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The ABCB1 Transporter in Alzheimer's Disease

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ABC genes, especially *ABCB1* (ATP-binding cassette, sub-family B (MDR/TAP), member 1; Doxorubicin resistance; Multidrug resistance 1; Multidrug resistance protein 1; P-glycoprotein 1; P glycoprotein 1/ multiple drug resistance 1;P-gp) (7q21.12), *ABCC1* (9q31.1), *ABCG2* (White1) (21q22.3), and other genes of this family encode proteins which are essential for drug metabolism and transport. The multidrug efflux transporters P-gp, multidrug-resistance associated protein 4 (MRP4) and breast cancer resistance protein (BCRP), located on endothelial cells lining brain vasculature, play important roles in limiting movement of substances into and enhancing their efflux from the brain. Transporters also cooperate with Phase I/Phase II metabolism enzymes by eliminating drug metabolites. Their major features are their capacity to recognize drugs belonging to unrelated pharmacological classes, and their redundancy, by which a single molecule can act as a substrate for different transporters. This ensures an efficient neuroprotection against xenobiotic invasions. The pharmacological induction of ABC gene expression is a mechanism of drug interaction, which may affect substrates of the up-regulated transporter, and over expression of MDR transporters confers resistance to anticancer agents and CNS drugs [1,2]. Mutations in ABC transporters influence pathogenesis and therapeutics of brain disorders [3].

ABCB1 is probably the most important drug transporter in the brain. The *ABCB1* gene maps on 7q21.12 spanning 209.39 kb (29 Exons) with the structure of a P-glycoprotein and a Y-box sequence 5'-CTGATTGG-3' in its cis-regulatory elements. Several transcripts/ variants (ABCB1-001: 4645 bp. ABCB1-002: 3602 bp. ABCB1-003: 461 bp. ABCB1-004: 582 bp. ABCB1-005: 555 bp. ABCB1-006: 913 bp. ABCB1-007: 1864 bp. ABCB1-008: 642 bp. ABCB1-009: 787 bp. ABCB1-010: 539 bp. ABCB1-201: 345 bp) are highly expressed in adrenal gland, blood-brain barrier (BBB), brain, kidney, liver, placenta, small intestine, and uterus, and low expression is present in many other tissues. These transcripts encode a protein (ABCB1-001: 141.48 kDa; 1280 aa. ABCB1-002: 5.89 kDa; 51 aa. ABCB1-003: 5.68 kDa; 48 aa. ABCB1-201: 2.52 kDa; 22 aa) of the ATP binding cassette super-family, subfamily B (MDR/TAP) with two ATP binding and two transmembrane (2TM) domains (2 × 6 segments), acting as a transport carrier and a lipid translocase of broad specificity. This is a large transmembrane protein which is an integral part of the BBB and functions as a drug-transport pump transporting a variety of drugs from the brain back into the blood. Functions of this protein include the following: ABC transporter, traffic ATPase, energy-dependent efflux pump responsible for decreased drug accumulation in multidrug-resistant cells; potentially implicated in cholesterol transport; may maintain neural stem/progenitor cells in an undifferentiated state and could be a neural stem/progenitor marker [4].

About 1630 *ABCB1* variants have been identified [4]. Of interest, *ABCB1* has approximately 116 polymorphic sites in Caucasians and 127 in African-Americans with a minor allele frequency greater than 5%. Some of the most commonly studied variants are 1236C>T, 2677G>A/T and 3435C>T and the most commonly studied haplotype involves the 1236, 2677 and 3435 (TTT) SNPs and 3 intronic SNPs (intron 9, intron 13, intron 14) named *ABCB1*13*. There are many other *ABCB1* variants such as -129C>T (5'-UTR), 61A>G (Asn21Asp) and 1199G>A (Ser400Asn) that have been studied *in vivo* and *in vitro*. To date, there is no clear consensus on the impact of any of these variants on drug disposition, response or toxicity [4].

Variants of the *ABCB1* gene have been associated with a diverse number of diseases and with a great variety of drugs, natural products and endogenous agents [4]. Over 1270 drugs have been reported to be associated with the ABCB1 transporter protein (P-gp), of which 490 are substrates, 618 are inhibitors, 182 are inducers, and 269 additional compounds which belong to different pharmacological categories of products with potential ABCB1 interaction [4].

ATP-binding cassette (ABC) transporters, which are localized on the surface of brain endothelial cells of the BBB and brain parenchyma, affect Aβ transport (flux) across the BBB contributing to the pathogenesis of Alzheimer's disease (AD) [5-12]. One of the clearance pathways of amyloid-β is transport across the BBB via efflux transporters. Several BBB transporters have been implicated in Aβ exchange between brain parenchyma and the circulation [5-12]. Deficiency of either of the two major efflux pumps, ABCB1 and ABCG2, involved in Aβ trafficking across the BBB, results in increased accumulation of peripherally-injected $A\beta_{1\text{-}40}$ in the brain [13]. Decreased clearance of amyloid-β from the brain may lead to elevated amyloid-β levels. There is an age-related decrease in P-gp expression, $A\beta_{1\text{-}42}$ itself downregulates the expression of P-gp and other Aβ transporters, which could exacerbate the intracerebral accumulation of Aβ and thereby accelerate neurodegeneration in AD and cerebral β-amyloid angiopathy [11]. Amyloid efflux transporter expression at the BBB declines with aging in normal conditions [14], and expression of P-gp protein is significantly lower in hippocampal vessels of patients with AD compared to normal individuals [12].

