Eur Arch Psychiatry Clin Neurosci (2006) 256:281–286 DOI 10.1007/s00406-006-0662-6

SPECIAL ISSUE

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The role of the transporter P-glycoprotein for disposition and effects of centrally acting drugs and for the pathogenesis of CNS diseases

Published online: 16 June 2006

Abstract The *MDR1* gene product P-glycoprotein is an ATP-dependent efflux pump, which transports its substrates out of cells. It is not only expressed in tumor cells, but also in cells of normal tissues. For example, it is located in the apical membrane of enterocytes, in endothelial cells forming the blood–brain and blood–testis barriers and in the apical membrane of placental syncytiotrophoblast. Since P-glycoprotein transports a wide range of drugs (e.g. antidepressants, antiepileptics, HIV protease inhibitors, cyclosporine, digoxin), its location in these tissues limits bioavailability of orally administered drugs and prevents entry of xenobiotics into the brain, testis and the fetus. Recent data highlight the role of intestinal P-glycoprotein for drug interactions (e.g. digoxin), of P-glycoprotein expressed in the blood–brain barrier for drug penetration into the CNS (e.g. loperamide, amitriptyline), the role of pharmacological inhibition of P-glycoprotein function to increases drug concentrations in sanctuary sites (e.g. for the HI virus) and for the potential role of *MDR1* polymorphisms for P-glycoprotein expression, drug disposition, adverse drug reactions and disease risk. Taken together, active drug transport is now considered as an important additional mechanism limiting drug accumulation in multiple tissues including the CNS.

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Key words P-glycoprotein · drug therapy · blood–brain barrier

Introduction

The *MDR1* gene product P-glycoprotein (ABCB1) is a membrane protein, which functions as an ATP-dependent exporter of xenobiotics from cells. It was first described in tumor cells where it contributed to the occurrence of multidrug resistance (MDR) against anticancer agents [12]. In addition, it is expressed in normal tissues with excretory function such as intestine, liver and kidneys, in capillary endothelial cells of brain, placenta and testis and in peripheral blood cells [3, 15, 33]. Expression of P-glycoprotein in these normal tissues is believed to be a protective mechanism against xenobiotics, e.g. of the CNS due to its expression in capillary endothelial cells of brain forming the blood–brain-barrier. Intestinal P-glycoprotein has been shown to limit absorption of the immunosuppressant cyclosporine, the cardiac glycoside digoxin and the β-adrenoceptor antagonist talinolol in humans [10, 20, 41]. Moreover, modification of P-glycoprotein function is an underlying mechanism of drug interactions [7, 10]. For example, the herbal medicine St. John's wort which is frequently used as a treatment for mild depression, induces the major drug metabolizing enzyme CYP3A4 and P-glycoprotein, which can cause severe drug interactions with the CYP3A4 and P-glycoprotein substrates cyclosporine and HIV protease inhibitors [8, 25]. Accordingly, it has recently been shown that reduced plasma concentrations of the P-glycoprotein substrate digoxin during treatment with St. John's wort are due to the induction of intestinal P-glycoprotein by constituents of St. John's wort [5].

It is well established that mutations of genes encoding xenobiotic metabolizing enzymes (e.g. members of the cytochrome P450 family such as

Table 1 Summary of drugs, which are substrates of P-glycoprotein (modified from [30])

Centrally acting	Anticancer agents	Cardiac drugs	HIV protease inhibitors	Immunosuppressants	Antibiotics	Steroids	Lipid-lowering agents	Calcium channel blocker and metabolites	β-adrenoceptor antagonists	H_1 antihistamines	H_2 antihistamines	Others
Amitriptyline	Actinomycin D	β-acetyldigoxin	Amprenavir	Cyclosporine A	Erythromycin	Dexamethasone	Atorvastatine	Diltiazem	Bunitrolol	Fexofenadine	Cimetidine	Colchicine
Chlorpromazine	Etoposide	α-methyldigoxin	Indinavir	Tacrolimus	Levofloxacin		Lovastatine	Mibefradil	Celiprolol	Terfenadine	Ranitidine	Debrisoquine
Citalopram	Docetaxel	Digitoxin	Nelfinavir		Sparfloxacin			Verapamil	Talinolol			Domperidon
Doxepine	Doxorubicin	Digoxin	Saquinavir					D-617				Loperamide
Morphine	Daunorubicin	Quinidine	Ritonavir					D-620				Losartan
Nortriptyline	Irinotecan											Rifampin
Ondansetron	Mitomycin C											
Paroxetine	Mitoxantrone											
Phenytoin	Paclitaxel											
Quetiapine	Teniposide											
Risperidone	Topotecan											
Trimipramine	Vinblastine											
Venlafaxine	Vincristine											

