Eur Arch Psychiatry Clin Neurosci (2006) 256:294–298 DOI 10.1007/s00406-006-0664-4

SPECIAL ISSUE

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ABC drug transporter at the blood–brain barrier

Effects on drug metabolism and drug response

Published online: 16 June 2006

Abstract At the blood–brain barrier (BBB) many cellular and dynamic mechanisms influence the cerebral drug metabolism and the drug response. In this review, we focus mainly on the role P-glycoprotein (P-gp) plays at the BBB. This protein is a 170-kDa ATP-dependent drug transport protein, located in the apical membrane of endothelial cells. Utilizing ATP hydrolysis as an energy source, it exports molecules which attempt to pass through the cell membrane from the outside to the inside, protecting cells from toxins and a wide range of substances. We briefly summarize some of the currently available *in vivo* and *in vitro* methods to investigate P-gp and its substrates. Hitherto, no chemical characteristic has been discovered that clearly distinguishes substrates from non-substrates of P-gp. We discuss some examples of substrates stressing the diversity of drugs and endogenous substances that relate to P-gp either as a substrate, an inhibitor, an inducer or as a combination of the above. Finally, we discuss genetic polymorphisms of the genes encoding for P-gp and their effects on drug response.

Key words P-glycoprotein · SNPs · blood–brain barrier · drug response

P-glycoprotein at the blood–brain barrier

The blood–brain barrier (BBB) is a diffusion barrier. It hampers influx of most compounds from blood to brain. Two general mechanisms underlie the function of the BBB: first, tight junctions seal the capillary endothelium, and the cells themselves exhibit a low rate of endocytosis. Secondly, there are numerous specific membrane transporters expressed by the endothelial cells [1]. Endothelial cells, astrocyte endfeet, and pericytes compose the BBB at the cellular level. Tight junctions prevent most blood-borne substances from entering the brain. Astrocytic endfeet tightly ensheath the vessel wall and appear to be critical for the induction and maintenance of the tight junction barrier [2].

ABC (formerly called MDR) transporters, nucleoside transporters, organic anion transporters, and large amino-acid transporters; receptor-mediated transport systems, such as the transferrin-1 and -2 receptors; and the scavenger receptors SB-AI and SB-BI belong to the membrane transporters expressed at the BBB [3]. P-glycoprotein (Pgp) was the first of the ABC transporters to be described, followed by the multidrug resistance-associated proteins (MRP) and more recently breast cancer resistance protein (BCRP) (Sarkadi et al. 4). All are expressed in the BBB and blood–cerebro spinal fluid barrier (BCSFB) and combine to reduce the 'brain penetration of many drugs. This phenomenon of "multidrug resistance" is a major hurdle when it comes to the delivery of therapeutics to the brain, not to mention the problem of cancer chemotherapy in general [5]. This review mainly focuses on the role P-gp plays at the BBB on drug metabolism and drug response. In humans, P-gp, encoded by the multiple drug resistance (ABCB1) gene, shares many features with numerous bacterial and eucaryotic ATP-binding cassette (ABC) transport proteins and is a member of a phylogenetically highly conserved superfamily of transport proteins (Devault and Gros 6–8). P-gp is a 170-kDa ATP-dependent drug transport protein, located in the apical membrane of endothelial cells. Utilizing ATP hydrolysis as an energy source, it exports molecules

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EAPCN 664

which attempt to pass through the cell membrane from the outside to the inside, protecting cells from toxins and a wide range of substances. The current model proposes that P-gp intercepts the drug as it moves through the membrane and flips it from the inner leaflet to the outer leaflet into the extracellular space [9, 10]. P-gp belongs to a large and growing group of transmembrane transporters [11, 12], which are increasingly recognized as an important part of the BBB and BCSFB [7, 13–15]. The physiological function of P-gp at the BBB is to protect the brain from potentially harmful substances. This view is supported by results such as a significant association between patients with parkinsonism exposed to pesticides and C3435T polymorphism of the ABCB1 gene; thus, it appears that mutation of the ABCB1 gene predisposes to damaging effects of pesticides, and possibly other toxic xenobiotics transported by P-gp, leading to Parkinson's disease [16]. In addition, first evidence in human brain tissue that the accumulation of beta-amyloid is influenced by the expression of P-gp in blood vessels suggests that P-gp may play a role in the development of Alzheimer disease [17].

