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Review

Alzheimer's and ABC transporters — new opportunities for diagnostics and treatment

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ABSTRACT

Much has been said about the increasing number of demented patients and the main risk factor 'age'. Frustratingly, we do not know the precise pattern and all modulating factors that provoke the pathologic changes in the brains of affected elderly. We have to diagnose early to be able to stop the progression of diseases that irreversibly destroy brain substance. Familiar AD cases have mislead some researchers for almost 20 years, which has unfortunately narrowed the scientific understanding and has, thus, lead to insufficient funding of independent approaches. Therefore, basic researchers hardly have been able to develop causative treatments and clinicians still do not have access to prognostic and early diagnostic tools. During the recent years it became clear that insufficient Aβ export, physiologically facilitated by the ABC transporter superfamily at the brain's barriers, plays a fundamental role in disease initiation and progression. Furthermore, export mechanisms that are deficient in affected elderly are new targets for activation and, thus, treatment, but ideally also for prevention. In sporadic AD disturbed clearance of β-amyloid from the brain is so far the most important factor for its accumulation in the parenchyma and vessel walls. Here, we review findings about the contribution of ABC transporters and of the perivascular drainage/glymphatic system on β-amyloid clearance. We highlight their potential value for innovative early diagnostics using PET and describe recently described, effective ABC transporter-targeting agents as potential causative treatment for neurodegenerative proteopathies/dementias.

Contents

Abbreviations: AD, Alzheimer's disease; Aβ, amyloid-beta; ABC, ATP binding cassette; BBB, blood–brain barrier; BP_{ND}, non-displaceable binding potential; CAA, cerebral amyloid angiopathy; CSF, cerebrospinal fluid; CP, choroid plexus; DLB, dementia with Lewy bodies; FTLD, frontotemporal lobar degeneration; GWAS, genome wide association study; HEK263, human embryonic kidney cell line 263; LC-MS, liquid chromatography-coupled mass spectrometry; LLC, Lewis lung carcinoma cells; LRP1, Lipoprotein related receptor protein 1; MDCK, Madin-Darby canine kidney cells; MSA, multiple systems atrophy; NCL, neuronal ceroid neurolipofuscinose; PD, Parkinson's disease; PET, positron emission tomography; PSP, progressive supranuclear palsy; SNP, single nucleotide polymorphism.

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Introduction

Life expectancy rises in most countries as prevalence of aging-associated diseases does. This is not only true for AD and PD, but also for other neurodegenerative disorders (Savica et al., 2013; Vann Jones and O'Brien, 2014; Vardarajan et al., 2014). Common to all is the irreversible degeneration of distinct subsets of neurons and the accumulation of aggregated peptides/proteins within the cell body or in their near vicinity. In AD accumulation of Aβ is thought to be the initial pathogenic trigger leading to progressive neuronal dysfunction of the hippocampal formation, temporal and frontal cortex and later spreading to the occipital cortex (Braak and Braak, 1991; Hardy and Allsop, 1991). Reasons for this region specific, temporal pattern are barely known. In fact, also other proteopathies show distinct temporal patterns of neurodegeneration and peptide accumulation (Braak et al., 2003). In PD, α-synuclein accumulates preferentially in neurons of the substantia nigra. In DLB or MSA the same protein affects very different sets of neurons (Braak et al., 2003). Deposits of Tau-proteins or TDP-43 in FTLD appear in the eponymic regions of the brain but in PSP, tauopathy is restricted to distinct nuclei in the basal ganglia. Symptoms of the different diseases highly correlate with the region specific deposition of the respective proteins.

Familiar AD cases were the foundation of AD research for almost 20 years. Focusing research and funding on hypotheses derived thereof led to the understanding that Aβ accumulations arise from pure overproduction or misled processing by cleavage or processing enzymes (Haass and De Strooper, 1999). However, any treatment approach targeting these processes, e.g. γ-secretase for AD treatment, has proven insufficient and has not found its way into the clinics (Doody et al., 2013).

