distribution and pharmacokinetics of dexamethasone, digoxin, and cyclosporin A. J Clin Invest 96:1698–1705
50. Evans DC, O'Connor D, Lake BG et al (2003) Eletriptan metabolism by human hepatic CYP450 enzymes and transport by human P-glycoprotein. Drug Metab Dispos 31:861–869
51. Tahara H, Kusuhara H, Fuse E et al (2005) P-glycoprotein plays a major role in the efflux of fexofenadine in the small intestine and blood-brain barrier, but only a limited role in its biliary excretion. Drug Metab Dispos 33:963–968
52. van der Sandt IC, Smolders R, Nabulsi L et al (2001) Active efflux of the 5-HT(1A) receptor agonist flesinoxan via P-glycoprotein at the blood-brain barrier. Eur J Pharm Sci 14:81–86
53. Kawamura K, Yamasaki T, Yui J et al (2009) In vivo evaluation of P-glycoprotein and breast cancer resistance protein modulation in the brain using [(11)C] gefitinib. Nucl Med Biol 36:239–246
54. Yu XY, Lin SG, Zhou ZW et al (2007) Role of P-glycoprotein in limiting the brain penetration of glabridin, an active isoflavan from the root of Glycyrrhiza glabra. Pharm Res 24:1668–1690
55. Chen C, Hanson E, Watson JW et al (2003) P-glycoprotein limits the brain penetration of nonsedating but not sedating H1-antagonists. Drug Metab Dispos 31:312–318
56. Lagas JS, Sparidans RW, van Waterschoot RA et al (2008) P-glycoprotein limits oral availability, brain penetration, and toxicity of an anionic drug, the antibiotic salinomycin. Antimicrob Agents Chemother 52:1034–1039

57. de Lange EC, Marchand S, van den Berg D et al (2000) In vitro and in vivo investigations on fluoroquinolones; effects of the P-glycoprotein efflux transporter on brain distribution of sparfloxacin. Eur J Pharm Sci 12:85–93
58. Huang Y, Okochi H, May BC et al (2006) Quinacrine is mainly metabolized to mono-desethyl quinacrine by CYP3A4/5 and its brain accumulation is limited by P-glycoprotein. Drug Metab Dispos 34:1136–1144
59. Schinkel AH, Smit JJ, Tellingen O van et al (1994) Disruption of the mouse mdr1a P-glycoprotein gene leads to a deficiency in the blood-brain barrier and to increased sensitivity to drugs. Cell 77:491–502
60. Dallas S, Schlichter L, Bendayan R (2004) Multidrug resistance protein (MRP) 4- and MRP 5-mediated efflux of 9-(2-phosphonylmethoxyethyl)adenine by microglia. J Pharmacol Exp Ther 309:1221–1229