P-gp was first discovered in multiple drug resistant cancer cells, but can also be found in normal tissue. This includes the apical membrane of intestinal epithelial cells (Mukhopadhyay et al. 18), the cornea (Dey et al. 19], the biliary canalicular membrane of hepatocytes, and the lumenal membrane of proximal tubular epithelial cells in the kidney [20, 21]. High levels of ABCB1 P-gp have been found in the luminal membrane of the endothelial cells that line small blood capillaries and form the BBB, BCSFB, and blood–testis barrier [10, 22–24], reflecting the important role P-gp plays in the function of the BBB. Although P-gp is highly expressed in both intestinal epithelial cells and endothelial cells of brain capillaries, the impact of P-gp on intestinal absorption and brain uptake of drugs is quantitatively very different. The effect of P-gp on drug absorption is not quantitatively as important as suggested. Many drugs are good human P-gp substrates and yet exhibit reasonable oral bioavailability. In contrast, P-gp plays a quantitatively very important role in blocking the brain uptake of P-gp substrates [25]. In pathologic cases, the distribution of P-gp can change. For example, in normal brain tissue P-gp is expressed almost exclusively by endothelial cells (EC), while in epileptic cortex both EC and perivascular astrocytes express P-gp [26]. In many cancers, expression of P-gp rises too [27].

Methods to study P-gp

To study the effects of P-gp at the BBB, there is a variety of methodological approaches, including cellular monolayers [28, 29]. Positron emission tomography (PET) might play another important role in the investigation of P-gp [30]. Expression of P-gp can be evaluated by immunohistochemical methods and by sestamibi single photon emission computed tomography (SPECT) too [31]. In our laboratory, we use a mouse model lacking abcb1ab. In mice, P-gp is encoded by the abcb1a (formerly called mdr1a) and the abcb1b (formerly called mdr1b) gene [32]; the overall distribution in mice tissue overlaps well with the single ABCB1 gene in humans. The generation of transgenic mice with a disruption of the abcb1a gene has provided an excellent experimental tool in the study of P-gp function in the BBB [33]. In addition to the mouse model, *in vitro* cell lines that over-express P-gp, and clinical trials using P-gp modulators have allowed the comparison of *in vitro–in vivo* and species-related difference in P-gp activity. Species-related differences of systemic drug disposition seem to be modest. For the most part, studies have shown reasonable *in vitro–in vivo* correlations [34]. However, there are exceptions. Citalopram was no substrate of P-gp *in vitro* [61] but it was in our *in vivo* experiments [62].

Substrates of P-gp

Hitherto, no chemical characteristic has been discovered that clearly distinguishes substrates from non-substrates of P-gp [35]. Therefore, it is necessary to test each drug separately. There is a vast number of very distinct medications as well as endogenous substances that have shown properties as a substrate, or an inhibitor, or an inducer or combinations of the above, including anticancer and antihypertensive agents, antiarrhythmics, antidepressants, antiviral agents, antibiotics and antimycotics, immunosuppressants, neuroleptics and many more [36]. There is also evidence for the pharmacological role of ABCB proteins in the efficacy of several anti-rheumatic drugs, notably disease modifying anti-rheumatic drugs (DMARDs), as well as the physiological role of ABCB proteins in transporting signaling molecules important in inflammatory processes [37]. Further, cortisol [38] as well as some antidepressants [39] are substrates of P-gp. Cortisol has a major impact on affective disorders such as depression [40]. It was recently proposed that antidepressants inhibit P-gp, and thus increase the access of cortisol to the brain [41]. Thus the data imply that the interaction with P-gp could in fact partly be responsible for some pharmacological effect of antidepressants on intracerebral concentrations of cortisol (Müller et al. 42].

Inhibition of P-gp improves intestinal absorption and tissue distribution while reducing the substrate metabolism and its elimination [43]. Keeping in mind the protective role P-gp plays at the BBB, P-gp modulators should be carefully used, since some modulators that reverse P-gp efflux action *in vitro* may lead to alterations of tissue function and increase toxicity of xenobiotics in normal tissues [44].

Moreover, dietary components and pharmaceutical excipients may modulate P-gp activity, and as a result affect *in vivo* drug disposition and therapeutic efficacy; examples include grapefruit juice, Pluronic P85, and PEG 300 [45].

Some substances can induce P-gp. For example, P-gp expressed in rats brain microvessel endothelial cells was increased by a factor of 1.3 by dexamethasone and the human immunodeficiency viral protease inhibitor (HIP) ritonavir [46]. Most of the currently available studies describe HPIs as P-gp substrates. Studies are more controversial when investigating HPIs as inhibitors of P-gp. HPIs seem to be able to inhibit efflux proteins of *in vitro* cell models but with limited consequences *in vivo*. Moreover, after repeated administrations of HPIs, most of them are also able to induce the expression and functionality of P-gp. For these reasons, certain combinations of HPIs may not efficiently increase brain uptake of HPIs as would combinations of more potent efflux inhibitors [47]. As in the case of substrates of P-gp, inducers can also be endogenous substances. For instance, it was speculated that glutamate could up-regulate P-gp expression in rat brain microvessel endothelial cells by an NMDA receptor-mediated mechanism [48]. While there is a growing interest in developing inhibitors of this transporter as an approach to increasing drug bioavailability, the utility of exploiting inducers of the protein is less clear [49].