However, especially for AD but as well for PD, MSA, DLB, and PSP, it becomes increasingly clear that the pathologic aggregation of proteins and peptides is due to disturbed clearance mechanisms of the brain's barriers. In this review, we summarize the current knowledge about the contribution of ABC transporters to the clearance of peptides/proteins over the blood–brain barrier, possible roles of the choroid plexus and the potential use of ABC transporters for treatment and diagnostics of various proteopathies of the brain.

ATP-binding cassette transporters are known since the introduction of p-glycoprotein (ABCB1) by Juliano and Ling (1976). By now, the ABC transporter superfamily comprises 49 human proteins divided into 7 subfamilies that have been designated ABCA to ABCG. They are expressed in every cell type of the brain and mediate the transport of a wide variety of substances. Detailing each family would be beyond the scope of this review, however, there have been comprehensive reviews about the function of ABC transporters as well as their expression within the central nervous system and the BBB (Hartz and Bauer, 2011; Kim et al., 2008; Linton, 2007; Löscher and Potschka, 2005; Pahnke et al., 2008; Schinkel and Jonker, 2003). We have recently started to systematically analyze ABC transporter expression throughout the human brain because this has not been done before. The expression pattern of these transporters differs drastically between different functional areas of the brain, which is not only true for endothelial cells of the BBB but as well for neurons and glia (unpublished data). Currently, the role of ABC transporters in neurodegenerative diseases is mainly attributed to their function or dysfunction at the BBB, which is also the focus of this review. However, it seems to be possible that differential transporter expression also plays a role in the susceptibility of specific brain regions for distinct neurodegenerative diseases. The BBB is a sophisticated system, made up of endothelial cells, pericytes, and neuronal and astrocytic endfeet. This system highly regulates the import and export of nutrients, metabolites and immune cells as well as of xenobiotics. Development and function of the BBB has been nicely reviewed recently (Obermeier et al., 2013)

ABC transporters and Aβ — 13 years of research

The first report that Aβ interacts with an ABC transporter was published by Lam et al. (2001). They used HEK263 cells, ABCB1-enriched membrane preparations and inside-out vesicles to clearly show that Aβ binds to ABCB1 and is actively transported. One year later, we found first implications for this association in human brains (Vogelgesang et al., 2002). In non-demented elderly amyloid plaques are increasingly recognized near blood vessels without ABCB1 expression but much less next to vessels expressing abundant ABCB1 proteins. In the same year, first evidences pointed to an involvement of ABCA1 in Aβ extrusion from neuronal cells (Fukumoto et al., 2002) which has been reviewed in detail by (Gosselet et al. (2013)(also include review by I. Lefterov in this special issue). In 2004, we presented first evidence for the impact of ABCB1 on CAA (Vogelgesang et al., 2004). CAA first develops in arterioles and spreads to smaller vessels and capillaries only during later stages. When only arterioles were affected ABCB1 expression was high in unaffected capillaries, but as CAA spread to smaller vessels ABCB1 was lost here as well. The age-dependent decline of ABCB1 expression completed the pathologic link between ABCB1 and AD in humans. One year later, Cirrito et al. (2005) published the first mouse study showing impaired Aβ clearance in ABCB1 knockout mice, and also in control mice after treatment with ABCB1 inhibitors. Following these studies a lot more attention was drawn toward the role of ABCB1 in AD. In the following years different *in vivo* approaches confirmed ABCB1 as an important Aβ exporter. Hartz et al. (2010) confirmed the previous findings in mice showing that ABCB1 expression was diminished before plaques were visible and were also able to reduce brain amyloid burden by ABCB1 induction *in vivo*. This has been later again confirmed by Brenn et al. (2011) in a different mouse model and very recently also by Carrano et al. (2014) using material from patients. In 2011, Jeynes et al. analyzed brain tissue of controls and AD patients. ABCB1 positive capillaries were inversely correlated with the presence of neurofibrillary tangles and senile plaques, again confirming our publication from 2004 (Jeynes and Provias, 2011; Vogelgesang et al., 2004). In 2011, our experimental work revealed a strong effect of ABCB1 deficiency in APPPS1 mice and in a mouse model of CAA (Krohn et al., 2011). Interestingly, Qosa et al. (2012) found that rifampicin and caffeine treatment enhanced Aβ clearance via (a possibly combined) action of ABCB1 and/or LRP1. Caffeine intake has been found to reduce cognitive decline in aging men and one study found decreased risk for AD (Maia and de Mendonca, 2002; Ritchie et al., 2007; van Gelder et al., 2007). However, some *in vitro* experiments, designed to investigate ABCB1 functionality in Aβ transport, gave conflicting results. Using MDCK cells transfected with either LRP1 or ABCB1, Nazer et al. (2008) found no effect of ABCB1 on Aβ transport. Kuhnke et al. (2007) showed that ABCB1-transfected LLC cells transported Aβ from the basolateral to the apical compartment. In an immortalized human brain endothelial cell line (hCMEC/D3) ABCB1 inhibition affected only apical to basolateral transport of Aβ (Tai et al., 2009). In bovine brain capillary endothelial cells similar effects were found (Candela et al., 2010; Saint-Pol et al., 2013). Qosa et al. (2014) did mechanistic modeling in murine and human endothelial cells. The inconsistency of *in vitro* and *in vivo* results points to interactions *in vivo* that we do not fully understand, yet. It is conceivable that cell monolayers *in vitro* do not recapitulate certain factors that are apparent *in vivo* but, of course, the differences between epithelial (MDCK) cells, carcinoma cells and endothelial cells must be also taken into account. However, it is unclear how Aβ, produced in the brain (i.e. at the basolateral side of endothelial cells), gets in contact with ABCB1 at the apical side of the blood–brain barrier. Here, LRP1, RAGE, and PrP may contribute to the export system (Pflanzner et al., 2011, 2012).

