CNPT The Japanese Society of Clinical Neuropsychopharmacology
Clinical Neuropsychopharmacology and Therapeutics
scnp

The Role of Drug Transporters on Psychotropic Penetration of the Blood–Brain Barrier

Yumiko Akamine, B.S., Kayoko China, M.S., and Tsukasa Uno, Ph.D.

Department of Hospital Pharmacy, Faculty of Medicine,
University of the Ryukyus, Okinawa, Japan

ABSTRACT

At the blood–brain barrier (BBB), the superfamily of ATP-binding cassette (ABC) transporters includes the ABCB1 subfamily corresponding to P-glycoprotein (P-gp), the ABCC subfamilies of multidrug resistance-associated proteins (MRPs), and the ABCG2 subfamily corresponding to breast cancer resistance protein (BCRP). These efflux transporters are located mainly in the endothelial cells forming the BBB and prevent the entry of xenobiotics into the brain. Since psychotropics act on target sites of the central nervous system (CNS) in the brain, it is very important to know these transporters' roles at the BBB and to determine the brain drug concentrations at the targeted sites of the CNS. However, there is little information on human brain concentrations of psychotropics. Recent studies have demonstrated that brain concentrations of many psychotropics are significantly higher in P-gp-knockout mice than in wild-type mice. This result implies that P-gp may be a key player in the regulation of brain psychotropic pharmacokinetics and possibly causes the P-gp-mediated drug interaction at the BBB. In this review, we discuss the current findings concerning the role of drug transporters on the concentrations of psychotropics in the brain and summarize the available in vivo studies related to psychotropics.

Keywords: psychotropic drugs, drug transporters, P-glycoprotein, blood–brain barrier

Received January 16, 2012 / Accepted March 30, 2012 / Published May 11, 2012

INTRODUCTION

Since the central nervous system (CNS) is separated from peripheral blood circulation by physiological barriers, e.g., the blood–brain barrier (BBB), the CNS is not directly exposed to drugs in systemic circulation [1-4]. Although many psychotropic medications reach specific sites within the CNS via the circulatory system (Figure 1), the precise concentrations of the psychotropic drugs in the CNS cannot be determined in each patient [5]. Therefore, ensuring drug delivery to the CNS and achieving appropriate drug concentrations in the CNS are the final targets of rational psychiatric pharmacotherapy. The BBB is composed of the tight junctions of capillary endothelial cells attached to the brain. It protects the CNS from potentially toxic substances by limiting the paracellular movement of endogenous and exogenous compounds [6,7]. The endothelial cells of the BBB contain numerous membrane transporters related to the influx or efflux of various important therapeutic drugs [6-8]. Previous reports suggest that the expression and activity of drug transporters at the BBB limit the entry of psychotropics and regulate their effects and toxicity [9].

In recent years, although many drug transporters, including the ATP-binding cassette (ABC) protein family and the solute carrier (SLC) family, have been identified at the BBB [8-11], one focus of study has been the role of the superfamily of ABC transporters in drug penetration into the brain [12]. The subfamilies at the BBB include the ABCB1 subfamily

Corresponding Author: Tsukasa Uno, Ph.D., Department of Hospital Pharmacy, Faculty of Medicine, University of the Ryukyus, 207 Uehara, Nishihara, Okinawa 903-0215, Japan
Tel.: +81-98-895-1346 Fax: +81-98-895-1487 Email: u370409@med.u-ryukyu.ac.jp

corresponding to P-glycoprotein (P-gp), the ABCC subfamilies of multidrug resistance-associated proteins (MRPs), and the ABCG2 subfamily corresponding to breast cancer resistance protein (BCRP) [12]. These transporters are responsible for an efflux pump to prevent toxic substrates and many therapeutic medications from entering the brain [12]. Of these efflux transporters, P-gp has been established as a key factor at the BBB [13]. Multiple studies have reported the presence of P-gp at the BBB [14,15], which is associated with the clinical response of many CNS-acting drugs as psychotropics [8,9,16-18]. In addition, several studies of drug interactions in humans have found that P-gp-mediated transport activity is modulated by its own inhibition and induction under polypharmacy, which can affect drug pharmacokinetics [19,20].

