



## Drug transporters in the central nervous system

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**Abstract:** Drug targets in the central nervous system (CNS) are numerous and important for drug therapy, e.g., of epilepsy or pain. Drugs and other xenobiotics as well as nutrients cannot freely cross the blood-brain barrier or freely enter cells across plasma membranes and therefore require transport systems. This overview summarizes the current knowledge on the expression of drug transporters in barriers shielding the CNS from the systemic circulation and as such controlling the pharmacokinetics of drugs in the CNS. The main drug transporter families covered are SLCO, SCL22A, ABCB, and ABCC, as genes of these families code for numerous drug transporters. While knowledge on messenger RNA expression in humans, rats, and mice is remarkable, there is clearly a gap in knowledge on the subcellular expression of transporters in specific cells in the CNS and in the barriers shielding the CNS from the systemic circulation. Recent methodologic developments including synthesis of drugs and endogenous substances for imaging will in the future allow the investigation of the function and physiologic role of transporters in the CNS including difficult-to-access systems such as the choroid plexus.

DOI: <https://doi.org/10.1007/s40262-015-0241-y>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-109614>

Journal Article

Accepted Version

Originally published at:

Stieger, Bruno; Gao, Bo (2015). Drug transporters in the central nervous system. *Clinical Pharmacokinetics*, 54(3):225-242.

DOI: <https://doi.org/10.1007/s40262-015-0241-y>

# Drug Transporters in the Central Nervous System

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## Abstract

1 Drug targets in the central nervous system are numerous and important for drug therapy e.g.  
2 of pain, psychiatric disorders or epilepsy. Drugs and other xenobiotics as well as nutrients  
3 cannot freely cross the blood brain barrier or freely enter cells across plasma membranes and  
4 therefore require transport systems. This overview summarizes the current knowledge on the  
5 expression of drug transporters in barriers shielding the central nervous system from the  
6 systemic circulation and as such controlling the pharmacokinetics of drugs in the central  
7 nervous system. The main drug transporter families covered are *SLCO*, *SCL22A*, *ABCB* and  
8 *ABCC*, as genes of these families code for numerous drug transporters. While knowledge on  
9 mRNA expression in humans, rats and mice is remarkable, there is clearly a gap in knowledge  
10 on the subcellular expression of transporters in specific cells in the central nervous system and  
11 in the barriers shielding the central nervous system from the systemic circulation. Recent  
12 methodological developments including synthesis of drugs and endogenous substances as  
13 markers for imaging will in the future allow investigating the function and physiologic role of  
14 transporters in the central nervous systems including difficult to address systems like the  
15 choroid plexus *in vivo*.  
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## Introduction

1 All organs in the mammalian body are connected via the blood circulatory system, which  
2 provides both the supply of vital nutrients and disposes waste products. In most instances,  
3 drugs also reach their target via the circulatory system regardless of the route of application.  
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5 Organs are separated from the circulatory system by barriers, which may be leaky like e.g. in  
6 the liver or very tight like in the brain. The brain is separated from the blood by the blood-  
7 brain barrier (BBB) and from the cerebrospinal fluid (CSF) by the choroid plexus (CP) [1, 2].  
8  
9 In addition, the brain also communicates with body extracellular fluids via the arachnoid  
10 epithelium [3], but this pathway contributes only minor to the exchange and is not subject of  
11 this overview. In order to cross barriers, which ultimately are always plasma membranes,  
12 transport systems are needed [4, 5]. Moreover, a tissue specific expression of transporters  
13 allows the body to accumulate substances, like e.g. drugs in an organ-specific manner [1, 4].  
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15 The tightness of the BBB severely limits the access of drugs to the brain and presents major  
16 challenge in the development of drugs with targets in the central nervous system (CNS) [6-8].  
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18 Therefore, the aim of this review is to summarize the current knowledge on the expression of  
19 drug transporters in the BBB and in the CP. As the retina is also part of the CNS, transporters  
20 in the blood-retina barrier (BRB) will also be addressed. Furthermore, we will also highlight  
21 the role of the transporters encountered by drugs and other substances once they have crossed  
22 the barriers surrounding the tissues of the CNS.  
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## Drug Transporters

36 Solutes, like drugs need transporters to enter or exit cells. Generally, transporters mediating  
37 the cellular uptake of drugs belong to the superfamily of solute carriers (SLC). Efflux of drugs  
38 (or their metabolites) frequently occurs against a concentration gradient and is often mediated  
39 by members of the ATP-binding cassette (ABC) transporters. Numerous reviews have been  
40 published on both superfamilies of transporters. The SLC superfamily represents currently 52  
41 families and 395 genes for individual transporters and has been covered recently in a special  
42 issue [9]. Human ABC transporter genes number to 48 members and are divided into seven  
43 families [10], but not all of them act as transporters [11]. It is beyond the scope and space of  
44 this review to describe the individual drug transporter families. This overview will focus on  
45 members of the *SLCO* and *SLC22A* gene families, which are well known to mediate in  
46 addition to endogenous substrates the transport of drugs. Among the ABC protein families,  
47 multidrug resistance protein 1 (MDR1) (*ABCB1*), ABCG2 (also called BCRP, *ABCG2*) and  
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members of the *ABCC* family are known to be important drug and drug metabolite transporters and will therefore be covered here.

