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Review

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Role of ABC Transporters in the Pathogenesis of Alzheimer's Disease

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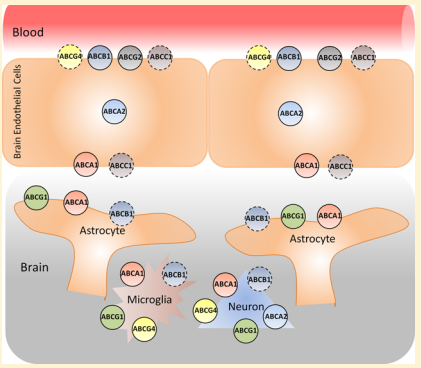
ABSTRACT: Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common form of age-related dementia that begins with memory loss and progresses to include severe cognitive impairment. A major pathological hallmark of AD is the accumulation of beta amyloid peptide (Aβ) in senile plaques in the brain of AD patients. The exact mechanism by which AD takes place remains unknown. However, an increasing number of studies suggests that ATP-binding cassette (ABC) transporters, which are localized on the surface of brain endothelial cells of the blood-brain barrier (BBB) and brain parenchyma, may contribute to the pathogenesis of AD. Recent studies have unraveled important roles of ABC transporters including ABCB1 (P-glycoprotein, P-gp), ABCG2 (breast cancer resistant protein, BCRP), ABCC1 (multidrug resistance protein 1, MRP1), and the cholesterol transporter ABCA1 in the pathogenesis of AD and Aβ peptides deposition inside the brain. Therefore, understanding the mechanisms by which these transporters contribute to Aβ deposition in the brain is important for the development of new therapeutic strategies against AD. This review summarizes and highlights the accumulating evidence in the literature which describe the role of altered function of various ABC transporters in the pathogenesis and progression of AD and the implications of modulating their functions for the treatment of AD.



KEYWORDS: *ABC transporters, Alzheimer's disease, blood-brain barrier, ABCA1, P-glycoprotein, MRP1, BCRP*

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common form of age-related dementia that begins with memory loss and progresses to include severe cognitive impairment.[1] The pathogenesis of AD is complex, and involves molecular, genetic, cellular, and physiological alterations to the brain and blood-brain barrier (BBB) that are still not completely understood.[2,3] The prevalence of AD is going up rapidly worldwide, with about 30 million people suffering from this disease nowadays, and it has an increasing socioeconomic impact.[4] Despite the huge demand for treatments, existing drugs have limited or no efficacy for AD.[5,6]

AD is characterized by a significant loss of neurons and atrophy of the hippocampus and cerebral cortex.[7] It begins as mild short-term memory disturbances and ends in total loss of cognition and executive functions.[8−10] The neuropathology of AD is characterized by two pathogenic hallmarks: the intraneuronal neurofibrillary tangle (NFT) and the extracellular amyloid plaque.[11,12] NFTs are largely composed of hyperphosphorylated fibrillar forms of a protein called microtubule associated protein tau which accumulates in the entorhinal cortex and the pyramidal neurons of the CA1 region of the hippocampus and subiculum.[7] The well-known amyloid cascade hypothesis suggests that AD is precipitated by the accumulation of amyloid plaques that are mainly composed of fibrils of peptides collectively known as beta amyloid (Aβ) which are produced by the sequential cleavage of amyloid precursor protein (APP) by β- and γ-secretases.[2,13,14] As AD progresses, these peptides usually aggregate in several forms ranging from diffuse oligomers into compact neuritic plaques which accumulate into the neocortical and hippocampal regions of the brain, causing disruption of the corticocortical circuits in neocortex and the perforant path that projects from the entorhinal cortex leading to memory deficit and loss of cognition (Figure 1).[15,16]

Amyloid plaques consist predominantly of two major peptides, Aβ_{40} and Aβ_{42}, and the experimental findings showed that both Aβ_{40} and Aβ_{42} are involved in the formation of insoluble fibrils in the brain extracellular space and eventually form diffuse and dense-cored amyloid plaques, resulting in neurotoxicity and neuronal death.[17−19] There are two pathways known to result in accumulating Aβ in the brain: (i) the overproduction of Aβ in the brain and (ii) the reduced clearance of Aβ from the brain.[20−23] Both genetic and environmental factors can contribute to the development of AD in early onset familial AD (EOAD) and sporadic late onset AD (LOAD).[21] Only 5% of AD (familial cases) is due to the overproduction of Aβ because of mutations in the APP gene or in the APP processing enzymes,[24,25] while the majority (95%) of so-called sporadic AD cases are likely caused by dysfunctions in Aβ solubility or aggregation, endocytosis, degradation, transcytosis, and removal.[26,27] Several mechanisms are involved in clearing Aβ from the brain including degradation by a variety of proteases such as neprilysin and/or insulin-degrading

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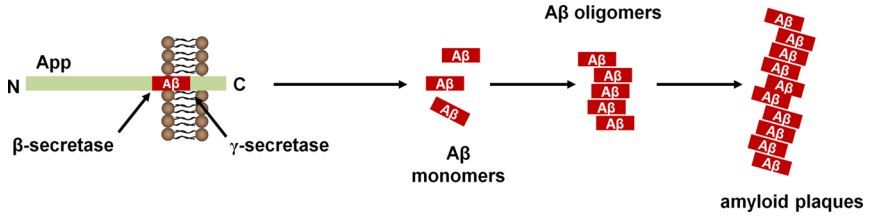

Figure 1. Amyloid precursor protein (APP) is cleaved sequentially by β-secretase and γ-secretase, releasing various Aβ peptides. In AD, increased production and/or decreased clearance of Aβ peptides results in the formation of oligomers and amyloid plaques.