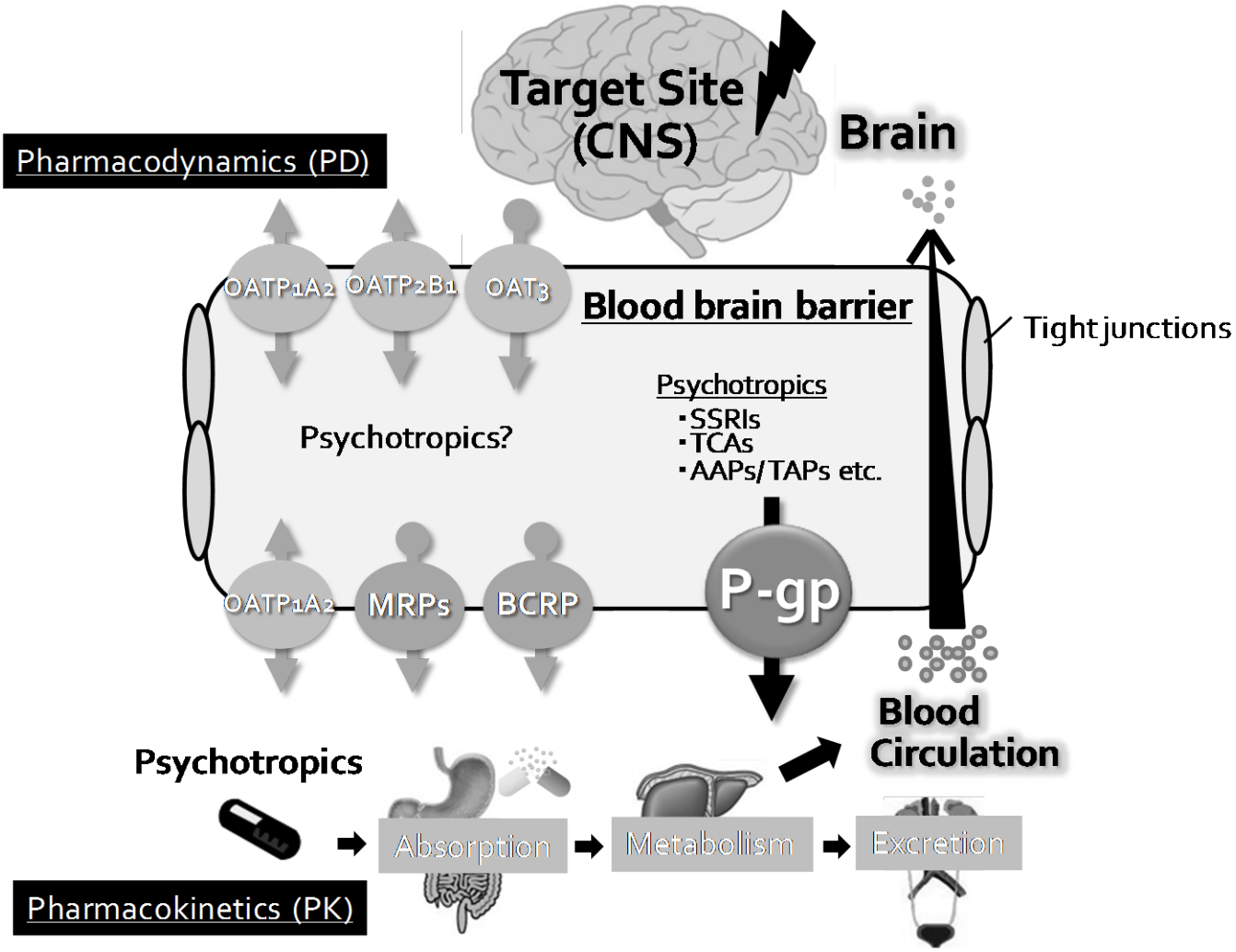

Fig. 1. Drug Delivery of Psychotropics

However, in the case of clinically significant drug interactions at the BBB, it is difficult to tell if these interactions are based on pharmacokinetic or pharmacodynamic changes. For example, although the interaction between quinidine and loperamide is known to induce respiratory depression as a severe side effect, it has been reported that there was no change in the loperamide plasma concentrations [21]. The mechanism of this interaction may be an elevation in the brain concentrations of loperamide caused by quinidine coadministration. It has also been reported that, in P-gp knock-out mice models, the CNS concentrations of loperamide were increased by 10- to 100-fold [14]. Since many psychotropics are known as P-gp substrates, a greater understanding of the functional changes in P-gp activity at the BBB is needed in clinical practice, as this will enable more accurate prediction of the actual therapeutic response to psychotropics. In this review, we describe the role of drug transporters, mainly P-gp, on psychotropic penetration of the BBB.

INFLUENCE OF P-GP IN ANIMAL STUDIES

The role of P-gp at the BBB has frequently been studied using the *mdr1a* (encoding P-gp)-knockout mouse (*mdr1a(-/-)* mouse) [22]. This mouse model is a unique and valuable pharmacologic tool in examining the *in vivo* P-gp function at the BBB. Two types of *mdr1a* and *mdr1b* (encoding P-gp) were detected in this mouse study, each of which showed different tissue distribution [23]. Recent studies have established that only P-gp-based mdr1a is expressed at the BBB, not mdr1b [9,24,25]. Accordingly, a model study using the *mdr1a(-/-)* mouse has clearly demonstrated a lack of P-gp at the BBB. Many psychotropics have been investigated using this knockout mouse model, and dramatic differences in the brain concentrations of psychotropics between knockout and wild-type mice have been consistently confirmed [9,16,26,27]. For example, the brain concentrations of risperidone and its active metabolite 9-hydroxyrisperidone (paliperidone) were reported to be at least 10 times greater in knockout mice than in wild-type mice [28]. These findings suggest that P-gp is a key determinant of the brain pharmacokinetics of various psychotropics.