ABCA1 and ABCB1 are not the only ABC transporters found to be associated with Aβ transport. In 2009, Xiong et al. presented data showing that ABCG2 is up-regulated in AD patients with CAA. Furthermore,

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peripherally injected Aβ40 accumulated stronger in ABCG2-deficient mice brains than in wild-type animals, suggesting that ABCG2 acts as a gatekeeper that prevents Aβ40 from entering the brain. Shen et al. (2010) used cell culture experiments to show that ABCG2 prevents cells from reactive oxygen stress via modulation of the NF-κβ pathway. Other studies found a contribution of ABCG2 to Aβ transport *in vitro* using different cell lines (Candela et al., 2010; Do et al., 2012; Tai et al., 2009). Do et al. (2012) also proposed ABCG4 to be an Aβ40 transporter. In contrast, Carrano et al. (2014) found a decrease of protein abundance in brain samples of patients with severe capillary CAA and Kania et al. (2011) could not detect any regulation of ABCG2 in hCMEC/D3 cells after Aβ40 treatment. The only study that used APP-expressing mouse models crossed with ABCG2 knockout mice found no difference in amyloid burden when compared to the corresponding ABCG2 wild-type mice (Krohn et al., 2011). Despite these conflicting results *in vitro* and *in vivo* ABCG2 reached "potential candidate" status in a genome wide association study (Kim et al., 2011). Feher et al. (2013) analyzed a Hungarian cohort of nearly 600 patients and found a significant interaction of the ABCG2 missense mutation C421A and the APOE-ε4 allele on AD risk. Thus, additional studies are needed to elucidate the role of ABCG2 in the pathogenesis of AD.

In 2011, two further ABC transporters appeared on the stage of AD. ABCA7 was recognized in a GWAS and it has gained much attention during the past 2 years, because it is the first ABC transporter detected by the large genomics initiatives and rs3752246 is the only coding non-synonymous SNP found in any AD-related GWAS so far (Hollingworth et al., 2011). After its first publication other GWAS and several focused genetic studies confirmed the hit in other cohorts and subpopulations (Cascorbi et al., 2013; Chung et al., 2013; Kamboh et al., 2012; Liu et al., 2013; Reitz et al., 2013). Besides the non-synonymous SNP another one (rs3764650) has been found to influence expression of the ABCA7 gene (Vasquez et al., 2013). The minor allele, which is associated with higher AD risk, shows lower expression levels. However, in AD patients ABCA7 expression was found to be higher than in non-demented people. Thus, ABCA7 seems to be upregulated in a compensatory manner, a mechanism that might be attenuated by the minor allele (Vasquez et al., 2013). Karch et al. (2012) found the minor allele as well to be associated with the age of onset and disease duration, but in contrast no influence on ABCA7 expression levels. Holton et al. (2013) found ABCA7 to be expressed only weakly throughout different analyzed brain regions with no differential expression patterns, regardless of the occurring SNP. Although ABCA7 is highly homologous to ABCA1, its functions are still under discussion. Therefore, it is hard to predict functional aspects of the non-synonymous amino acid change. Phospholipid and cholesterol export to lipoproteins was indicated to depend on ABCA7 function *in vitro* (Abe-Dohmae et al., 2004; Kaminski et al., 2000). In contrast, *in vivo* data point to another major function of ABCA7. Macrophages from ABCA7-deficient mice do not differ in cholesterol and phospholipid efflux from wild-type animals, although females had significantly less cholesterol in the serum and in high-density-lipoprotein vesicles (Kim et al., 2005). Interestingly, specific plasma phospholipid levels are currently being discussed as early marker for AD (Mapstone et al., 2014).