Human drug transporters being members of the SLC superfamily and expressed in cerebral blood tissue barriers are listed together with rodent transporters in tables 1 to 5. Rodent species are included as they are used as preclinical species in drug development and as they allow *in vivo* experiments not possible in humans for investigating their role in drug transport in the CNS. In these tables a selection of references (we apologize for omissions) had to be made and data on transport systems obtained from microperfusion experiments as well as from work with microcapillary endothelial cell lines are not included. Microperfusion experiments are most valuable for the elucidation of the *in vivo* situation for drug access to brain tissue but face the difficulty that many drug transporters have an overlapping substrate specificity [12-14]. Brain capillary endothelial cell lines and very likely also other established cell lines display altered transporter expression levels in comparison to their *in vivo* counterparts [15, 16]. It should be realized that there are often conflicting data in the literature. Good examples are the members of the *ABCC* family, about which conflicting data on the expression in the BBB exist up to date [17]. This may relate to the fact that for animals, within a species, different strains show different transporter expression. E.g. in mice, mouse multidrug resistance-associated protein 2 (MRP2) could be detected in the BBB of C57BL/6, Swiss and SvJ, but not FVB mice, while liver and kidney showed positive staining in all strains [18]. Similarly, the expression levels of the mouse monocarboxylate transporter MCT1 in the BBB of C57BL/6J mice were significantly lower than in ddY or FVB mice, while the expression of mBCRP was significantly higher in C57BL/6J mice compared to ddY or FVB mice when analyzed by quantitative targeted proteomics [19]. In human studies, tissue procurement and storage prior to analysis as well as sampling biases will considerably contribute to variable data sets. For protein expression, preference to data obtained from proteomic approaches where available was given over data obtained by Western blotting. Transporter expression in blood neural tissue barriers has additionally been covered in many overviews [17, 20-31].

### **Blood-Brain-Barrier**

In order to provide a stable environment for the CNS, the BBB needs to be able to tightly control the access of substances to the brain. To this end, the endothelial cells lining the walls of the brain capillaries form together with tight junctions an impervious barrier [2]. Brain

1 access of substances (e.g. nutrients like e.g. D-glucose) is consequently controlled by  
2 transport proteins specifically expressed in the luminal and/or abluminal membrane of brain  
3 capillary endothelial cells [2]. Nutrients are transported into the brain by influx systems such  
4 as for example amino acids by members of the *SLCIA* family [32]. Many of these transporters  
5 are equilibrative, i.e. they cannot work against concentration gradients. Extrusion of  
6 substances from brain occurs at the luminal membrane and is mediated by ABC transporters  
7 like MDR1 [33]. ABC transporters utilize energy provided from ATP hydrolysis and can  
8 therefore establish steep concentration gradients. While SLC transporters expressed in plasma  
9 membranes are often uptake transporters, some members act as exchanger of solutes and  
10 consequently mediate may mediate efflux of a substrate in exchange for uptake of another  
11 substance [9]. Consequently, the direction of solute transport by such transporters has to be  
12 determined experimentally, ideally *in situ* in the organ of interest.  
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23 Drug transporters being members of the SLC superfamily and expressed in BBB are listed in  
24 table 1. Specifically, the protein expression of several SLC superfamily members involved in  
25 drug transport (4 organic anion transporting polypeptides (OATPs) (*SLCO*), two organic  
26 cation transporters (OCTs) (*SLC22A*), one organic cation transporter novel type (OCTN)  
27 (*SLC22A*), one concentrative nucleoside transporter (CNT) (*SLC28A*) and two equilibrative  
28 nucleoside transporters (ENTs) (*SLC29A*)) has been reported for human BBB (Table 1). SLC  
29 family members are either facilitating uptake transporters secondary active transporters  
30 capable of working against concentration gradients [9]. Consequently, drug transporters  
31 expressed in the luminal membrane of the BBB are potential entry sites for drugs or toxins  
32 into the BBB. In the case of non-polar expression (i.e. in the luminal and in the abluminal  
33 membrane of the BBB, these transporters may allow their substrates to cross the endothelial  
34 cells of the BBB and the entry into the brain. The number of substrates including drugs for  
35 SLC family members known today is overwhelming and listing them is beyond the scope of  
36 this overview. Lists of substrates can be found in the following (as well as many additional)  
37 reviews: for OATPs [13, 34, 35]; for OATs [36-38]; for OCTs [37, 39]; for CNTs [40, 41];  
38 for ENTs [41, 42]and for MATEs [43, 44].  
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54 Several examples demonstrate indirectly and directly the pharmacologic and toxicologic role  
55 of SLC transporters in the BBB of humans. Drugs used for treatment of pain often need to  
56 enter the CNS [45]. Triptans are drugs used to treat migraine. It was recently demonstrated  
57 that several triptans are substrates of OATP1A2 expressed in BBB (table 1) [46]. Hence, it is  
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1 reasonable that hydrophilic triptans may use OATP1A2 to cross the BBB. The relative  
2 transport rate of OATP1A2-mediated transport decreases from triptans with tertiary to triptans  
3 with primary amines in heterologous expression systems [46]. While transport of drugs across  
4 the BBB is considered to be beneficial this is not the case for toxins. This is exemplified by an  
5 incidence in Brazil, where 126 patients of a hemodialysis unit suffered from a microcystin  
6 intoxication and 60 patients subsequently died [47]. The patients developed acute  
7 neurotoxicity and subacute hepatotoxicity. Expressing OATP1A2 in *Xenopus laevis* oocytes  
8 allowed demonstrating that this transporter mediates uptake of microcystin [48]. Moreover,  
9 OATP1A2 expression was required for microcystin to exert its toxic effects on oocytes.  
10 Lately, it was reported that OATP1A2 is expressed in neurons in human brain [49]. This  
11 finding adds an additional piece to the mechanistic understanding of microcystin toxicity:  
12 Microcystin inhibits protein phosphatases at nanomolar concentrations [50]. Hence the  
13 expression of OATP1A2 in neurons may allow microcystin, once it has crossed the BBB, the  
14 entry into neurons followed by impairment of neuronal functions. Looking at an endogenous  
15 compound, thyroid hormones are instrumental for the development of brain and in adult life  
16 for metabolic adaptation [51]. OATP1C1, which is expressed at the BBB (table 1) [52] is a  
17 high-affinity thyroid hormone transporter [53] and consequently allows the entry of thyroid  
18 hormones into brain. These examples clearly demonstrate that expression of transport proteins  
19 in the BBB in addition to endogenous substances allows the entry of xenobiotics into the  
20 brain. Hence, understanding the molecular properties of transporters working in the BBB will  
21 contribute to a better understanding of the penetration of drugs across the BBB to reach  
22 pharmacodynamics targets in the brain. Therefore, the relevance of the BBB as a selective  
23 guard of the brain is not only recognized by physiologists and pharmacologists but has also  
24 initiated large efforts for developing tools to study the impact of BBB early in drug  
25 development [8, 54].