Interestingly, in this study, no significant differences in the plasma concentrations of risperidone and paliperidone were found between wild-type and knockout mice (1.4-fold for risperidone, 1.1-fold for paliperidone, respectively) [28]. This indicates that increased brain concentrations of P-gp-associated psychotropics independently occur irrespective of changes in the blood concentrations of the drugs, which may potentially cause CNS-related side effects. Furthermore, despite the fact that P-gp is expressed in the liver, intestine and kidney as well as the BBB [11], the discrepancy in brain and blood concentrations of the drugs implies that these P-gp psychotropics have different tissue distributions and organ transitions in relation to whole body drug pharmacokinetics. Therefore, these studies demonstrate the significant influence of P-gp on CNS pharmacotherapy, and it would be useful to know to what extent P-gp activity is pathophysiologically modulated under polypharmacy with possibly interacting drugs.

P-GP AND POSITION EMISSION TOMOGRAPHY (PET) STUDY

In recent clinical studies, positron emission tomography (PET) was used to study the human activity of P-gp at the BBB. Since a radioligand [11C]-verapamil has been shown to be effectively transported by P-gp at the BBB in humans, this substrate is a suitable probe for clinical PET study to evaluate P-gp function [29]. Langer O et al. [30] reported that the enhanced P-gp activity in PET studies using R-[11C]-verapamil might contribute to drug resistance in some patients with treatment-refractory epilepsy. In addition, de Klerk OL et al. [31] showed that patients with chronic schizophrenia had significantly decreased [11C]-verapamil uptake in the brain compared with healthy volunteers, and the decrease of [11C]-verapamil uptake correlated with increased P-gp activity. These results suggest that overexpression of P-gp in brain tissue may limit the penetration of CNS drugs to their sites of action and may cause pharmacoresistance.