enzyme (IDE), endocytosis by microglia and astrocytes, and removal through the interstitial fluid-CSF bulk flow into the bloodstream, perivascular lymphatic drainage and active transport across the BBB.[28−30]

The role of ATP-binding cassette (ABC) transporters in the pathology of AD has been recently recognized. ABC transporters, such as ABCB1 (P-glycoprotein, P-gp), ABCC1 (MRP1), ABCG2 (BCRP), and ABCA1, transport a vast array of lipophilic, amphipathic substrates against their concentration gradients by ATP hydrolysis limiting substrate cellular influx and retention.[31,32] In the CNS, ABC transporters are localized at different cell types including the endothelial cells of the BBB and brain parenchymal cells (Figure 2). Such

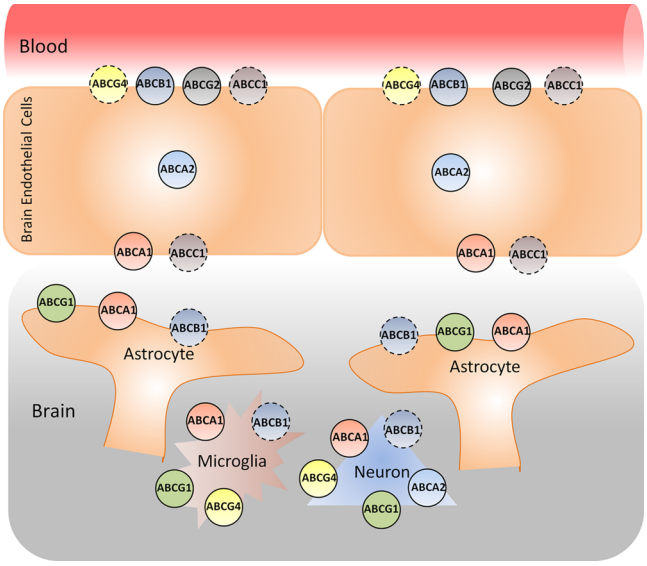

Figure 2. Expression of ABC transporters in the brain. Dotted circles indicate transporter localization that requires confirmation due to limited information or conflict in reporting.

strategic localization of ABC transporters to protect the brain against endogenous and exogenous compounds demonstrates their critical role in the maintenance of brain microenvironment.[32] ABC transporters are implicated in several CNS and non-CNS related diseases.[33] Some of these ABC transporters confer resistance to chemotherapeutics and thereby lower their therapeutic efficiency against cancers and possible in tumor stem cells.[32,34] Moreover, ABC transporters may be up-regulated on some cell membranes under certain pathophysiological conditions. For example, increased expression of ABC transporters at the BBB contribute significantly to the antiepileptic drug resistance in refractory epilepsy and thus uncontrolled epilepsy.[32,35] In brain tumors, ABC transporters may be found on the tumor in the vicinity of blood microvessels and thus lower the therapeutic efficiency of anticancer agents.[36] In addition to their physiological role as gatekeepers, the role of ABC transporters in neurodegenerative disorders such as AD is also intriguing because they may hold part of the key to understanding the pathogenesis of this disease. Recent studies have suggested ABC transporters to play a pivotal role in controlling Aβ levels in the brain and that alteration of expression and functional activity of these transporters may contribute to the aggregation of Aβ in the brain and/or brain endothelial cells, leading to increased risk for developing AD.[37−39] Impaired clearance of Aβ from the brain across the BBB, due to decreased expression and function of ABC transporters at the luminal side, for example, may lead to its accumulation on blood vessels and in brain parenchyma. The accumulation of Aβ on the brain blood vessels, known as cerebral amyloid angiopathy (CAA), is associated with cognitive decline. CAA is the leading cause of vascular dementia in the elderly, and is present in more than 80% of AD cases, highlighting an important role for CAA in AD. Furthermore, alterations in the expression and function of ABC transporters may impact Aβ production and amyloid deposition promoting the formation of toxic Aβ oligomeric and aggregated species.[40]

This review highlights and summarizes recent reports on the role of ABC transporters in the pathogenesis and progression of AD, and investigates their potential to serve as therapeutic targets for the treatment of AD.

■ ABCB FAMILY

ABCB1 (P-Glycoprotein, P-gp). ABCB1 or P-gp, the product of the *MDR1* gene, is the best-known and studied efflux transporter which, under normal physiological conditions, is widely expressed in barrier and excretory tissues.[41] ABCB1 is highly expressed on the luminal membrane of the endothelial cells at the BBB,[42] serving as a defense mechanism against a wide spectrum of nonpolar, therapeutic drugs and xenobiotics.[43] In contrast to its established localization at the BBB, ABCB1 expression in brain parenchyma, neuronal, and glial cells remains controversial. Several studies have demonstrated rat astrocytes and microglial cultures to express a variety of transporters including the efflux transporter ABCB1,[44−46] however, at lower levels when compared to rat brain endothelial cultures.[44] On the other hand, several other studies could not detect ABCB1 in neuronal or glial cells,[47,48] and have suggested that its expression in these cells may occur in pathologic human CNS conditions such as seizures, focal cortical dysplasia, and glioneuronal tumors.[49−51]

Due to its strategic location on the luminal membrane of the endothelial cells at the BBB, and its wide substrate selectivity, ABCB1 is widely believed to be the most important transporter in modulating the entry of drugs into the CNS.[43] While its endogenous function is not fully understood, the recent