Phagocytic activity of peritoneal macrophages from ABCA7 knockout mice is decreased as compared to wild-type mice, and induction of phagocytosis by ApoA lipoproteins is dependent on ABCA7 *in vivo* and in J774 macrophages (Tanaka et al., 2010). A year later, the same laboratory demonstrated that statins induce phagocytosis in an ABCA7-dependent manner (Tanaka et al., 2011). Additionally, ABCA7 was found to be involved in response to typhoid fever in children (Khoo et al., 2011). These data indicate a role of ABCA7 in the host response system in conjunction with cholesterol homeostasis. Since ABCA7 was found to play a role in T-cell proliferation (Meurs et al., 2012) its effects for AD could also be attributed to its functions in the immune system. Here, a closer look on microglial function should add some pieces to the puzzle. Kim et al. (2013) evaluated the effect of ABCA7 on Aβ pathology using ABCA7 knockout mice that were crossed to the J20 AD model. They found a robust increase of insoluble Aβ and plaque load in the brains of ABCA7-deficient mice, but were unable to fully elucidate the mechanism behind this observation. Using bone marrow derived macrophages they showed a decreased ability of ABCA7 knockout cells to phagocytose oligomeric Aβ, pointing toward a possible mechanism of action. However, microglial phagocytosis was not determined and tested animals were only males. It will be interesting to assess effects also in females in future studies because of the reported gender differences in ABCA7 knockout mice (Kim et al., 2005). Since ABCA7 has been shown to be expressed in bovine BBB cells it cannot be excluded that it is involved in Aβ transport processes at the BBB (Gosselet et al., 2009).

The latest, so far most effective, ABC transporter that was found to influence Aβ brain burden is ABCC1. An up to 14-fold increase of Aβ42 in ABCC1 knock-out mice is the so far greatest impact of an ABC transporter in AD mouse models. Moreover, we were able to reduce amyloid burden by up to 80% in APPPS1 mice via functional activation of ABCC1 (Krohn et al., 2011). Very recently, we exploited this mechanism for treatment by using special extracts of St. John's wort to alleviate the consequences of Aβ accumulation in APPPS1 mice (Hofrichter et al., 2013). ABCC1 is expressed in capillary endothelia of the blood–brain barrier, in neural stem and progenitor cells (Schumacher et al., 2012) and distinct subsets of neurons with diverse pattern in different diseases (yet unpublished data). Its function is regulated by mitochondria and influenced by mitochondrial polymorphisms (Scheffler et al., 2012). However, it is also different to the other transporters reviewed here, because one important site of high expression in the brain is the choroid plexus.