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47 ABC transporters are mostly cellular efflux transporters and either act as cellular defense  
48 systems for substances or export them from the cytoplasm [9]. They are often located in  
49 strategic organ boundaries including BBB, where they are most important for controlling  
50 access to body sanctuaries [55]. The importance of ABC transporters is further emphasized by  
51 the observation that more than 20 (out of 48) human ABC transporters are important in  
52 various acquired and inherited human diseases [56]. Drug transporters being members of the  
53 ABC superfamily and expressed in human BBB are listed in table 2. The protein expression  
54 of several ABC transporter superfamily members involved in drug transport (one MDR)  
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(*ABCB*), four MRPs (*ABCC*), and one ABCG (*ABCG*) has been reported for human BBB (Table 2). With respect to drug transport, members of the *ABCB*, *ABCC* and *ABCG* family are capable of transporting numerous drugs. List of substrates including drugs for drug transporting ABC family members can be found e.g. in the following reviews: [27, 57-67].

The brain protective role of ABC transporters at the BBB is best illustrated with the clinical studies aimed at inhibiting MDR1 in drug treatment of cancer. For example, in a phase I trial coadministration of etoposide and cyclosporine lead to more severe nausea in some patients receiving both drugs [68]. In another phase I study where etoposide and the second generation MDR1 inhibitor PSC 833 were combined to treat cancer patients, severe ataxia was observed as dose-limiting toxicity of PSC833 [69]. In this case, the MDR1 inhibitor allowed etoposide to cross the BBB inducing neurotoxicity. The same toxicity was later observed in a phase III trial [70]. Similarly, a high-dose oral tamoxifen phase I trial in combination with verapamil revealed dose-limiting neurologic side effects [71]. Taken together, these few examples in humans demonstrate the importance of luminal ABC-transporters in BBB as gate keepers preventing or lowering the exposure of the brain to potentially neurotoxic agents. In principle, given access of a substrate into BBB, abluminal ABC-transporters should enhance the exposure of the brain to their substrates. To the best of our knowledge we found no such examples in the literature.

### Choroid Plexus

The CP is located in the lateral third and forth brain ventricles and produces the cerebrospinal fluid. It is a highly vascularized organ containing in the stroma loose connective tissue and a fenestrated endothelium. A tight monolayer of CP epithelial cells connected by tight junctions near the apical surface forms the blood cerebrospinal fluid barrier (BCSFB) [72-74]. In addition to its central role in the production of cerebrospinal fluid (CSF), it also removes organic anions as well as drugs and drug metabolites from the CSF, making the CP an important detoxifying system for the CSF [72, 73].