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discovery that $A\beta_{40}$ and $A\beta_{42}$ are substrates for ABCB1[52] revealed a new and perhaps highly important physiological role for BBB-suited ABCB1. Its expression pattern at the BBB suggests a key role of ABCB1 in the etiology of AD, and it has been shown to play substantial role in controlling $A\beta$ levels in the brain.[52−56] Studies have demonstrated a progressive decline in the level of ABCB1 at the BBB during normal aging, and this decline was positively correlated with accumulation of $A\beta$ in AD.[55,57]

In vitro binding studies showed that efflux of $A\beta_{40}$ and $A\beta_{42}$ are mediated by ABCB1 as a result of direct interaction between $A\beta$ and ABCB1.[52] This observation was then followed by several in vitro and in vivo studies demonstrating the ABCB1 role in the clearance of $A\beta$ from the abluminal to the luminal side of the membrane. For example, in MDR1-transfected LLC-PK1 cells grown in a polarized cell layer, Kuhnke et al. have demonstrated that when FITC-$A\beta_{40}$ and FITC-$A\beta_{42}$ were delivered from the basolateral to the apical compartment in the presence of cyclosporine A (ABCB1 inhibitor), both peptides transport was significantly decreased suggesting impaired clearance of $A\beta$ peptides by ABCB1 inhibition. The authors concluded the important role ABCB1 plays in the clearance of $A\beta_{40}$ and $A\beta_{42}$ from the brain.[53] In addition, when labeled $A\beta_{40}$ and $A\beta_{42}$ peptides were micro-injected into the CNS of ABCB1 knockout mice, the clearance rate of $A\beta$ across the BBB was reduced to half compared to the wild-type mice.[54] In this study, the importance of ABCB1 in $A\beta$ clearance was made quite evident by the observation that $A\beta$ concentrations in brain ISF were elevated in transgenic mice overexpressing APP with normal levels of ABCB1 at the BBB when these mice were administered an ABCB1 inhibitor.[54] Studies with human brain tissues further support such essential role for ABCB1 in the clearance of $A\beta$. In a study of ABCB1 expression in 243 nondemented elderly human cases of CAA, blood vessels with high ABCB1 expression showed no $A\beta$ deposition in the vessel walls, whereas those with low ABCB1 expression showed high deposition of $A\beta$. Also, in the same tissues, the $A\beta$ immunoreactive plaques in the parenchyma were found to be inversely related to the expression of endothelial ABCB1.[53,55] In a later study, the same authors explained this inverse relation between ABCB1 and $A\beta$ as a consequence of $A\beta$ on ABCB1 where high amounts of $A\beta$ down-regulated ABCB1 expression at the BBB.[58] Another study, however, reported an indirect effect of $A\beta$ on ABCB1 where higher levels of $A\beta$ in the brain result in an up-regulation of Dickkopf-1 (Dkk-1) expression, which causes reduction in Wnt signaling leading to impairment of BBB function including reduction in ABCB1 expression.[59]

Nonetheless, conflicting data about the role of ABCB1 in $A\beta$ clearance from the brain also exists. For example, in an in vitro model of polarized epithelial cells (MDCK) transfected with ABCB1, $A\beta$ transport from the basolateral to the apical compartment was very low and was not altered by ABCB1 inhibition when compared to wild type control cells.[60] The authors concluded overexpression of ABCB1 does not promote $A\beta$ clearance.[60] Furthermore, in an in vivo study using rats, the preadministration of quinidine or verapamil, ABCB1 inhibitors, to the rat brain did not significantly affect $A\beta$ clearance.[61] This result was supported by an in vitro transport study where addition of the ABCB1 inhibitors tariquidar or vinblastine did not affect the brain-to-blood transport of ^{125}I-$A\beta_{40}$; however, both inhibitors facilitated blood-to-brain transport of ^{125}I-$A\beta_{40}$, which suggests the minor or lack of ABCB1 contribution to $A\beta$ clearance from the brain and emphasizes ABCB1 role in limiting $A\beta$ access to the brain.[62] The authors of these studies concluded that ABCB1 at the BBB does not play a role in the clearance of $A\beta$, but its strategic position at the luminal side of the BBB limits $A\beta$ entry into the brain.[60−62]

Further studies on the role of ABCB1 in $A\beta$ efflux have shown that ABCB1 inhibition by verapamil, a competitive inhibitor of ABCB1, revealed a slight effect, but not significant, on $A\beta$ peptide transport whereas GF120918 (elacridar) increased $A\beta$ peptides transport across brain capillary endothelial cells from bovine origin.[63] According to these findings, the authors concluded that ABCB1 does play role in limiting $A\beta$ access to the CNS and that the choice of ABCB1 inhibitor is crucial to demonstrate ABCB1 contribution to the process. However, it should be noted that GF120918 is ABCB1 and ABCG2 (BCRP) inhibitor,[64] and $A\beta$ peptides have been reported as a substrate for ABCG2 as well.[62] Thus, being a dual inhibitor, it is possible that GF120918 enhanced the transport of $A\beta$ peptide across the endothelial cells as a result of inhibition of the efflux functions of both proteins, ABCB1 and ABCG2.