CYP2D6) and drug targets (e.g. receptors) determine efficacy or toxicity of a broad variety of drugs and carcinogens. Recently, multiple mutations were also found in the human *MDR1* gene [11, 22]. More details on the potential influence of *MDR1* polymorphisms on drug disposition and effects have recently been published in other review articles [6, 21]. The goal of this paper is to provide selected examples for the role of P-glycoprotein for disposition and effects of centrally acing drugs and for the pathogenesis of CNS diseases. The role of ABC transporters and of other transporters expressed in the CNS is further discussed in recent review articles [1, 13, 19, 34].

P-Glycoprotein substrates

P-glycoprotein has a very broad substrate specificity and transports many structurally unrelated compounds. These substances are usually hydrophobic and amphipathic. Table 1 provides a summary of drugs, which are substrates of P-glycoprotein. In addition to anticancer agents, this transporter translocates antiepileptics, antidepressants, neuroleptics, cardiac drugs, HIV protease inhibitors, immunosuppressants antibiotics, β-adrenoceptor antagonists and antihistamines. The majority of P-glycoprotein substrates and inhibitors also interact with the major drug metabolizing enzyme CY3A4 [40].

P-Glycoprotein and blood–brain barrier

The blood–brain barrier is formed by capillary endothelial cells in the brain. Similar to gut wall mucosa, the blood–brain barrier was considered a passive anatomical structure determining brain entry of molecules, e.g. by lipophilicity and protein binding. Its is now well established that active efflux by P-glycoprotein and other transporters (e.g. BCRP) contributes to brain permeability of drugs in addition to the factors mentioned above. Insights into the role of P-glycoprotein in the blood–brain barrier were obtained by P-glycoprotein knockout mice. The particular importance of P-glycoprotein to the brain in comparison to most other tissues is shown by the considerable higher accumulation of several drugs in the brain of P-glycoprotein knockout mice than in the plasma. Brain entry of the HIV protease inhibitors indinavir, nelfinavir and saquinavir is reduced due to P-glycoprotein expression in the endothelial cells of the blood–brain barrier. Thus, it was speculated that the ability of these drugs to achieve therapeutic concentrations in the brain is limited, thereby creating a potential sanctuary for viral replication [14].

Therapeutic effects of centrally active drugs also depend on adequate brain concentrations. Accordingly, centrally acting drugs such as haloperidol, clozapine, midazolam and flunitrazepam easily enter

the CNS and are not substrates of P-glycoprotein [29]. The peripherally acting opioid loperamide, which penetrates the CNS poorly and is used as an antidiarrheal agent, is a substrate of P-glycoprotein. P-glycoprotein knockout animals have 14-fold higher brain concentrations after oral administration of loperamide in comparison to control animals. Moreover, P-glycoprotein-deficient mice show typical, morphine-like effects after administration of loperamide [29]. The relevance of these data was confirmed by a study in healthy volunteers. Administration of loperamide alone did not cause any respiratory depression, but respiratory depression occurred during coadministration of loperamide with the P-glycoprotein inhibitor quinidine [28]. Taken together, these data indicate that P-glycoprotein in the blood–brain barrier is the major cause of the selective peripheral effects of loperamide in humans.

In general, inhibition of drug transporters in the blood–brain barrier might be an option for improving drug delivery to the brain, thereby possibly increasing access of anticancer agents or antiretroviral drugs to the CNS in humans [13, 34].

Nortriptyline-induced postural hypotension

Data obtained with P-glycoprotein knockout mice indicate that nortriptyline might be a P-glycoprotein substrate [38]. Accordingly, Roberts et al. [27] tested the hypothesis whether side effects of the antidepressant nortriptyline might be associated with the *MDR1* 3435 polymorphism. Indeed, the presence of one or more T alleles at position 3435 of the *MDR1* gene was associated with a higher risk for the occurrence of postural hypotension in nortriptyline-treated patients in comparison to patients with the 3435 CC genotype [27].