The protein expression of several SLC superfamily members involved in drug transport has so far been reported for CP. In humans (two OATPs and two OATs are identified in CP (Table 3) and one member of the *ABCB* and two members of the *ABCC* family have been demonstrated at the protein level (table 4). Inferring from rodent tissues, the two MRPs likely are expressed in the basolateral membrane of human CP epithelial cells and consequently



1 mediate export of substances from the CSF back into blood after their uptake across the apical  
2 membrane. The individual role of these transporters in drug transport cannot be directly  
3 assessed in humans despite the fact that e.g. analgetics and anticancer drugs are administered  
4 to patients via an intrathecal route. Clearance of such drugs from the CSF is obvious, but in  
5 addition to the CP, the villi of the arachnoids may also be involved in elimination of  
6 substances from the CSF. Drug transporter expression in arachnoid villi is still a largely  
7 uncharted area. In addition, the hydrodynamics of the cerebrospinal fluid, which may  
8 contribute to drug elimination from this body compartment is rather controversial [74, 75].  
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### 16 **Blood Ocular Barrier**

17 The retina is an organ rich in neurons. The retina is exposed on the anterior side to the  
18 vitreous humor and at the posterior side to the choroid. In the retina, there exist two BRB,  
19 namely the inner BRB formed by retinal capillary endothelial cells and the outer BRB formed  
20 by the retinal pigmented epithelial cells [21, 76]. These two barriers prevent uncontrolled  
21 entry of blood constituents into the eye. Consequently, either one or both of these barriers  
22 needs to be overcome by drugs, which are systemically administered for treatment of retinal  
23 diseases.  
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32 The protein expression of several SLC superfamily members involved in drug transport (three  
33 OATPs, one OATs and one member of the ABCB and ABCC families each has so far been  
34 reported for human BRB (Table 5). Direct information on the role of transporters in drug  
35 permeation through the BRB in humans is missing, but it should be noted that systemically  
36 administered antibiotics reach the vitreous humor, e.g. ciprofloxacin [77] or daptomycin [78].  
37 Ciprofloxacin is known to interact with OATPs [79]. Also, prostaglandins are used as first  
38 line treatment of glaucoma [80] and are substrates of OATPs [81, 82]. While these examples  
39 do not prove that transport systems are involved in the ocular disposition of drugs, they are  
40 nevertheless strongly indicative, as in particular daptomycin is rather membrane impermeable.  
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### 51 **Animal models for investigating the role of drug transporters in the central nervous** 52 **system**

53 Animal models are a potent means to investigate the role of transporters in the CNS. Such  
54 models yield most valuable information on the function of drug transporters both at blood  
55 tissue barriers in the CNS as well as on their physiologic role in the CNS. For example, more  
56 than 50 years ago it was demonstrated in a goat model that phenolsulfonphthalein (also called  
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1 phenol red), which at physiologic pH is a dianionic compound and the anionic angiographic  
2 contrast agent diodrast are actively transported out from the CSF into blood [83]. The  
3 understanding and consequently appreciation of the role of transporters in the BBB changed  
4 with the seminal work by Schinkel and coworkers who demonstrated that in mice with an  
5 inactivated *Mdr1a* gene the issue concentration in brain was 87-fold increased in comparison  
6 to controls and 22.4 fold for vinblastine [84]. In addition, the same team found no negative  
7 effect on the physiology of mice when both *Mdr1* genes were inactivated, indicating that in  
8 this species mMDR1 (table 2) plays no vital role [85]. In contrast, mice with a disrupted  
9 *Abcg2* gene gave conflicting results on the role of mABCG2 in the BBB (table 2) [86].  
10 However, if studies were performed in mice, which in addition to *Abcg2* had also disrupted  
11 *Mdr1* genes, it became clear that for some drugs *Abcg2* contributes to preventing drugs from  
12 crossing the BBB. This example nicely illustrates the complexity of *in vivo* studies with drugs  
13 sharing multiple transporters. Also the role of mOATPs (table 1) in penetrating the BBB  
14 became evident in mice with a knockout of *Slco1a4* [87] as well as with the *Slco1a1b* locus,  
15 as in such animals statins showed a considerably lower entry into brain [88].  
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29 Genetically modified mice can also be used to study the efflux of drug metabolites produced  
30 in brain. Oseltamivir is an ethylester prodrug for Ro 64-0802. The latter is an inhibitor of  
31 neuraminidase and as such used in the prophylaxis and treatment of influenza virus infections  
32 [89]. This drug is associated with adverse psychiatric effects [90]. Oseltamivir is activated by  
33 carboxylesterase 1 [89], which is among other organs also expressed in brain [91]. Studies  
34 with *Abcb1* knockout mice showed that mMDR1 isoforms limit brain access of oseltamivir  
35 across the BBB [92]. Microinjection of RO 64-0802 into the brain of rats deficient either for  
36 *Abcc4* or *SLC22a8* demonstrated that both, mMRP4 (table 2) and mOAT3 (table 1) are  
37 involved in the elimination of RO 64-0802 from the brain across the BBB [93].  
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47 The opposite localization with respect to the lumen of blood vessels in the BBB (table 4) and  
48 in the CP (table 5) of MDR1 and ABCG2 leads to differential effects on the brain entry of  
49 drugs across the BBB and into the CSF. Mice with an *Abcb1* or *Abcg2* knockout show an  
50 increased accumulation of topotecan in the brain parenchyma, while its penetration into the  
51 CSF is reduced [94]. In double knockout animals, these effects were additive for both  
52 barriers. In mice with and inactivated *Slc22a8* gene, accumulation of fluorescein into the  
53 isolated CP was greatly reduced in comparison to wild type animals [95]. Hence, knock-out  
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1 mice provide a most valuable tool to investigate the impact of transporters not only in the  
2 BBB but also in CP [96].  
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5 OATP1C1 was identified as a high affinity thyroxine transporter [53], which is expressed at  
6 the BBB (table 1) and in the CP (table 5). Mice having an inactivated *Oatp1c1* gene showed a  
7 significantly reduced brain content of T4 and T3 with no change in the plasma concentration  
8 of these two thyroid hormones [97], clearly demonstrating the important role of this  
9 transporter for thyroid hormone supply to the brain. In the same knockout mice strain, uptake  
10 of sulforhodamine 101 into astrocytes of the hippocampus is severely impaired [98].  
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## 17 **Outlook**