Collectively, given that different cell lines, inhibitors, and animal models have been used in the above studies, the observed discrepancy would not be surprising. Findings from our laboratory from transport and uptake studies utilizing different cells lines, including epithelial and brain endothelial cells, demonstrated variable results ranging from obvious effect of ABCB1 on $A\beta$ transport to none.[38,66] Overall, the above findings demonstrate ABCB1 plays a major role in $A\beta$ transport; however, its relative expression to other transport proteins of $A\beta$ such as RAGE (receptor for advanced glycation end products)[66] and LRP1 (low density lipoprotein receptor-related protein-1),[19] that are variable among different cell lines, could be responsible for such discrepancy. In vitro and in vivo studies from our laboratory supported both roles of ABCB1, that is, extrusion from the luminal side and clearance from the abluminal side, which is the expected function of ABCB1 to control and limit its substrates levels in the brain. In vitro accumulation studies using the human colon adenocarcinoma cell line LS-180, which endogenously expresses ABCB1 and pregnane-X-receptor (PXR),[67] demonstrated that the cotreatment of $A\beta_{40}$ with the ABCB1 inhibitor verapamil significantly increased $A\beta_{40}$ cellular accumulation, confirming its role in limiting $A\beta$ cellular entry.[38] Moreover, utilizing in vivo brain efflux index (BEI%) studies conducted on C57BL/6 mice provided further evidence to the important role of ABCB1 in the clearance of ^{125}I-$A\beta_{40}$ from the brain where inhibition studies with valspodar (ABCB1 inhibitor) caused 18% reduction in ^{125}I-$A\beta_{40}$ clearance ($P < 0.05$).[65]

Overall, the above observations demonstrated ABCB1 as a significant player in determining $A\beta$ levels in the brain, and suggest that a small decline in its expression and/or activity is expected to result in decreased clearance of $A\beta$ and subsequent increase in cerebral vessels $A\beta$ deposits and in brain parenchyma, and extracellular and intracellular deposits. Considering the established role of age-associated decline in ABCB1 mediated brain removal of $A\beta$ peptides in AD, strategies to up-regulate ABCB1 expression and/or activity have been investigated to enhance $A\beta$ clearance across the BBB as a potential preventive approach. Available findings from limited number of studies demonstrated the validity of this approach. For example, in vivo induction of ABCB1 expression at the BBB of hAPP transgenic mice via PXR activation

significantly reduced Aβ deposition in the mice brains as a result of increased ABCB1 mediated Aβ efflux across the luminal membrane of the BBB.[68] In addition, in vitro and in vivo up-regulation of ABCB1 by different ABCB1 inducers significantly modulated Aβ levels.[38,65] The in vitro treatment of LS-180 cells with rifampicin, caffeine, verapamil, hyperforin, and β-estradiol, and to a lesser extent pentylenetetrazole and dexamethasone, resulted in significant decrease in the intracellular accumulation of $Aβ_{40}$ when compared to control as a result of ABCB1 up-regulation.[38] Furthermore, in vivo BEI% studies conducted on C57BL/6 mice treated with rifampicin or caffeine significantly enhanced $Aβ_{40}$ clearance by more than 20% when compared to control vehicle treated mice.[65] ABCB1 inhibition studies using valspodar confirmed the importance of ABCB1 to the clearance of Aβ, and that enhanced clearance following drugs treatment was caused specifically by ABCB1 up-regulation at the mouse BBB.[65] These findings support the validity of increasing Aβ clearance via ABCB1 up-regulation as a therapeutic approach to slowing or halting the progression of AD.

■ ABCA FAMILY

ABCA1. ABCA1 plays major role in regulating the intracellular cholesterol efflux, which is a rate-limiting step in the formation of HDL and allows the removal of excess cholesterol from tissues thus limits the risk of atherosclerosis.[69] ABCA1 is highly expressed in astrocytes, glial cells, neurons, and brain capillary endothelial cells.[70] Abnormalities in cholesterol metabolism in brain appear as an important element in AD risk and pathogenesis, since cholesterol levels regulate membrane fluidity and size and distribution of lipid rafts where enzymes necessary for Aβ production are localized.[71]

Although the molecular mechanisms by which ABCA1 impacts Aβ production and amyloid deposition is not fully understood, a substantial body of evidence has accumulated during the past years to suggest critical roles of ABCA1 in the development of AD. Unlike ABCB1, ABCA1 does not directly transport Aβ.[72,73] In *Abca1* knockout mice, the elimination of cerebral microinjected ^{125}I-$Aβ_{40}$ across the BBB was not significantly different from that of wild type mice, suggesting that most likely in AD ABCA1 affects the production and/or degradation system of Aβ rather than its efflux transport across the BBB.[72] ABCA1 regulates both the level of apoE as well as its state of lipidation via regulation of neuronal cholesterol efflux to apoE. apoE is reported to act as a chaperone for Aβ by binding the peptide and altering its conformation, thereby influencing its clearance and ability to aggregate.[74−76] In humans, apoE exists in three isoforms, apoE2, apoE3, and apoE4; differs by amino acids at positions 112 and 158. apoE4 is known as the strongest genetic risk factor for late-onset AD.[77,78] apoE4 affects the onset of AD possibly by promoting Aβ aggregation into amyloid plaques in the brain as a result of impaired Aβ clearance and/or enhanced formation of Aβ fibrils.[79−81] Several studies have shown differences in the binding of apoE isoforms to Aβ. In vitro studies investigated the binding affinity of lipid-associated and delipidated apoE3 and apoE4 isoforms to Aβ using transfected eukaryotic cell lines found that apoE3 affinity to complex with Aβ is 20-fold greater than that of apoE4, and that delipidation of apoE decreased its affinity for Aβ by 5−10-fold and abolished the isoform-specificity, while lipid-associated apoE3 binds to Aβ peptides with 2−3-fold higher affinity than lipid-associated apoE4. [82] Consistent with these in vitro findings, in vivo studies using AD mice expressing human apoE2, apoE3, and apoE4 demonstrated isoform-specific differences in amyloid load with apoE4 > apoE3 > apoE2.[83,84] In addition to affecting amyloid deposit, Deane et al. demonstrated that apoE disrupts Aβ clearance across the mouse BBB in an isoform-specific manner where apoE4 had a greater disruptive effect than either apoE3 or apoE2.[79] This study found that Aβ binding to apoE4 redirected the rapid clearance of free Aβ from LRP1 to the VLDL receptor, which internalized apoE4 and Aβ-apoE4 complex at the BBB more slowly than LRP1 compared to apoE2 and apoE3 and their Aβ complexes which cleared much faster via both VLDLR and LRP1.[79] Findings from recent studies have shown that apoE may play role in regulation of ABCA1[85] and the ABC transporters ABCB1 and ABCC1.[86] Activation of apoE receptor 2 (apoER2) following treatment of mouse macrophages with human apoE3 significantly increased ABCA1 mRNA and protein levels via the activation of the PI3K-PKCζ-Sp1 signaling cascade. [85] Furthermore, in vivo activation of apoER2 on mouse brain capillaries by elevated levels of apoE in the brain parenchyma, as a result of methamphetamine treatment, increased the expression of ABCB1 and reduced the expression of ABCC1 at the brain capillaries through the apoE/apoE receptor-2/c-Jun N-terminal kinase 1/2 pathway. [86]