P-Glycoprotein and the hypothalamic–pituitary–adrenocortical (HPA) system

It could be shown that the access of the endogenous glucocorticoids corticosterone and cortisol to the brain are regulated by P-glycoprotein in vivo [37]. A study in mice investigated the influence of the blood–brain barrier on the regulation of the hypothalamic–pituitary–adrenocortical (HPA) system [23]. Abcb1ab (−/−) mice showed consistently lower plasma ACTH levels and lower evening plasma corticosterone levels. CRH mRNA expression in the hypothalamic paraventricular nucleus was decreased and pituitary POMC mRNA expressing cells were significantly reduced in number in abcb1ab (−/−) mutants. Activation of the HPA system following CRH stimulation was in the normal range. These results provide evidence for a sustained suppression of the HPA system at the hypothalamic level in abcb1ab (−/−) mice and suggest that blood–brain barrier function significantly regulates HPA system activity. Thus, alterations of the P-glycoprotein function could influence the development of anxiety, stress induced behavior and affective disorders via the HPA system. In this context it is worth mentioning that Pariante et al. suggested that antidepressants in humans could inhibit steroid transporters localized on the blood–brain barrier and in neurones, like the multidrug resistance P-glycoprotein, and thus increase the access of cortisol to the brain and the glucocorticoid-mediated negative feedback on the HPA axis [24].

P-Glycoprotein and psychoactive substrates—antidepressants and antipsychotics

Mice with a genetic disruption (knockout) of the multiple drug resistance *mdr1a* gene were used to examine the effect of the absence of the drug-transporting P-glycoprotein at the blood–brain barrier on the uptake of amitriptyline, citalopram, doxepine, fluoxetine, paroxetine, mirtazapine, trimipramine and venlafaxine into the brain [35, 36, 38]. Significantly higher brain concentrations were found in knockout mice compared to controls for amitriptyline, citalopram, doxepine, paroxetine, trimipramine and venlafaxine demonstrating that these drugs are substrates of the drug-transporting P-glycoprotein and that the presence of P-glycoprotein reduces the effective bioavailability of these substances in the brain. In contrast mirtazapine and fluoxetine reached similar concentrations in the brain of knockout mice and of controls showing that both substances do not represent P-glycoprotein substrates [36, 38]. Based on these results it was suggested that individual differences in the multiple drug resistance gene (*MDR1*) activity may account for variable response patterns at different episodes and development of therapy resistance [38]. Furthermore, the resulting differences in brain penetration of antidepressant drugs could also explain—at least in part—the discrepancies between plasma levels of an antidepressant and its clinical effects and side effects.

Little is known about the specificity of the drug-transporting P-glycoprotein for antipsychotics. An in vitro study investigated the affinity of chlorpromazine, clozapine, haloperidol, olanzapine, quetiapine and risperidone by assessing their P-glycoprotein ATPase activity as a putative measure of P-glycoprotein affinity [2]. The P-glycoprotein ATPase activity of the P-glycoprotein substrate verapamil was determined for direct comparison. The atypical antipsychotics quetiapine and risperidone showed relatively high affinity to P-glycoprotein, although their affinities were not as high as verapamil. Olanzapine showed intermediate affinity and clozapine

showed the least affinity of the drugs studied. These results indicate that P-glycoprotein is likely to influence the access to the brain of all of the atypical antipsychotics studied to various degrees. In vivo studies confirming these findings are still lacking.

P-Glycoprotein and CNS diseases

Alzheimer's disease

The neuritic plaques typically for Alzheimer's disease are primarily composed of β-amyloid and are believed to be the site of local inflammatory processes. P-glycoprotein has been shown to actively transport a wide range of lipophilic and amphipathic molecules from cells. It was hypothesized that P-glycoprotein could be involved in the transport of β-amyloid from brain cells [18]. Lam et al. tested this hypothesis investigating the secretion of β-amyloid in cells transfected with *MDR1* in the presence of potent P-glycoprotein reversal agents [17]. This pharmacological blockade of P-glycoprotein rapidly decreased extracellular levels of β-amyloid secretion. In vitro binding studies showed that synthetic β-amyloid interact directly with P-glycoprotein in highly purified hamster P-glycoprotein reconstituted into membrane vesicles. Finally, it could be shown that the transport of β-amyloid across plasma membranes of P-glycoprotein enriched vesicles is ATP- and P-glycoprotein dependent. Subsequent to this study, Vogelgesang et al. imunohistochemically assessed P-glycoprotein expression at the blood–brain barrier and the number of β-amyloid plaques in brain tissue samples from routine autopsies of 243 non-demented subjects [17, 39]. An inverse correlation could be demonstrated between β-amyloid accumulation and the degree of P-glycoprotein expression at the blood–brain barrier. Taken together these results suggest that increasing P-glycoprotein activity at the blood–brain barrier could represent a new approach for eliminating or at least regulating the accumulation of β-amyloid peptides in Alzheimer's disease.