18 Ample evidence accumulated in recent years indicates the importance of transporters  
19 expressed in BBB, CP and BRB for mediating the passage of drugs as well as nutrients and  
20 metabolites. Great progress has also been made, in particular in model animals, in the  
21 identification and quantification of transport proteins in these barriers. The depth of  
22 knowledge however varies considerably between the different barriers and the different  
23 species as the availability of CP and even more so of the BRB is very limited, in particular  
24 from humans. Hence, alternate tools such as good antibodies are urgently needed for defining  
25 the transporter inventory in these barriers. Importantly, antibodies have a major advantage in  
26 that they are key to define the subcellular expression of transporters in barriers. As movement  
27 of substances across barriers into and out from the CNS is often unidirectional and in some  
28 instance may occur against concentration gradients, exact knowledge on the subcellular  
29 expression of transporters together with and understanding in their transport mechanism is  
30 key for understand the contribution of individual transporters to the passage or blockage of  
31 compounds across these barriers. Progress in this area may in future come from a systems  
32 biology approach aimed at generating antibodies against a larger number of human proteins,  
33 like for example the Human Protein Atlas project [99]. In addition, advances in the field of  
34 targeted proteomics should certainly help to increase the knowledge needed for developing  
35 pharmacokinetic models for the uptake of drugs into the brain and for the export of drug  
36 metabolites from the brain [16]. In addition, for developing novel kinetic models for brain  
37 uptake and export, the contribution of drug metabolism, e.g. in BBB has to be taken into  
38 account [23].  
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Imaging methods and in particular positron emission tomography (PET) have made rapid and large progress in recent years such that PET becomes a feasible tool for studying the function of transporters *in vivo* [100]. First studies with healthy subjects [101] and with patients suffering from epilepsy [102, 103] have clearly provided data demonstrating that imaging of *in vivo* function of transporters not only in animal models but also in humans will soon become a very valuable tool for understanding drug transport across barriers shielding the brain. It is important to note that transporter function *in vivo* cannot only be monitored by PET, but also by single-photon emission-coupled tomography [104]. The development of novel imaging probes should in the future certainly help the development of novel drugs with targets in the CNS, as their passage through the barriers can be followed *in vivo*. This methodology, together with stringent quality control of the label [105], will certainly also help to address issues of transporter based drug-drug interactions at the BBB, where clearly more information for clinics is needed [20, 106, 107].

**Acknowledgements**

1 Bruno Stieger is supported by Grant # 310030\_144195 from the Swiss National Science  
2 Foundation and by the National Center of Competence in Research (NCCR) TransCure  
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4 (University of Berne, Switzerland).  
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**Table 1** Expression of SLC transporters at the blood brain barrier

<b>transporter</b>	<b>mRNA expression</b>	<b>protein expression</b>	<b>cellular localization</b>
<i>human</i>			
OATP1A2	brain [108, 109]	brain [110]	brain capillary endothelial cells [110]
OATP1C1	brain [53]		brain capillary endothelial cells [52]
OATP2B1	brain microcapillaries [32]	brain microcapillaries [111]	brain capillary endothelial cells [49]
<i>rat</i>			
rOATP1A4	brain [112], brain microcapillaries [113]	brain [114]	brain capillary endothelial cells: luminal and abluminal [114]
rOATP1C1	brain microcapillaries [115]	Brain microcapillaires [116]	brain capillary endothelial cells: luminal and abluminal [52, 117]
rOATP2B1	brain [118], brain microcapillaries [113]		brain capillary endothelial cells: abluminal [113]
<i>mouse</i>			
mOATP1A1	brain microcapillaries [119]		
mOATP1A4	brain microcapillaries [119, 120]	brain microcapillaries [87, 116, 121-125]	brain capillary endothelial cells: luminal and abluminal [87]
mOATP1A5	brain microcapillaries [119]		brain capillary endothelial cells [119]
mOATP1A6	brain microcapillaries [119]		
mOATP1C1	brain microcapillaries [120, 126, 127]	brain microcapillaries [121, 123-125]	brain capillary endothelial cells [52]