Modulation of ABCA1 expression and/or activity is, thus, expected to influence apoE/Aβ interactions along with Aβ deposition and consequent undesirable effect in the brain. Reduced levels or absence of ABCA1 produce lower levels of apoE that is poorly lipidated.[87] PDAPP Abca1−/− mice, which have ∼25% of normal apoE levels at 3 months of age, develop increased Aβ deposition by 12 months of age, suggesting poorly lipidated apoE formed in the absence of ABCA1 strongly promotes Aβ fibrillogenesis in an age-dependent manner relative to normally lipidated murine apoE.[88] Several other available in vivo studies using both ABCA1-deficient and ABCA1-overepxressing animal models supported the role of ABCA1-mediated lipidation of apoE in facilitating the clearance of Aβ peptides.[74,81,88−90] Consistent with these in vivo data, several in vitro findings demonstrated the level of apoE lipidation contributes to Aβ deposition by altering its interactions with Aβ.[82,91,92] Jiang et al have reported apoE and its lipidation status influences its capacity to promote Aβ degradation,[93] and loss of either of apoE or ABCA1 activity showed impaired ability of primary microglia to degrade Aβ, while enhanced ABCA1 expression stimulated Aβ degradation.[74] Other studies, on the other hand, demonstrated ABCA1 role in regulating Aβ brain levels is independent of cholesterol efflux from cells, rather via suppression of APP processing to generate Aβ peptides.[92,94] Membrane cholesterol has been reported to regulate processing of APP and generation of Aβ.[95,96] Reduced membrane rafts as a result of depletion of cellular cholesterol caused a reduction in Aβ secretion as a result of increased alpha cleavage of APP, and reduced beta cleavage.[97] A subsequent study suggested that ABCA1 acts as a cholesterol translocase at the plasma membrane.[94] Cholesterol translocation causes changes in plasma membrane morphology[94,98,99] that may lead to a decrease in γ-secretase cleavage either by altering sensitivity of γ-secretase activity to membrane environment or trafficking of C99 to the site of γ cleavage, which affects Aβ production that is highly sensitive to its membrane lipid environment.[102,106,107] These findings indicate that decrease in Aβ production is related to the intrinsic cellular activity of ABCA1.

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Collectively, the above findings demonstrate ABCA1 profoundly influences AD pathology, and modulation of ABCA1 function and levels hence may be a novel therapeutic target for AD. Because a decrease in ABCA1 results in more amyloid deposition, increasing ABCA1 protein or function might be predicted to decrease amyloid deposition via increasing apoE lipidation or suppression of Aβ production. The treatment of mice with liver-X-receptor (LXR) agonists resulted in LXR activation and increased expression of brain ABCA1 which in turn induced lipid efflux from glial cells.[100,101] These observations led several investigators to propose that activation of LXR induces ABCA1, thus affecting Aβ deposition and clearance.[91−93,102−104] The LXR agonists TO901317 and GW3965 have been demonstrated to alter Aβ production in APP overexpressing neuronal and non-neuronal cells.[91,92,102] In vivo, short-term administration of TO901317 and GW3965 to 5-month-old Tg2576 mice improved fear conditioning,[93,103] and treatments with TO901317 have shown small reduction in soluble Aβ isoforms Aβ_{40} and Aβ_{42},[102] or only Aβ_{42}, in hippocampus of Tg2576 mice.[103] Long-term treatment with TO901317 restored object recognition in APPSwxPS1 mice,[104] and with GW3965 has shown to reduce plaque formation by 50% in aged Tg2576 mice.[93] Together, the above studies indicated the positive effect of LXR agonists on Aβ deposition and cognitive function. In addition to effect of increased ABCA1 on Aβ deposition, Terwel et al. demonstrated the effect of long-treatment with TO901317 on increased expression of ABCA1 and apoE in aged APP23 and control mice. This increase led to increased amounts of lipidated ApoE, which was able to ameliorate Aβ pathology, but only mildly improved spatial memory performance.[105] The authors concluded that TO901317 may affect the clearance of insoluble Aβ by stimulation of microglial phagocytosis of fibrillar Aβ, which is dependent on increased lipidated apoE through LXR activation.[105] Sun et al, on the other hand, showed that LXR activation and ABCA1 up-regulation induced changes in membrane lipid organization, which had favorable effects on the processing of APP,[94] suggesting a new approach to the treatment of AD.