Genetic polymorphisms and effects on drug response

The changes in pharmacokinetics due to genetic polymorphisms and drug–drug interactions involving transporters can often have a direct and adverse effect on the therapeutic safety and efficacy of many important drugs [50]. Reports in the literature, particularly focusing on the C3435T polymorphism, have provided discordant results with respect to functional modification *in vitro*, and P-gp expression and disposition of probe drugs *in vivo*. Strong linkage disequilibrium has been detected between several ABCB1 polymorphisms, and discrepancies in the literature may be due to the focus on the influence of single nucleotide variations instead of on linked nucleotide variations [51].

An increasing number of studies have also implicated certain commonly occurring SNPs in ABCB1 in problems including altered drug levels and host susceptibility to diseases such as Parkinson's disease, inflammatory bowel disease, refractory seizures, and CD4 cell recovery during human immunodeficiency virus therapy. However, in many such cases, the reported effects of ABCB1 SNPs have been inconsistent and, in some cases, conflicting [36].

As mentioned above, P-gp is overexpressed at baseline in chemotherapy-resistant tumors, such as colon and kidney cancers, and is up-regulated after disease progression following chemotherapy in malignancies such as leukemia and breast cancer. Other transporter proteins mediating drug resistance include those in the MRP family. These transporters are also involved in normal physiologic functions. The expressions of MRP family members have not yet been examined sufficiently in cancer. Increased drug accumulation and drug resistance reversal with P-gp inhibitors have been well documented *in vitro*, but only suggested in clinical trials. Limitations in the design of early resistance reversal trials contributed to disappointing results. Despite this, three randomized trials have shown statistically significant benefits with the use of a P-gp inhibitor in combination with chemotherapy. Improved diagnostic techniques aimed at the selection of patients with tumors that express P-gp should result in more successful outcomes. Further optimism is warranted with the advent of potent, non-toxic inhibitors and new treatment strategies, including the combination of new targeted therapies with therapies aimed at the prevention of drug resistance [27].

In our view, it is quite likely that to identify the individual polymorphism of ABCB1 may help to predict the drug response of a patient, if the drug given is a substrate of P-gp [52]. According to the genotype, dose requirements may be necessary. In this respect, the data presented by Fellay et al. [53] are encouraging. They found a relationship between expression of P-gp in peripheral blood mononuclear cells of HIV-infected patients and CD4 lymphocyte response to treatment. Patients with the 3435T allele in exon 26 had a significantly greater rise in CD4-cell counts 6 months after starting antiretroviral therapy. Another recently identified association with ABCB1 exon 26 polymorphism relates to epilepsy. The frequency of the exon 26 3435C allele was noted to be significantly greater in subjects with drug-resistant seizure disorders [54]. Homozygosity of the T allele of the ABCB1 3435C/T polymorphism has been associated with reduced enterocyte expression of P-gp resulting in increased drug absorption [55]. On the other hand, despite a weak association found for the ABCB1 C1236T SNP, ABCB1 SNPs are unlikely to be useful for cyclosporine dose optimization in clinical practice [56]. Further, differences in physiological levels of ABCB1 expression did not modify HIV-1 infection *in vitro*, nor did ABCB1 alleles and haplotypes significantly influence either permissiveness to infection *in vitro* or disease progression *in vivo* before the initiation of treatment [57]. No association between antidepressant-induced mania and the ABCB1 alleles or genotypes was found [58]. Of course, these studies depend to a great extent on the choice of SNPs under investigation. For example, there was no association between the ABCB1 C3435T variation and plasma levels or central nervous system effects of the P-gp substrate loperamide in a white population [59]. In contrast, other data support a functional importance of the ABCB1 haplotype G2677 for plasma

concentrations and central nervous actions of loperamide [60].

Conclusion

P-gp has a major impact on the pharmacological behavior of many drugs in use today. Pharmacological properties affected by ABC transporters include the oral bioavailability, hepatobiliary, direct intestinal, and urinary excretion of drugs and drug-metabolites and conjugates. Moreover, the penetration of drugs into a range of important pharmacological sanctuaries, such as brain, and the penetration into specific cell and tissue compartments can be extensively limited by P-gp. These interactions with P-gp determine to a large extent the clinical usefulness, side effects, and toxicity risks of drugs. Many other xenotoxins, carcinogens, and endogenous compounds are also influenced by P-gp, with corresponding consequences for the well-being of the individual [4]. For future pharmacological studies in this field, there is an urgent need to identify chemical characteristics that clearly distinguish substrates from non-substrates of P-gp. Pharmacogenetic investigations may provide valuable information on SNPs that might have a significant impact on drug response.

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