Another human study using PET [32] showed that the P-gp inhibitor cyclosporine A significantly increased the brain concentrations of [11C]-verapamil in healthy subjects. Therefore, PET studies using [11C]-verapamil may provide a clinical indicator of the P-gp activity of psychotropics and drug–drug interactions associated with P-gp at the BBB.

INFLUENCE OF ABCB1 POLYMORPHISM ON PSYCHOTROPICS

Polymorphisms in genes encoding transport proteins may play an important role in the interindividual variability of drug pharmacokinetics and therapeutic response. Many researchers have studied single nucleotide polymorphisms (SNPs) or haplotypes to determine their frequency and to establish their impact on transport functions [33].

P-gp is encoded by the *ABCB1* genes. To date, more than 50 SNPs have been identified [34]. One of these, C3435T, has been associated with the expression and function of P-gp in humans. Carriers homozygous for this polymorphism (TT) showed more than a 2-fold lower *ABCB1* expression than the CC group, which resulted in high plasma concentrations of substrate drugs [35]. Many studies have reported associations between functional SNPs in *ABCB1* and the therapeutic response to psychotropics. Tricyclic antidepressants (nortriptyline, amitriptyline, and imipramine) are P-gp substrates [36,37]. In patients with a mutated P-gp gene C3435T (TT group), P-gp activity was reduced, and the incidence of orthostatic hypotension was significantly increased as a result [38]. Furthermore, such selective serotonin reuptake inhibitors as fluvoxamine and paroxetine are both inhibitors and substrates of P-gp [39,40], and therapeutic response to these drugs can be affected by P-gp gene polymorphism. In fact, recent pharmaco-

genetic research has demonstrated that responses to fluvoxamine and paroxetine were significantly affected by *ABCB1* polymorphisms, including C3435T genotypes [34,41]. The fluvoxamine plasma concentrations were significantly higher in the 3435TT group compared to the 3435CC group [41]. In the case of paroxetine treatment, patients with the haplotype combination 3435C-2677G-1236T of the *ABCB1* gene showed minimal improvement in their Hamilton Rating Scale for Depression scores [34]. In addition, patients with the 3435CC genotype had significantly lower dose-normalized clozapine concentrations than CT or TT patients [42]. This study suggests that 3435CC patients require higher clozapine doses to achieve the same plasma concentrations as CT or TT patients, and *ABCB1* genotyping should be considered as a novel strategy that could improve drug use. However, since there is little information on the relationship between *ABCB1* polymorphism and clinical efficacy, prospective clinical trials will be needed to clarify this relationship.

OTHER ABC TRANSPORTERS AND SOLUTE CARRIER (SLC) TRANSPORTERS

In recent years, the other ABC efflux transporters (MRPs and BCRP) have been thought to affect drug penetration into the brain (Figure 1), although there is yet little information on whether these transporters affect the pharmacokinetics of psychotropics. MRPs expressed at the BBB play some role in xenobiotic elimination at the BBB and the brain-cerebrospinal fluid barrier [43-45]. The MRP subtypes at the BBB consist of MRP1, MRP4 and MRP5 (MRP2?). It has been reported that citalopram is a substrate of MRP1, and that MRP1 polymorphism affected citalopram clinical response [46]. Because 4002G>A MRP1 genotype was associated with greater expression and function of MRP1, patients with the AG or AA genotype receiving citalopram were 5.8 times more likely to experience remission at 8 weeks than patients with the GG genotype [46].

A recent study also found that BCRP plays an important role in xenobiotic elimination at the BBB and that the brain concentrations of BCRP substrates were higher in BCRP-knockout mice [47]. So far, an in vitro study has suggested that risperidone and clozapine are BCRP inhibitors [48]. However, in the case of commonly prescribed drugs, except for psychotropics, there is often overlap in substrates of ABC transporters among P-gp, BCRP and MRPs [49,50]. Thus, further evidence is needed to evaluate the extents of their effects on the pharmacokinetics of these drugs.