1	mOATP2B1	brain microcapillaries [120]		
2				
3				
4				
5	<i>human</i>			
6				
7	OCT1	brain [128]	cultured brain microvessel endothelial cells: luminal [129]	cultured brain microvessel endothelial cells: luminal [129]
8				
9				
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11				
12	OCT2	brain [130]	cultured brain microvessel endothelial cells: luminal [129]	cultured brain microvessel endothelial cells: luminal [129]
13				
14				
15				
16				
17				
18	OCT3	brain microcapillaries [32, 126]	brain microcapillaries [131]	brain capillary endothelial cells [131]
19				
20				
21				
22	OCTN2	brain microcapillaris [32], cultured brain microvessel endothelial cells [132]		
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31	<i>rat</i>			
32				
33	rOCT1	brain [133]	cultured brain microvessel endothelial cells: luminal [129]	cultured brain microvessel endothelial cells: luminal [129]
34				
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39	rOCT2	brain [133]	cultured brain microvessel endothelial cells: luminal [129]	cultured brain microvessel endothelial cells: luminal [129]
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44	<i>mouse</i>			
45				
46	mOCT1			cultured brain microvessel endothelial cells: luminal [129]
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52	mOCT2	brain [134]		cultured brain microvessel endothelial cells: luminal [129]
53				
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57	mOCT3	brain microcapillaries [126]		
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61	mOCTN2	brain microcapillaries		
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65				

	[126]		
<i>rat</i>			
rOAT2		brain microcapillaries [135]	
rOAT3	brain microcapillaries [136]	brain microcapillaries [123, 125, 135, 137]	brain microcapillaries: luminal and abluminal [138]
<i>mouse</i>			
mOAT2	brain microcapillaries [126]		
mOAT3	brain microcapillaries [120, 126, 136]	brain microcapillaries [121, 124, 137]	brain microcapillaries: abluminal [139]
<i>rat</i>			
rCNT2	brain microcapillaries [140]		
<i>human</i>			
ENT1		brain microcapillaries[32, 123, 141]	
<i>mouse</i>			
mENT1		brain microcapillaries [123, 124]	
<i>human</i>			
MATE1	brain microcapillaries [131]	brain microcapillaries [131]	brain microcapillaires [131]

Expression at the mRNA level was demonstrated by Northern blot analysis, PCR of isolated brain microcapillaries or by in situ hybridization. Protein expression was demonstrated by

Western blotting or by proteomic methods using isolated brain microcapillaries. Cellular localization was demonstrated by immunohistochemistry and in some instances by domain-specific biotinylation experiments.

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**Table 2** Expression of ABC transporters at the blood brain barrier

<b>transporter</b>	<b>mRNA expression</b>	<b>protein expression</b>	<b>cellular localization</b>
<i>human</i>			
ABCG2(BCRP)	brain microcapillaries [142]	brain microcapillaries [32, 123, 141]	brain microcapillaries: luminal [143, 144]
MDR1	brain microcapillaries [142]	brain microcapillaries [32, 123]	brain microcapillaries: luminal [33]
MRP1	brain microcapillaires [142]	brain microcapillaries [141, 145]	brain microcapillaries: luminal [146]
MRP2	brain [143]		
MRP3	brain microcapillaries [142]		
MRP4	brain microcapillaries [142]	brain microcapillaries [32, 123, 141]	brain microcapillaries: luminal [146]
MRP5	brain [142, 143]		brain microcapillaries, luminal [146]
MRP6	brain microcapillaries [142]		
<i>rat</i>			
rABCG2	brain microcapillaries [142, 147]	brain microcapillaries [116, 137]	brain microcapillaries: luminal [147]
rMDR1A	brain microcapillaries[113, 142]	brain microcapillaries [137]	brain microcapillaries: luminal [145, 148]
rMRP1	brain microcapillaries [142, 149]	brain microcapillaries [116]	brain microcapillaries: abluminal [113]
rMRP2	brain microcapillaries [150]	brain microcapillaries [151]	brain microcapillaris: luminal [150]
rMRP3	brain microcapillaries [152]	brain microcapillaires [116]	
rMRP4	brain microcapillaires [113, 142]	brain microcapillaries [116, 137]	brain microcapillaries: luminal [113, 153]

rMRP5	brain microcapillaries [113, 142]	brain microcapillaries [116]	brain microcapillaries: abluminal [113]
rMRP6	brain microcapillaries [142]	brain microcapillaries [116]	
<i>mouse</i>			
mABCG2	brain microcapillaries [120, 142, 154] [155]	brain microcapillaries [19, 123-125, 137]	brain microcapillaries: luminal [156]
mMDR1A	brain microcapillaries[120, 157]	brain microcapillaries [19, 121, 124, 125]	brain microcapillaries: luminal [18]
mMRP1	brain microcapillaries [142]		brain microcapillaries: abluminal [18]
mMRP3	brain microcapillaires [142]	brain microcapillaries [158]	
mMRP4	brain microcapillaries [120, 142]	brain microcapillaries [19, 121, 123, 125]	brain microcapillaries: luminal [153]
mMRP5	brain microcapillaries [142]		brain microcapillaries: luminal [18]
mMRP6	brain microcapillaries [142]		

Expression at the mRNA level was demonstrated by Northern blot analysis, PCR of isolated brain microcapillaries or by in situ hybridization. Protein expression was demonstrated by Western blotting or by proteomic methods using isolated brain microcapillaries. Cellular localization was demonstrated by immunohistochemistry and in some instances by domain-specific biotinylation experiments.