Alzheimer's disease and the glymphatic system

The choroid plexus is a structure that has been nearly ignored with regard to AD but regained interest of researchers during the past few years. Its function and implications for brain disorders have recently been reviewed (Damkier et al., 2013; Lehtinen et al., 2013; Papadopoulos and Verkman, 2013). However already in the 1990s, Roy Weller and colleagues defined perivascular drainage pathways in the brain, and speculated about its influence on Aβ clearance from the brain (Pollock et al., 1997; Weller et al., 1992; Zhang et al., 1990). Since the choroid plexus, as a producer of cerebrospinal fluid, is one of the driving forces behind the drainage pathways of the brain, its function, dysfunction and signaling to and from the brain needs to be subject of future research. The second driving force of this fluid drainage is the pulsation of brain arteries (Iliff et al., 2013b; Schley et al., 2006). Both effects together generate a flow of cerebrospinal fluid and interstitial fluid throughout the brain that is a crucial part of Aβ clearance (Iliff et al., 2012). CSF enters the brain via arterial pathways along perivascular spaces to be eventually cleared from the brain along the large veins. This system is now being called the glymphatic system (Iliff et al., 2012). The probably largest part of this glymphatic system is made up by the capillaries of the brain. As the perivascular flow drains along the capillary beds, peptides and proteins are actively exchanged by their specific transport processes. Recent research shows that CSF is not only produced by the CP but also at the blood–brain barrier (for a review see (Chikly and Quaghebeur, 2013)). As reorganization of the capillary basement membranes with age preferentially occurs in brain regions prone to CAA (Hawkes et al., 2013) we hypothesize that not only a hindrance of peptide clearance occurs at these sites. Thickening of the basement membrane of capillaries might be analogues to the same process in the choroid plexus which goes along with a reduced secretory function (reviewed in Serot et al. (2003)). Consequently, the brain wide exchange of interstitial fluid and CSF slows down, peptide concentrations have more time to rise and aggregation prone peptides start to build large clusters that, at a certain point,

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are sticky and no longer transportable. Supporting findings for this hypothesis were published by Meyer et al. in 2008 who found Aβ 'crystals' associated with capillaries already in pre-depositing, 3-month-old APP23 mice (Meyer et al., 2008). These seeds disturb the perivascular flow by destroying capillaries (leading to CAA in higher vessels) and give rise to Aβ plaques. Stiffening of arterial vasculature due to metabolic syndrome, hypertension, hyperlipidemia, diabetes or aging must be taken into account as well since it decelerates the glymphatic flow (Iliff et al., 2013b).

It has been discussed earlier that if age-dependent impaired active (transport) and passive (glymphatic) Aβ clearance are not counteracted beforehand, immunization of AD patients will not be successful (Pahnke et al., 2009; Weller et al., 2009). Without a route out of the brain, re-solubilized Aβ from senile plaques only worsens the situation as seen by an increase in CAA and microhemorrhages in immunized patients (Boche et al., 2008; Holmes et al., 2008). Approaches to restore or improve active and passive Aβ clearance will have double benefit (Pahnke et al., 2009). On one hand, accumulation of Aβ peptides and thus progression of AD could be attenuated or even stopped and on the other hand immunization could clear existing deposits to support overall regeneration.

ABC transporter function in other proteopathies of the brain

ABC transporters are also implicated to play a role in other neurodegenerative disorders. ABCB1 function is discussed to influence the risk for PD. SNP analyses show an association of PD risk with different SNPs in ABCB1 (Tan et al., 2005; Westerlund et al., 2009) or an increased susceptibility after exposure to pesticides in people carrying the ABCB1 3435C/T SNP (Zschiedrich et al., 2009). However, there are cohorts in which no association between different haplotypes and PD risk was found (Funke et al., 2009; Kiyohara et al., 2013). Since these cohorts were always far smaller than those currently used for genome-wide AD studies, a concerted analyses approach might give clearer results. Nonetheless, Bartels et al. (2008) found some evidence for a possible reduction of ABCB1 function at the BBB of patients diagnosed with advanced PD, using positron emission tomography with the radiolabeled ABCB1 substrate [^{11}C]verapamil. Most interestingly, in the same work they reported reduced ABCB1 function in patients with PSP and MSA as well. This highlights the ubiquitous and important role of ABC transporters in blood–brain barrier clearance for different neurodegenerative diseases.