Additionally, several solute carrier (SLC) drug transporters are expressed at the BBB, including organic anion-transporting polypeptide (OATP) 1A2, OATP2B1, and organic anion transporter 3 (OAT3) (Figure 1) [51]. These transporters are localized at the luminal and abluminal membranes of brain capillary endothelial cells and regulate the delivery of CNS drugs to systemic circulation [8,51]. Methotrexate (MTX), a folate antimetabolite, is known as an OATP1A2 substrate [52], and methotrexate chemotherapy has been reported to cause severe CNS toxicity [53]. SLCO1A2 (encoding OATP1A2) polymorphism may account for interindividual differences in MTX treatment response and MTX-induced toxicities [52]. Therefore, OATP1A2 may be another important factor in determining the response to drugs that act on the CNS, including psychotropics. However, we may need to wait for the results of future studies, because the substrate specificity of OATPs with regard to psychotropics is still being investigated.

CONCLUSIONS

We have shown that P-gp affects the efficacy and side effects of psychotropics. P-gp plays a key role not only in the gastrointestinal tract but also at the BBB. As previously described, it appears to be very important to estimate the effects of P-gp, especially with regard to drug transport to the CNS, which is closely tied to drug efficacy. Understanding the competitive action among and direct inhibitory effects of P-gp substrates and modulators will enable us to more correctly predict potential drug–drug interactions and establish safer and more effective dosage schedules.

REFERENCES

[1] Neuwelt EA, Bauer B, Fahlke C, Fricker G, Iadecola C, Janigro D. Engaging neuroscience to advance translational research in brain barrier biology. Nat Rev Neurosci 2011; 12: 169-182.

[2] Pardridge WM. Blood–brain barrier delivery. Drug Discov Today 2007; 12: 54-61.

[3] Pariante CM. The role of multi-drug resistance p-glycoprotein in glucocorticoid function: studies in animals and relevance in humans. Eur J Pharmacol 2008; 583: 263-271.

[4] Abbott NJ, Patabendige AA, Dolman DE, Yusof SR, Begley DJ. Structure and function of the blood–brain barrier. Neurobiol Dis 2010; 37:

13-25.
[5] Pardridge W. Blood–brain barrier biology and methodology. J. Neurovirology 1999; 5: 556-569.
[6] Tamai I, Tsuji A. Transporter-mediated permeation of drugs across the blood–brain barrier. J Pharm Sci 2000; 89: 1371-1388.
[7] Hawkins BT, Davis TP. The blood–brain barrier/neurovascular unit in health and disease. Pharmacol Rev 2005; 57: 173-185.
[8] Urquhart BL, Kim RB. Blood–brain barrier transporters and response to CNS-active drugs. Eur J Clin Pharmacol 2009; 65: 1063-1070.
[9] Linnet K, Ejsing TB. A review on the impact of P-glycoprotein on the penetration of drugs into the brain. Focus on psychotropic drugs. Eur Neuropsychopharmacol 2008; 18: 157-169.
[10] Kusuhara H, Sugiyama Y. Active efflux across the blood–brain barrier: role of the solute carrier family. Neuro Rx 2005; 2: 73-85.
[11] Giacomini KM, Huang SM, Tweedie DJ, Benet LZ, Brouwer KL, Chu X, Dahlin aevers R, Fischer V, Hillgren KM, Hoffmaster KA, Ishikawa T, Keppler D, Kim RB, Lee CA, Niemi M, Polli JW, Sugiyama Y, Swaan PW, Ware JA, Wright SH, Yee SW, Zamek-Gliszczynski MJ, Zhang L. Membrane transporters in drug development. Nat Rev Drug Discov 2010; 9: 215-236.
[12] Shen S, Zhang W. ABC transporters and drug efflux at the blood–brain barrier. Rev Neurosci 2010; 21: 29-53.
[13] Demeule M, Régina A, Jodoin J, Laplante A, Dagenais C, Berthelet F, Moghrabi A, Béliveau R. Drug transport to the brain: key roles for the efflux pump P-glycoprotein in the blood–brain barrier.Vascul Pharmacol 2002; 38: 339-348.
[14] Lin JH, Yamazaki M. Clinical relevance of P-glycoprotein in drug therapy. Drug Metab Rev 2003; 35: 417-454.
[15] Bauer B, Hartz AM, Fricker G, Miller DS. Modulation of p-glycoprotein transport function at the blood–brain barrier. Exp Biol Med (Maywood) 2005; 230: 118-127.
[16] O'Brien FE, Dinan TG, Griffin BT, Cryan JF. Interactions between antidepressants and P-glycoprotein at the blood–brain barrier: clinical significance of in vitro and in vivo findings. Br J Pharmacol 2012; 165: 289-312.
[17] Moons T, de Roo M, Claes S, Dom G. Relationship between P-glycoprotein and second-generation antipsychotics. Pharmacogenomics 2011; 12: 1193-1211.
[18] Thuerauf N, Fromm MF. The role of the transporter P-glycoprotein for disposition and effects of centrally acting drugs and for the pathogenesis of CNS diseases. Eur Arch Psychiatry Clin Neurosci 2006; 256: 281-286.
[19] Ayrton A and Morgan P. Role of transport proteins in drug absorption, distribution and excretion. Xenobiotica 2001; 31: 469-497.
[20] Kim RB. Drugs as P-glycoprotein substrates, inhibitors, and inducers. Drug Metab Rev 2002; 34: 47-54.
[21] Sadeque AJ, Wandel C, He H, Shah S, Wood AJ. Increased drug delivery to the brain by P-glycoprotein inhibition. Clin Pharmacol Ther 2000; 68: 231-237.
[22] Schinkel AH, Smit JJ, van Tellingen O, Beijnen JH, Wagenaar E, van Deemter L, Mol CA, van der Valk MA, Robanus-Maandag EC, te Riele HP. Disruption of the mouse mdr1a P-glycoprotein gene leads to a deficiency in the blood–brain barrier and to increased sensitivity to drugs. Cell 1994; 77: 491-502.
[23] Schinkel AH, Mayer U, Wagenaar E, Mol CA, van Deemter L, Smit JJ, van der Valk MA, Voordouw AC, Spits H, van Tellingen O, Zijlmans JM, Fibbe WE, Borst P. Normal viability and altered pharmacokinetics in mice lacking mdr1-type (drug-transporting) P-glycoproteins. Proc Natl Acad Sci U S A 1997; 94: 4028-4033.
[24] Barrand MA, Robertson KJ, von Weikersthal SF. Comparisons of P-glycoprotein expression in isolated rat brain microvessels and in primary cultures of endothelial cells derived from microvasculature of rat brain, epididymal fat pad and from aorta. FEBS Lett 1995; 374: 179-183.
[25] Regina A, Koman A, Piciotti M, El Hafny B, Center MS, Bergmann R, Couraud PO, Roux F. Mrp1 multidrug resistance-associated protein and P-glycoprotein expression in rat brain microvessel endothelial cells. J Neurochem 1998; 7: 705-715.
[26] Doran A, Obach RS, Smith BJ, Hosea NA, Becker S, Callegari E, Chen C, Chen X, Choo E, Cianfrogna J, Cox LM, Gibbs JP, Gibbs MA, Hatch H, Hop CE, Kasman IN, Laperle J, Liu J, Liu X, Logman M, Maclin D, Nedza FM, Nelson F, Olson E, Rahematpura S, Raunig D, Rogers S, Schmidt K, Spracklin DK, Szewc M, Troutman M, Tseng E, Tu M, Van Deusen JW, Venkatakrishnan K, Walens G, Wang EQ, Wong D, Yasgar AS, Zhang C. The impact of P-glycoprotein on the disposition of drugs

targeted for indications of the central nervous system: evaluation using the MDR1A/1B knockout mouse model. Drug Metab Dispos 2005; 33: 165-174.