Several in vitro studies investigated the effect of ABCA1 modulation on Aβ production. Fukumoto et al. demonstrated treatment of neuroblastoma Neuro2a cells with endogenous or synthetic LXR ligands to up-regulate ABCA1 levels caused significant increase in secreted Aβ_{40} and Aβ_{42}, which was reversed by RNAi blocking of ABCA1 expression, suggesting ABCA1 is involved in increased production of Aβ.[106] However, subsequent in vitro studies were not able to obtain a similar effect. For example, in non-neuronal and neuronal cells overexpressing hAPPSw gene, Koldamova et al. demonstrated treatment with LXR ligands induced ABCA1 expression and increased apoA-I-mediated cholesterol efflux, thus decreasing cellular cholesterol content.[91] More importantly, they have shown that these ligands alone or in combination with apoA-I caused a reduction in Aβ production as a result of significant decrease in the stability of APP C-terminal fragments. This finding was supported by in vitro studies demonstrating ABCA1 significant role in the regulation of neuronal cholesterol efflux to apoE and in suppression of APP processing to generate Aβ peptides,[92,94] contradicting those reported by Fukumoto et al.[106] Furthermore, results from in vitro studies performed in pericytes demonstrated that treatment of primary pericytes culture with 24S-OH-cholesterol, a cholesterol metabolite and a natural agonist of LXR, increased expression of ABCA1, and such an increase in ABCA1 expression correlated with cholesterol transfer to apoE, apoA-I, and HDL particles, the key players in brain cholesterol homeostasis and amyloid accumulation and deposition, and its inhibition decreased this efflux.[73] Yet the increase in ABCA1 expression was not associated with any change in Aβ_{40} and Aβ_{42} peptide accumulation inside pericytes.[73] Besides, in vitro inhibition studies supported the role of ABCA1 in Aβ production. Recently, in their in vitro study, Kim et al. demonstrated using the mouse neuroblastoma N2a cells that suppression of ABCA1 expression by miR-106b impaired cellular cholesterol efflux and increased the levels of secreted Aβ. The proposed mechanism for such an effect was via facilitation of APP processing toward Aβ production and impaired Aβ clearance.[107]

In the brains of AD patients, interestingly, neuronal ABCA1 mRNA and protein levels were found to be significantly up-regulated in the hippocampus of AD brains compared to unaffected AD brain region, the cerebellum, suggesting that this up-regulation is associated with the AD pathological process.[71,108] This finding was further confirmed in the hippocampus of the AD model APP/PS1 where Abca1 expression was up-regulated in an age dependent fashion when compared to wild-type control mice.[108] Increased Abca1 expression in APP/PS1 was only observed in the presence of extensive Aβ levels, suggesting induction of ABCA1 expression may be associated with late stage Alzheimer's neuropathology.[109]

ABCA2. ABCA2, the second identified member of the ABCA subfamily, is highly expressed in brain, especially in the white matter,[110] and is enriched in pluripotent neural progenitor cells in the subventricular zone of lateral ventricles and dentate gyrus of the hippocampus.[111] At the subcellular level, ABCA2 localizes to late endosomes, lysosomes, trans-Golgi, and endoplasmic reticulum.[112,113] ABCA2 has been identified as a possible regulator of lipid metabolism. ABCA2 decreased low-density lipoprotein receptor (LDLR) mRNA and protein levels and increased its turnover rate. Reduction of endogenous ABCA2 expression by RNAi treatment of N2a cells and rat primary cortical neurons resulted in increased protein levels of LDLR, suggesting ABCA2 as a key regulator of cholesterol homeostasis and LDLR metabolism in neuronal cells.[114] In addition, a possible role of ABCA2 in the intracellular trafficking of lipoprotein-derived cholesterol from late endosomes/lysosomes to the endoplasmic reticulum for esterification has been reported.[115] The endosomal-lysosomal pathway is known to be the major site of Aβ generation,[116] and further studies demonstrated a colocalization of ABAC2 and APP in intracellular vesicles of neuroblastoma cells.[113]

Genetic variation in *ABCA2* gene has been linked to increased risk of AD. The synonymous SNP (rs908832) was found significantly associated with AD.[117,118] One of the studies has associated this SNP as a genetic risk for early onset AD,[117] while in another study this SNP was population-dependent and considered as a genetic risk for sporadic AD.[118] Nonetheless, both studies demonstrated a significant support for the role of ABCA2 to cholesterol and phospholipid homeostasis and AD, presenting a rationale for testing novel cholesterol homeostasis-related therapeutic strategies in AD.

In vitro studies have shown ABCA2 as a key regulator of endogenous APP expression and processing linking it to AD.[119,120] The overexpression of ABCA2 in N2a neuronal cells elevated endogenous APP expression and promoted amyloidogenic processing through β-secretase cleavage at the β'-site/

Glu11 of Aβ in APP to generate the β′-CTF/89 fragment. Cleavage of the β′-CTF/89 fragment by γ-secretase generates *N*-terminally truncated Aβ peptides that are linked with AD pathology.[119] The pathologic effects of *N*-terminally truncated Aβ peptides may be due to the fact that they are less soluble and enhance aggregation of Aβ into neurotoxic β-sheet fibrils.[121] On the other hand, in mammalian cells, siRNA-mediated knockdown of Abca2 expression resulted in decreased Aβ production as a result of lowered γ-secretase processing of APP.[120] The authors showed that Abca2 knockdown affected the glycosylation pattern and subcellular localization of Nicastrin, one of the four γ-components including Presenilins 1 and 2, and Aph1, leading to altered γ-secretase complex formation.[120] These results were confirmed in vivo, where Abca2 knockout mice displayed reduced Nicastrin protein levels and decreased Aβ production without affecting APP levels.[120] Overall, the findings from this study suggested Abca2 as an important regulator of γ-secretase-mediated APP proteolysis and therefore of Aβ production.