Recently, ABC transporters came into view of another neurodegenerative entity. Although not strictly age-related, neuronal ceroid lipofuscinoses comprise a group of progressive neurodegenerative disorders in childhood and adults characterized by cognitive and motor decline, seizures, blindness, early death, and accumulation of lipofuscin in various cell types. NCLs belong to the lysosomal storage diseases and are characterized by lysosomal dysfunction leading to intralysosomal storage of autofluorescent material. Several ABC transporters are expressed in lysosomes. Among them are ABCA2 (Zhou et al., 2001), ABCB1, ABCC1 and ABCG2 (Rajagopal and Simon, 2003), and deficiency in ABCA5 leads to NCL-like pathology in mice (Kubo et al., 2005). Recently, ABCB1 was described to be abrogated in type 3 NCL endothelia (Tecedor et al., 2013). Interestingly, type 11 (NCL11, juvenile) represents a direct link to FTLDs both having mutations in the same progranulin gene but different disease onset. However, the underlying modifier for early (NCL) or late (FTLD) clinical representation is currently in debate (Gotzl et al., 2014). Since no causal therapy is yet available for NCLs, ABC transporters might serve as promising modifier treatment targets in future.

ABC transporters — an outlook

The search for causative treatments of AD held a lot of draw-backs during the past two decades. Considering the knowledge that we gained in the past 13 years, it is time to shift therapeutic approaches toward reconstitution and/or enhancement of clearance mechanism. Although ABC transporter research was mainly driven by the role of ABC transporters in multidrug resistance of tumors and attempts to inhibit these transporters to render chemotherapy more effective (Szakacs et al., 2006), the ways for induction of ABC transporter function are numerous. It was shown that ABCB1 expression is induced by endothelial cell-specific TGF-β1 receptor (ALK1) (Baello et al., 2014). An ALK1 specific agonist, BMP-9, was able to increase ABCB1 activity by up to 60% for at least 24 hours in cell culture experiments (Baello et al., 2014). Since the structure of the active BMP-9 dimer has been resolved (Brown et al., 2005), a specifically designed peptide or small molecule drug could be developed for *in vivo* ABCB1 induction. Furthermore, NMDA receptor agonists can induce ABCB1 expression at the BBB via a COX-2 dependent mechanism (Bauer et al., 2008). Recently, Paganetti et al. (2014) reported that induction of muscarinic acetylcholine receptors at the BBB has beneficial effects in three different mouse models of AD. Treatment with pirenzepine, a selective M1 receptor antagonist, leads especially to a marked reduction of vessel associated Aβ deposits. qPCR analyses of brain capillaries proved the induction of LRP1, ABCB1, GLUT1 and claudin 5 along with a decreased expression of RAGE. Of note, pirenzepine does not cross the blood–brain barrier thus avoiding central side effects. Well-known inducers of ABC transporters are, of course, chemotherapeutics like bexarotene and Paclitaxel, and antiviral drugs like efavirenz, but these will elicit substantial side effects in AD therapy. However, the most recent bexarotene study did not analyze these effectors (Cramer et al., 2012).

Many plant-derived substances bear the potential to induce ABC transporter function. The most prominent example is St. John's wort, *Hypericum perforatum*, with its main active substance hyperforin. Hyperforin is known to induce ABCB1 expression in humans through binding to the pregnane X receptor (PXR) (Hartz et al., 2010; Lemmen et al., 2013). Most interestingly, hyperforin is not the only ABC transporter activating substance in St. John's wort. Using a specific extraction method, we were able to directly induce ABCC1 activity in a hyperforin-independent manner (Hofrichter et al., 2013). In line with this, a clinical Phase IIa trial for AD/MCI treatment using thiethylperazine as another ABCC1 inducer will be launched in near future (Krohn et al., 2011).

Sporadic AD tends to be maternally inherited (Mosconi et al., 2010). Besides the X chromosome, the most prominent and exclusively maternal genetic material belongs to the mitochondria. Already single mitochondrial SNPs are able to influence Aβ deposition drastically in mouse models (Scheffler et al., 2012) and energy efficiency of mitochondria declines as ROS productions increases with age and especially during AD (Gruber et al., 2013). In Chinese traditional medicine so called Yang and Yin tonifying herbs are known to possess the potential to prolong a healthy life span. Mechanisms of action of such herbs have been studied and revealed that Yang herbs increase ATP generation and Yin herbs exert immunomodulatory functions, besides the antioxidant capacities of both groups (Ko and Leung, 2007). Since ABC transporter function crucially depends on ATP supply, investigations of these herbs as mitochondria protecting/supporting drugs would be of benefit for the clearance and energy homeostasis of aging and diseased brains.