[27] Uhr M, Grauer MT, Holsboer F. Differential enhancement of antidepressant penetration into the brain in mice with abcb1ab (mdr1ab) P-glycoprotein gene disruption. Biol Psychiatry 2003; 54: 840-846.

[28] Wang JS, Ruan Y, Taylor RM, Donovan JL, Markowitz JS, DeVane CL. The brain entry of risperidone and 9-hydroxyrisperidone is greatly limited by P-glycoprotein. Int J Neuropsychopharmacol 2004; 7: 415-419.

[29] Elsinga PH, Hendrikse NH, Bart J, Vaalburg W, van Waarde A. PET Studies on P-glycoprotein function in the blood–brain barrier: how it affects uptake and binding of drugs within the CNS. Curr Pharm Des 2004; 10: 1493-1503.

[30] Langer O, Bauer M, Hammers A, Karch R, Pataraia E, Koepp MJ, Abrahim A, Luurtsema G, Brunner M, Sunder-Plassmann R, Zimprich F, Joukhadar C, Gentzsch S, Dudczak R, Kletter K, Müller M, Baumgartner C. Pharmacoresistance in epilepsy: a pilot PET study with the P-glycoprotein substrate R-[(11)C]verapamil. Epilepsia 2007; 48: 1774-1784.

[31] de Klerk OL, Willemsen AT, Bosker FJ, Bartels AL, Hendrikse NH, den Boer JA, Dierckx RA. Regional increase in P-glycoprotein function in the blood–brain barrier of patients with chronic schizophrenia: a PET study with [(11)C]verapamil as a probe for P-glycoprotein function. Psychiatry Res 2010; 183: 151-156.

[32] Sasongko L, Link JM, Muzi M, Mankoff DA, Yang X, Collier AC, Shoner SC, Unadkat JD. Imaging P-glycoprotein transport activity at the human blood–brain barrier with positron emission tomography. Clin Pharmacol Ther 2005; 77: 503-514.

[33] König J, Seithel A, Gradhand U, Fromm MF. Pharmacogenomics of human OATP transporters. Naunyn Schmiedebergs Arch Pharmacol 2006; 372: 432-443.

[34] Kato M, Fukuda T, Serretti A, Wakeno M, Okugawa G, Ikenaga Y, Hosoi Y, Takekita Y, Mandelli L, Azuma J, Kinoshita T. ABCB1 (MDR1) gene polymorphisms are associated with the clinical response to paroxetine in patients with major depressive disorder. Prog Neuropsychopharmacol Biol Psychiatry 2008; 32: 398-404.

[35] Hoffmeyer S, Burk O, von Richter O, Arnold HP, Brockmöller J, Johne A, Cascorbi I, Gerloff T, Roots I, Eichelbaum M, Brinkmann U. Functional polymorphisms of the human multidrug-resistance gene: multiple sequence variations and correlation of one allele with P-glycoprotein expression and activity in vivo. Proc Natl Acad Sci U S A 2000; 97: 3473-3478.

[36] Ejsing TB, Linnet K. Influence of P-glycoprotein inhibition on the distribution of the tricyclic antidepressant nortriptyline over the blood–brain barrier. Hum Psychopharmacol 2005; 20: 149-153.

[37] Uhr M, Steckler T, Yassouridis A, Holsboer F. Penetration of amitriptyline, but not of fluoxetine, into brain is enhanced in mice with blood–brain barrier deficiency due to mdr1a P-glycoprotein gene disruption. Neuropsychopharmacology 2000; 22: 380-387.