Collectively, the above findings link ABCA2 to APP processing, either via β- or γ-secretases, and AD, which may suggest that, unlike ABCB1 and ABCA1, ABCA2 down-regulates to reduce the production of Aβ as a therapeutic approach for the treatment of AD.

■ ABCG FAMILY

ABCG2 (Breast Cancer Resistance Protein, BCRP). ABCG2 or BCRP is another ABC transporter predominantly expressed at the luminal membrane of the BBB cells.[122,123] ABCG2 shows substrate overlap with ABCB1 and its involvement in Aβ peptides transport was suggested at the microvessel cells level acting as gatekeeper at the BBB to prevent blood Aβ peptides from entering into the brain.[62,124,125]

The role of ABCG2 in Aβ extrusion at the BBB was investigated in *Abcg2*-null and wild-type mice after intravenous injection of labeled Aβ.[124] Optical imaging analyses of live animals and their brains showed that *Abcg2*-null mice significantly accumulated more Aβ in their brains than wild-type mice, suggesting ABCG2 may act as a gatekeeper at the BBB to prevent blood Aβ from entering into brain.[124] This role was further confirmed by in vitro studies utilizing ABCG2 overexpressing cells. The results demonstrated ABCG2 to restrict the apical-to-basolateral permeability of Aβ isoforms, suggesting a role for this efflux transporter in preventing blood-borne Aβ peptides from entering the brain, but not in transporting the brain Aβ into blood.[62,63,124,125]

Unlike ABCB1, expression analyses of 273 BBB-related genes performed by Xiong and colleagues showed that ABCG2 gene was significantly up-regulated in the brains of AD and CAA patients compared to age matched control group.[124] The authors explained ABCG2 gene up-regulation as a compensatory mechanism initiated by the pathological microenvironment in the neurovascular unit to reduce Aβ burden in the brain by preventing access of circulatory Aβ into the brain, or as an early vascular change involved in maintaining circulatory pool of Aβ and thus preventing Aβ clearance from perivascular or parenchymal pools. Accordingly, the authors concluded utilization of ABCG2 up-regulation as a biomarker of CAA vascular pathology.[124] Other groups, however, have suggested ABCG2 up-regulation in the brains of AD patients as a protective mechanism during oxidative stress and inflammatory response by inhibiting the NF-κB signaling pathway, leading to decreased expression of interleukin-8 and growth-related oncogene (GRO) inflammatory genes. In the brains of *Abcg2* knockout mice, NF-kB activation as a result of *Abcg2* deficiency increased Aβ deposition compared to controls. This result was further confirmed in vitro in N2a-695 cells where over-expression of ABCG2 significantly decreased the processing rate of APP and Aβ production as compared with controls.[126]

Lack of difference in ABCG2 expression in the brain vasculature of AD compared to normal cases has also been reported.[59] While further studies are necessary to confirm these results, this discrepancy could be related to regional variations, for example, hippocampal[59] vs occipital cortical[124] regions, in the extent of ABCG2 vascular changes in AD. These results clearly indicate the need for further investigations about the role of ABCG2 in the pathology of AD and confirm the validity of its therapeutic targeting in the treatment of AD,[62,63,125] or its utilization as a biomarker of CAA vascular pathology in AD.[124] Furthermore, taking into consideration that ABCB1 and ABCG2 are both involved in limiting Aβ access to the brain by clearance and/or extrusion, and that in AD brains while expression of ABCB1 is down-regulated[55] increased expression of ABCG2 has been observed,[124] studies investigating both transporters' expressions simultaneously in the same affected brain region are warranted. This is important to establish increased expression of ABCG2 as a compensatory mechanism for ABCB1 down-regulation and as one way to protect the brain.

ABCG1. ABCG1 is another member of the ATP binding cassette superfamily and part of a network of genes that regulate cellular lipid homeostasis.[127] In situ hybridization studies for *Abcg2* demonstrated its expression in neuronal cells and certain types of glial cells in the white matter, such as oligodendrocytes and fibrous astrocytes.[92,128,129] Available studies linking this protein to AD are limited with conflict results. In one of these studies, the transient transfection of ABCG1 into HEK293 cells expressing APP carrying the Swedish mutant (APPSwe) increased the production of Aβ peptides by approximately 30%.[130] On the other hand, Kim et al. observed that Aβ production was reduced by 64% in CHO cells coexpressing APP and ABCG1.[92] In an in vivo study utilizing PDAPP mice, the authors reported a 6-fold increase in ABCG1 levels did not alter Aβ, apoE levels, cholesterol efflux, or cognitive performance. Furthermore, in the same study, no alteration was observed in endogenous murine Aβ levels in ABCG1-overexpressing or ABCG1-deficient mice,[130] suggesting the absence of direct role of ABCG1 in AD.