Parkinson's disease

Many epidemiological studies suggest an association between pesticides, which are substrates for P-glycoprotein, and Parkinson's disease [16, 18, 31]. It was hypothesized that polymorphisms of the *MDR1* gene could influence the individual risk for the disease in subjects exposed to pesticides. In a pilot case–control study involving 107 Parkinson's disease patients (30 early onset and 77 late onset patients; 59 exposed to pesticides and 48 non-exposed) and 103 controls, the C3435T polymorphism of the gene was analyzed [4]. The authors found no statistically significant correlation between *MDR1* gene polymorphism and Parkinson's disease. However, a significant association between patients with parkinsonism exposed to pesticides and C3435T polymorphism of the *MDR1* gene was observed. It could be shown that in exposed versus non-exposed subjects, patients with at least one 3435T allele (i.e. homozygous and heterozygous) had a significant, 5-fold higher risk of Parkinson's disease. In line with this result another pilot case–control study involving 95 Parkinson's disease patients and 106 controls found no association of three common polymorphisms of the *MDR1* gene and Parkinson's disease [9]. However, the 3435T/T genotype, which had previously been associated with decreased P-glycoprotein expression and function in several, but not all studies, was highest in the early-onset Parkinson's disease group (36.0%), second-highest in the late-onset Parkinson's disease group (22.9%), and lowest in the control group (18.9%). Taken together, it appears that mutation of the *MDR1* gene predisposes to damaging effects of pesticides and possibly other toxic compounds characterizing *MDR1* and other drug transporter as plausible candidates as Parkinson's disease risk genes.

Epilepsy

Despite considerable advances in the pharmacological treatment of epilepsy, approximately one-third of epileptic patients are pharmacoresistant. In some of these pharmacoresistant patients blood concentrations of antiepileptic drugs are within normal therapeutic levels. Decreased drug uptake into the brain by elevated expression of drug transporters like P-glycoprotein could explain—at least in part—this phenomenon. In order to test this hypothesis Siddiqui et al. genotyped the C3435T polymorphism of the *MDR1* gene in 315 patients with epilepsy, classified as drug-resistant in 200 and drug-responsive in 115, and 200 control subjects without epilepsy [32]. Patients with drug-resistant epilepsy were significantly more likely to have the CC genotype at 3435 than the TT genotype. This study provided evidence for a genetic factor associated with resistance to antiepileptic drugs. Experiments in rats observed up-regulation of MDR1 mRNA following seizures but not following repetitive treatment with antiepileptic drugs [18, 26]. This result suggests that regulatory pathways induced by seizures but not the presence of antiepileptic drugs up-regulate the expression of P-glycoprotein. It should be mentioned that in addition to overexpression in epileptic brain tissue several animal studies provide evidence that some antiepileptic drugs may be P-glycoprotein substrates (for review [18]), but these data needs to be interpreted with care.

Summary and conclusion

P-glycoprotein is expressed in organs with excretory function such as small and large intestine, liver and

kidneys. Moreover, it limits tissue penetration of drugs due to it expression in the blood–brain and blood–testis barrier and in placenta. It determines absorption, tissue distribution and elimination of a wide range of structurally unrelated drugs such as centrally acting drugs, anticancer agents, HIV protease inhibitors, cardiac drugs and β-adrenoceptor antagonists. Inhibition of P-glycoprotein function results in increased drug concentrations and is now a well recognized mechanism of drug interactions in humans. In addition to these exogenous factors affecting P-glycoprotein function, we are now beginning to understand genetic factors determining interindividual variability in P-glycoprotein expression and function. It appears that mutations in the *MDR1* gene have an impact on drug disposition within and among ethnic populations. Moreover, an individual's P-glycoprotein function might determine the risk for certain disease and the therapeutic outcome from treatment with P-glycoprotein substrates as recently reported for the association between the *MDR1* 3435 polymorphism and drug-resistant epilepsy [32]. However, the relative importance of variability in P-glycoprotein function due to exogenous and genetic factors for drug disposition, therapeutic outcome and disease risk needs to be clarified in future studies.

Acknowledgement The own work cited is supported by grants of the Deutsche Forschungsgemeinschaft (FR 1298/2-4; Bonn, Germany) and the Robert Bosch Foundation (Stuttgart, Germany).

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