ATP binding cassette subfamily G member 2 (ABCG2) is involved in amyloid-β transport and was found to be up-regulated in AD brains. A functional polymorphism of the *ABCG2* gene (C421A; rs2231142) (*ABCG2* C/C genotype) was associated with AD in the Hungarian population. The *ABCG2* C/C genotype and the *APOE Ɛ4* allele may also exert an interactive effect on AD risk [15]. Genome-wide significance in fully adjusted models was observed for a single-nucleotide polymorphism (SNP) in ABCA7 (rs115550680, allele = G; frequency, 0.09 cases and 0.06 controls), which is in linkage disequilibrium with SNPs associated with AD in Europeans. The effect size for the SNP in

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ABCA7 was comparable with that of the APOE ε4-determining SNP rs429358 (allele = C; frequency, 0.30 cases and 0.18 controls) [5].

Single-nucleotide polymorphisms in the *ABCB1* gene have been associated with altered P-glycoprotein expression and function. Van Assema et al. [10] assessed the effects of C1236T, G2677T/A and C3435T single-nucleotide polymorphisms in *ABCB1* on BBB P-gp function in healthy subjects and patients with AD. In healthy controls, binding potential did not differ between subjects without and with one or more T present in C1236T, G2677T and C3435T. In contrast, patients with AD with one or more T in C1236T, G2677T and C3435T had significantly higher binding potential values than patients without a T. There was a relationship between binding potential and T dose in C1236T and G2677T. In AD patients, C1236T, G2677T/A and C3435T SNPs may be related to changes in P-gp function at the BBB, and genetic variations in *ABCB1* might contribute to the progression of amyloid-β deposition in the brain. Kohen et al. [16] investigated a possible association between 2 common *ABCB1* polymorphisms, G2677T/A (Ala893Ser/Thr) and C3435T, AD, and CSF levels of Aβ, and no strong evidence for association was found. Frankfort et al. [17] studied *ABCB1* SNPs (C1236T in exon 12, G2677T/A in exon 21 and C3435T in exon 26) and inferred haplotypes in patients with dementia and age-matched non-demented control patients and found no differences between both groups; however, in a transcriptome analysis of leukocytes from patients with mild cognitive impairment (MCI), AD, as well as normal controls only the *ABCB1* gene exhibited significantly positive correlation with *Mini-mental state examination* (MMSE) scores, representing a novel biomarker of AD [18].

The drug transporter ABCB1 directly transports Aβ from the brain into the blood circulation, whereas the cholesterol transporter ABCA1 neutralizes Aβ aggregation capacity in an Apolipoprotein E (ApoE)-dependent manner, facilitating Aβ subsequent elimination from the brain [19]. Cascorbi et al. [20] genotyped selected variants in *ABCA1*, *ABCA7*, *ABCB1*, *ABCC2* and *ABCG2* in DNAs from brain tissue of 71 AD cases with Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropathological stages B/C and 81 controls. The novel *ABCA7* SNP, rs3752246, tended to be associated with AD. *ABCB1* variants were significantly less frequent in AD cases older than 65 years of age and among females. This association of *ABCB1* 2677G>T (rs2032582) was more pronounced in APOE4-negative cases. Only *ABCC2* 3972C>T (rs3740066) was significantly associated with AD risk.

Efflux transporter P-gp at the BBB restricts substrate compounds from entering the brain and may thus contribute to pharmacoresistance in CNS disorders, cancer and brain infections. Positron emission tomography (PET) has become a promising method to study the role of P-gp at the BBB. The first PET study of P-gp function was conducted in 1998, and during the past 15 years two main categories of P-gp PET tracers have been investigated: tracers that are substrates of P-gp efflux and tracers that are inhibitors of P-gp function [21].

P-gp protects the brain from accumulation of lipophilic compounds by active efflux transport across the BBB. Molecular transporters that are expressed in brain, especially at the BBB, are therapeutic targets in the treatment of AD. A benzopyrane derivative with P-gp stimulating properties has been proposed as a candidate agent to decrease Aβ accumulation in AD [22]. Lipid transporters of the A-branch of ABC transporters are also potentially involved in AD pathogenesis. Induction of transporters via the activation of specific nuclear receptors may represent a novel approach to restoring diminished BBB function. Transporters in the brain capillary endothelium regulate the permeation of therapeutic compounds into the brain [23,24].

Vitamin D receptor (VDR) activation up-regulates Mdr1/MDR1 and P-gp protein in brain capillaries and microvascular endothelia, implicating a role for VDR in increasing the brain clearance of P-gp substrates, including $hA\beta_{42}$ in AD [25].

Since P-gp prevents the entry of compounds into the brain by an active efflux mechanism at the BBB, inhibition of P-gp may help to enhance drug penetration. New reversible inhibitors of P-gp have been developed. Some galantamine-like compounds inhibit the efflux of the fluorescent P-gp substrate rhodamine 123 in cancer cells that over-express P-gp, and also inhibit the efflux of therapeutic substrates of P-gp, such as doxorubicin, daunomycin and verapamil. These compounds modulate P-gp mediated efflux by competing for the substrate binding sites [26]. Activation of the Liver X receptors (LXRs) by natural or synthetic agonists decreases the amyloid burden and enhances cognitive function in transgenic murine models of AD. LXR activation may affect the transport of Aβ peptides across the BBB. LXR agonists (24S-hydroxycholesterol, 27-hydroxycholesterol and T0901317) modulate the expression of target genes involved in cholesterol homeostasis (ABCA1) and promote cellular cholesterol efflux to apolipoprotein A-I and high density lipoproteins. LXR stimulation increases the expression of the ABCB1 transporter, which restricts Aβ peptide influx [27].

It is also important that drugs for AD treatment optimize CNS penetration by minimizing hydrogen bond donors and reducing P-gp-mediated efflux [28-30]. The increase of P-gp expression and activity by a P-gp inducer could be an effective pharmacological strategy in slowing or halting the progression of AD [31].

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