ABCG4. Like ABCG1, ABCG4 is a member of the membrane cholesterol transporters implicated in high density lipoprotein (HDL) mediated cholesterol efflux,[128,129] Its precise localization in the brain is not clear; however, available studies have reported ABCG4 expression in radial glial and neuronal cells,[92,128,129] and a recent study has described its expression in brain microvessels.[125]

To our knowledge, two studies have investigated the role of ABCG4 in AD.[125,131] In AD brain, Uehara et al. have reported high ABCG4 protein and mRNA expression in microglial cells closely located to senile plaques, whereas in non-neurological cases ABCG4 positive cells were not detected.[131] The authors linked ABCG4 up-regulation to lipid metabolism in the brain and development or progression of AD. They reasoned ABCG4 up-regulation to enhance apoE lipidation and formation of apoE-HDL by the uptake of cholesterol from microglia to attenuate the neurotoxicity of apoE.[131] While the effect of

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ABCG4 on the clearance of Aβ from the brain is not clear, a recent study has reported the presence and function of ABCG4 at the BBB and its role in Aβ clearance.[125] Using the brain efflux index method to investigate the contribution of Abcg4 to the clearance of Aβ across the BBB of *Abcb1/Abcg2/*and *Abca1*-deficient mice, the authors proposed that the probucol-sensitive transporter Abcg4 is involved in the brain efflux of Aβ, which was confirmed by in vitro studies. Furthermore, the authors reported Abcg4 as 1.6-fold more abundant in the brain capillaries of *Abcb1/Abcg2*-deficient mice compared to wild type mice suggesting lack of both *Abcb1* and *Abcg2* is compensated by an increase in *Abcg4* and a decrease in *Abca1*.[125] Further studies are required to establish and confirm the roles of both ABCG1 and ABCG4 to the pathology of AD and their potential as novel targets in the development of therapeutics for the prevention of AD.

■ ABCC FAMILY

ABCC1 (Multidrug Resistance Protein 1, MRP1). Conflicting results of ABCC1 localization in several species have been published, with some showing a strong luminal ABCC1 localization at the BBB[132−135] and others reporting its expression in choroid plexus but not microvessels.[136−138] In vivo drug transport studies in rats and *Abcc1*-deficient mice have implicated Abcc1 in drug efflux across the BBB,[135] but other studies in *Abcc1*-deficient mice have demonstrated Abcc1 efflux across the choroid plexus (blood−CSF barrier) but not the BBB.[136,139,140]

A limited number of studies has demonstrated a role for ABCC1 in AD. Sultana and Butterfield reported a role for ABCC1 in conjunction with GST to remove lipid peroxidation products such as 4-hydroxy-2-transnonenal (HNE).[141] HNE has been linked to AD,[142−144] and significant increase in free HNE has been detected in cerebrospinal fluid,[145] amygdala, hippocampus, and parahippocampal gyrus in brain of AD patients.[146] GST functions by inactivating HNE via glutathione conjugation, which in turn is extruded by ABCC1. In the brains of AD, GST function is significantly reduced,[147] causing increased levels of free HNE that form adducts with both GST and ABCC1.[141] These findings suggest that HNE could be a mediator of oxidative stress-induced impairment of the detoxification system GST and ABCC1. Another study by Krohn et al. demonstrated ABCC1 in cerebral Aβ clearance and brain accumulation.[148] In their study, the authors showed that deficiency of ABCC1 in APP/PS1 (APP/PS1 × Abcc1−/−) substantially increased cerebral Aβ levels without altering the expression of most enzymes that would favor the production of Aβ from the APP. To converse such effect, the authors investigated the reversal effect of thiethylperazine, ABCC1 inducer, where they observed a significant reduction in Aβ levels in APP/PS1 mice brains, indicating a role of ABCC1 in Aβ deposition in the brain. These results identified ABCC1 as a potential target for treatment or preventing AD and CAA.

■ CONCLUSIONS

It is now obvious that the ABC transporters play important role, directly and/or indirectly, in the pathology of AD; however, we remain far from the exact contribution these transporters have to the disease. For example, whether alteration in the ABC members' expression and function is a cause or a consequence of AD is still unclear. Many questions remain about the mechanisms of these transporters in the regulation of Aβ production and clearance in the CNS. Further investigations are needed to understand the role of genetic variability in ABC transporters to the loss of neuroprotective function and inefficient Aβ clearance across the BBB, as a risk factor for the development of AD. Aβ oligomers have a major role in AD pathogenesis; while impaired clearance has shown to increase Aβ levels in the brain and risk of Aβ oligomer formation, studies investigating the role of ABC transporters in the clearance of Aβ oligomers are essential and still needed. Better understanding of the mechanisms by which ABC transporters' expression and function regulate and control Aβ production and clearance may not only reveal disease-modulating effects of the transporters but also disclose causative roles of disturbed transport functions in the neurodegeneration processes observed in AD. Furthermore, understanding the role of ABC transporters in the maintenance of BBB integrity is also expected to enhance our understanding of the disease processes.

The findings presented in this review strongly suggest ABC transporters function to protect the brain by preventing Aβ deposition by controlling its production or clearance, and hence probably against the development of AD. Thus, further clarification of these transporters in regulating both processes is essential to develop drugs that target these transporters especially ABCB1 and ABCA1. Both transporters are considered as the most studied with relatively strong evidence linking them to the pathology of AD. While results from these studies demonstrated some conflicting observations, the findings support their up-regulation as a therapeutic approach to improve, cure, or prevent the disease progression. The activity of ABC transporters can be modulated pharmacologically by different compounds including frequently used drugs. Thus, understanding the exact mechanism by which these drugs have demonstrated the positive effect on AD patients would allow development of more potent and specific modulators to prevent Aβ accumulation in the brain, especially in early stages of the disease.

ABC transporters activity and their subcellular and cellular distributions in the brain parenchyma and at the BBB underline their importance for maintaining the physiology and homeostasis of the brain including the control of Aβ levels. Their specific distribution patterns, their modulation by xenobiotics and endogenous molecules, and their genetic variations probably make ABC transporters key factors for the development of neurodegenerative disorders including AD. Thus, a better understanding of ABC transporters functions in the human brain is of major pharmacological importance to the development and optimization of therapeutic strategies that target these transporters.

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