[38] Roberts RL, Joyce PR, Mulder RT, Begg EJ, Kennedy MA. A common P-glycoprotein polymorphism is associated with nortriptyline-induced postural hypotension in patients treated for major depression. Pharmacogenomics J 2002; 2: 191-196.

[39] Weiss J, Dormann SM, Martin-Facklam M, Kerpen CJ, Ketabi-Kiyanvash N, Haefeli WE. Inhibition of P-glycoprotein by newer antidepressants. J Pharmacol Exp Ther 2003; 305: 197-204.

[40] Ela AA, Hartter S, Schmitt U, Hiemke C, Spahn-Langguth H, Langguth P: Identification of P-glycoprotein substrates and inhibitors among psychoactive compounds–implications for pharmacokinetics of selected substrates. J Pharm Pharmacol 2004; 56: 967-975.

[41] Fukui N, Suzuki Y, Sawamura K, Sugai T, Watanabe J, Inoue Y, Someya T. Dose-dependent effects of the 3435 C>T genotype of ABCB1 gene on the steady-state plasma concentration of fluvoxamine in psychiatric patients. Ther Drug Monit 2007; 29: 185-189.

[42] Consoli G, Lastella M, Ciapparelli A, Catena Dell'Osso M, Ciofi L, Guidotti E, Danesi R, Dell'Osso L, Del Tacca M, Di Paolo A. ABCB1 polymorphisms are associated with clozapine plasma levels in psychotic patients. Pharmacogenomics 2009; 10: 1267-1276.

[43] Miller DS, Bauer B, Hartz AM. Modulation of P-glycoprotein at the blood–brain barrier: opportunities to improve central nervous system pharmacotherapy. Pharmacol Rev 2008; 60:

196-209.
[44] He SM, Li R, Kanwar JR, Zhou SF. Structural and functional properties of human multidrug resistance protein 1 (MRP1/ABCC1). Curr Med Chem 2011; 18: 439-481.
[45] Okamura T, Kikuchi T, Irie T. PET imaging of MRP1 function in the living brain: method development and future perspectives. Curr Top Med Chem 2010; 10: 1810-1819.
[46] Lee SH, Lee MS, Lee JH, Kim SW, Kang RH, Choi MJ, Park SJ, Kim SJ, Lee JM, Cole SP, Lee MG. MRP1 polymorphisms associated with citalopram response in patients with major depression. J Clin Psychopharmacol 2010; 30: 116-125.
[47] Nicolazzo JA, Katneni K. Drug transport across the blood–brain barrier and the impact of breast cancer resistance protein (ABCG2). Curr Top Med Chem 2009; 9: 130-147.
[48] Wang JS, Zhu HJ, Markowitz JS, Donovan JL, Yuan HJ, Devane CL. Antipsychotic drugs inhibit the function of breast cancer resistance protein. Basic Clin Pharmacol Toxicol 2008; 103: 336-341.
[49] Sharom FJ. ABC multidrug transporters: structure, function and role in chemoresistance. Pharmacogenomics 2008; 9: 105-127.
[50] Zhou SF. Structure, function and regulation of P-glycoprotein and its clinical relevance in drug disposition. Xenobiotica 2008; 38: 802-832.
[51] Westholm DE, Rumbley JN, Salo DR, Rich TP, Anderson GW. Organic anion-transporting polypeptides at the blood–brain and blood-cerebrospinal fluid barriers. Curr Top Dev Biol 2008; 80: 135-170.
[52] Badagnani I, Castro RA, Taylor TR, Brett CM, Huang CC, Stryke D, Kawamoto M, Johns SJ, Ferrin TE, Carlson EJ, Burchard EG, Giacomini KM. Interaction of methotrexate with organic-anion transporting polypeptide 1A2 and its genetic variants. J Pharmacol Exp Ther 2006; 318: 521-529.
[53] Vezmar S, Becker A, Bode U, Jaehde U. Biochemical and clinical aspects of methotrexate neurotoxicity. Chemotherapy 2003; 49: 92-104.