**Table 3** Expression of SLC transporters in choroid plexus

<b>transporter</b>	<b>mRNA expression</b>	<b>protein expression</b>	<b>cellular localization</b>
<i>human</i>			
OATP1C1			choroid plexus epithelial cells: apical and basolateral [52]
OATP3A4 (v1 and v2)			choroid plexus epithelial cells: basolateral [159]
<i>rat</i>			
rOATP1A1	choroid plexus [160, 161]	choroid plexus [160, 161]	choroid plexus epithelial cells: apical [160]
rOATP1A3	choroid plexus [162]	choroid plexus [163]	choroid plexus epithelial cells: apical [162]
rOATP1A4	choroid plexus [114, 164-167]		choroid plexus epithelial cells: basolateral [114]
rOATP1A5	choroid plexus [161, 165, 167]	choroid plexus [161, 163]	choroid plexus epithelial cells: apical [113, 161]
rOATP1C1	choroid plexus [163, 167, 168]	choroid plexus [117]	choroid plexus epithelial cells: basolateral and apical [52]
rOATP2A1	choroid plexus [168, 169]		primary choroid epithelial cells: apical [169]
rOATP2B1	choroid plexus [165]		choroid plexus epithelial cells: apical [113]
rOATP3A1	choroid plexus [167]		
rOATP4A1	choroid plexus [165]		
<i>mouse</i>			
mOATP1A4	choroid plexus [119]	choroid plexus [87]	
mOATP1A5	choroid plexus [119]	choroid plexus	choroid plexus epithelial

		[119]	cells: apical[119]
mOATP1A6	choroid plexus [119]		
mOATP1C1	choroid plexus [127, 170]	choroid plexus [171]	choroid plexus epithelial cells: basolateral [171], apical and basolateral [52]
<i>rat</i>			
rOCT1	choroid plexus [165]		
rOCT2	choroid plexus[168, 172]		
rOCT3	choroid plexus [165, 172]		choroid plexus epithelial cells [173]
rOCTN1	choroid plexus [165]		
rOCTN2	choroid plexus [165, 167]		
<i>mouse</i>			
mOCTN1			choroid plexus epithelial cells [174]
mOCTN2			choroid plexus epithelial cells [174]
mOCTN3			choroid plexus epithelial cells [174]
<i>human</i>			
OAT1			choroid plexus epithelial cells [175]
OAT3			choroid plexus epithelial cells[175]
<i>rat</i>			
rOAT1	choroid plexus [95, 167, 168]		
rOAT2	choroid plexus [95, 165,		

	168]		
rOAT3	choroid plexus [165, 167]	choroid plexus [176]	choroid plexus epithelial cells: apical [113, 176]
<i>mouse</i>			
mOAT1	choroid plexus [3, 95, 177]		
mOAT2	choroid plexus [95]		
mOAT3	choroid plexus [3, 177]		
<i>rat</i>			
rCNT2	choroid plexus [165]Primary choroid plexus epithelial cells [167, 178]	primary choroid plexus epithelial cells [178]	
rCNT3	choroid plexus [165]Primary choroid plexus epithelial cells [167, 168, 178]		
<i>human</i>			
ENT1		choroid plexus [179]	
ENT2		choroid plexus [179]	
ENT3		choroid plexus [179]	
<i>human</i>			
CNT3		choroid plexus [179]	
<i>rat</i>			



rENT1	choroid plexus [165], choroid plexus epithelial cells [167, 180]	primary choroid plexus epithelial cells [178]	
rENT2	choroid plexus [165, 181]Primary choroid plexus epithelial cells [167, 178]	primary choroid plexus epithelial cells [178]	
rPEPT1	choroid plexus [165]		
rPEPT2	choroid plexus [165, 167, 168, 182]	choroid plexus [163, 183]	choroid plexus epithelial cells: apical [184], primary choroid plexus epithelial cells: apical {Shu, 2002 #8387
<i>mouse</i>			
mENT1		choroid plexus[123, 124]	

Expression at the mRNA level was demonstrated by Northern blot analysis, PCR of isolated choroid plexus or by in situ hybridization. Protein expression was demonstrated by Western blotting or by proteomic methods using isolated choroid. Cellular localization was demonstrated by immunohistochemistry.

**Table 4** Expression of ABC transporters in choroid plexus

<b>transporter</b>	<b>mRNA expression</b>	<b>protein expression</b>	<b>cellular localization</b>
<i>human</i>			
MDR1	choroid plexus [185]	choroid plexus [145, 186]	choroid plexus epithelial cells [144, 186]
MRP1	choroid Niehof, 2009 #8433}	choroid plexus [145, 186]	choroid plexus epithelial cells [144, 186]
MRP2	choroid plexus [185]		
MRP3	choroid plexus [185]		
MRP4	choroid plexus [185]		choroid plexus epithelial cells: basolateral [153]
MRP5	choroid plexus [185]		
MRP6	choroid plexus [185]		
<i>rat</i>			
rABCG2	choroid plexus [187, 188]	choroid plexus [188]	
rMDR1A	choroid plexus [165, 188]	choroid plexus [145, 186] (C219) [188]	choroid plexus epithelial cells [186] (C219)
rMDR1B	choroid plexus [165, 167]	choroid plexus [145, 186] (C219)	choroid plexus epithelial cells [186] (C219)
rMRP1	choroid plexus [165-167, 187, 188]	choroid plexus [145, 186, 189]	choroid plexus epithelial cells: basolateral [18, 113, 119, 145, 190]
rMRP2	choroid plexus [165, 168, 191]		
rMRP3	choroid plexus [165]		
rMRP4	choroid plexus	choroid plexus [163,	choroid plexus epithelial cells:

	[165, 167, 191]	187]	basolateral [113, 153]
rMRP5	choroid plexus [165, 167, 191]		
rMRP6	choroid plexus [165]	choroid plexus [163]	
mouse			
mABCG2	choroid plexus [3]	choroid plexus [192]	choroid plexus epithelial cells: apical [156]
mMDR1A	choroid plexus[3]		
mMRP1	choroid plexus [3]		choroid plexus epithelial cells: [193], basolateral [190]
mMRP4	choroid plexus [3, 170]	choroid plexus [153]	choroid plexus epithelial cells: basolateral [52, 153]

Expression at the mRNA level was demonstrated by Northern blot analysis, PCR of isolated choroid plexus or by in situ hybridization. Protein expression was demonstrated by Western blotting or by proteomic methods using isolated choroid plexus. Cellular localization was demonstrated by immunohistochemistry.

**Table 5** Transporter expression in blood retinal barriers

<b>transporter</b>	<b>mRNA expression</b>	<b>protein expression</b>	<b>cellular localization</b>
<i>human</i>			
OATP1A2	retina [82]	retina [49]	retinal pigmented epithelial cells [82]
OATP1B3	retina [194]		
OATP1C1			Choroid plexus epithelial cells: apical and basolateral [52]
OATP2B1	retina [82]	retina [49]	retinal pigmented epithelial cells [82]
<i>rat</i>			
rOATP1A4	retina [164, 195], retinal pigmented epithelial cells [196], blood retinal capillaries [197]	retina [196, 198]	blood retinal capillary endothelial cells: abluminal [198], retinal pigmented epithelial cells, apical [196, 198, 199]
rOATP1A5	retina [164, 196, 200]	retina [196]	retinal pigmented epithelial cells [201]
rOATP1C1	blood retinal capillaries [197]	retina [198]	blood retinal capillary cells: luminal and abluminal [198], retinal pigmented epithelial cells, basolateral [198]
rOATP2B1	retina [195]		
rOATP3A1	retina [195]		
rOATP4A1	retina [195, 201]	retina [201]	
<i>human</i>			
OCT1		retinal pigmented epithelium [202]	
OCT2	retina [194]		

OCT3	retina [194]		
OCTN2	retina [194]		
<i>rat</i>			
rOCT1	retina [195]{		
rOCT2	retina [195]{		
<i>mouse</i>			
mOCT3	retinal pigmented epithelial cells [203]		
mOCTN1	blood retinal capillary epithelial cells [204]		
mOCTN2	blood retinal capillary epithelial cells [204]		
<i>rat</i>			
rOAT2	retina [195]		
rOAT3	retina [195], Blood retinal capillaries [205]	primary cultured blood retinal capillary endothelial cells [205]	blood retinal capillary endothelial cells: abluminal [205]
<i>rat</i>			
rCNT2	retina [195]		
rCNT3	retina [195]		
<i>human</i>			
PEPT1		retinal pigmented epithelium [202]	
PEPT2		retinal pigmented epithelium [202]	
<i>rat</i>			

1	rENT1	retina [195]		
2	rENT2	retina [195]		
3				
4				
5	<i>human</i>			
6	ABCG2	retina [194]		
7	MDR1	retina [194,] primary cultured retinal pigmented epithelial cells [206]	primary cultured retinal pigmented epithelial cells [206]	retinal pigmented epithelial cells:apical and basolateral [206]
8	MRP1	retina [194], primary cultured retinal pigmented epithelial cells[207]	primary cultured retinal pigmented epithelial cells [207]	
9	MRP5	retina [194]		
10				
11	<i>rat</i>			
12	rABCG2	retina [195]		
13	rMDR1	blood retinal capillaries [197], retina [195]		blood retinal capillary endothelial cells: [208], luminal [205] retinal pigmented epithelial cells [208]
14	rMRP1	retina [195]		
15	rMRP2	retina [195]		
16	rMRP3	retina [195]		
17	rMRP4	retina [195]		
18	rMRP5	retina [195]		
19	rMRP6	retina [195]		
20				
21	<i>mouse</i>			
22	mABCG2	retina [209]	retina [209]	blood retinal capillary endothelial cells: luminal [209]
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mMRP1	blood retinal capillaries [210]		
mMRP3	blood retinal capillaries [210]		
mMRP4	blood retinal capillaries [210]		
mMRP6	blood retinal capillaries [210]		

Expression at the mRNA level was demonstrated by PCR of isolated retinal microcapillaries. Protein expression was demonstrated by Western blotting using isolated retinal microcapillaries and cellular localization was demonstrated by immunohistochemistry.