To measure the functionality of the above mechanisms new methods need to be developed. This is important for two reasons: (i) as a possibility for (early) diagnostics and (ii) to evaluate treatment effects. The main issue current clinical trials face is the lack of diagnostics to forecast if a person of interest will develop AD in the next 5 or even 10 years. The GWAS hits do not allow such a prediction of AD, not even together with ApoE status (Hennings-Yeomans and Cooper, 2012; Verhaaren et al., 2013). Since our current knowledge of a person's genetic background implicates that factors other than genes play a critical role in the pathogenesis of AD, we need to develop functional assays. Assessment of the functional state of a process known to be crucial for the pathogenesis of AD would intrinsically detect genetic and environmental factors. As we now know that Aβ clearance is such a crucial process, we

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need to establish it as a measureable value. One way could be enhanced contrast or conventional MRI approaches like the proof-of-concept studies by Iliff et al. (2013a) in rats, and by Tsutsumi et al. (2011) in humans. Another approach would be the measurement of ABC transporter function with non-invasive nuclear imaging methods, such as PET. PET with radiolabeled substrates of ABCB1, such as (R)-[^{11}C]verapamil or [11C]N-desmethyl-loperamide, has proven to be useful to measure the functional activity of ABCB1 at the blood–brain barrier in the healthy and diseased brain (Kannan et al., 2009; Mairinger et al., 2011). Using PET, cortical brain uptake of (*R*)-[^{11}C]verapamil (reported as BP_{ND}) was found to be 23% higher in AD patients as compared with age-matched healthy controls (van Assema et al., 2012a). This finding was interpreted as a decrease in ABCB1 function at the blood–brain barrier of AD patients, although it remains unclear why no differences in the influx rate constant K1 of (*R*)-[^{11}C]verapamil from plasma into brain, a parameter which was shown in previous studies to reflect ABCB1 function at the blood–brain barrier (Bauer et al., 2012; Muzi et al., 2009), was found. In another study, van Assema et al. (2012b) explored the effect of the C1236T, G2677T and C3435T SNPs in the ABCB1 gene on (*R*)-[^{11}C]verapamil brain distribution in AD patients. Although not showing up in a GWAS, carriers of at least one T allele had at least 24% higher global brain (*R*)-[^{11}C]verapamil BPND values compared to non-carriers. Interestingly, this effect was found in persons diagnosed with AD only. In healthy persons (MMSE > 26) no differences in (*R*)-[^{11}C]verapamil BP_{ND} values between carriers of a T allele and non-carriers were found (van Assema et al., 2012b). Thus, SNPs in ABCB1 might sensitize protein function or regulation of expression to AD-related changes at the blood–brain barrier. These preliminary findings need to be confirmed in larger patient cohorts. In contrast to ABCB1, the functional PET-based measurement of other ABC transporters implicated in AD is still in its infancy. Okamura et al. (2009) have developed 6-bromo-7-[^{11}C]methylpurine as the first PET tracer for visualization of ABCC1 activity at the murine blood–brain barrier based on the metabolite extrusion method. This PET probe enters the brain by passive diffusion. Inside the brain, it is converted by glutathione transferases into the corresponding glutathione conjugate, which is actively extruded from brain by ABCC1, thereby enabling the measurement of ABCC1 function from the efflux rate of activity from brain. However, it is not certain if this innovative approach to measure ABCC1 function can be translated to human subjects, as no clinical application of this PET tracer has been reported yet. Very recently, a fluorine-18-labeled version of this ABCC1 probe has been reported by another research group (Galante et al., 2014). Of course, the most accurate approach for estimating the risk for developing AD would be the direct measurement of Aβ clearance from the AD brain. However, measuring Aβ clearance from brain with PET and radiolabeled Aβ is complicated by the fact that such radiotracers will not be able to cross the blood–brain barrier when administered systemically. The brilliant approach introduced by Bateman et al. (2006) using radio-labeled Aβ would be another method to determine Aβ homeostasis in the brain of patients, but is currently not suitable for daily clinical settings. Patients would need to be hospitalized for about 48 hours, two intravenous and a subarachnoid catheter need to be in place for 36 hours. Furthermore, Aβ-immunoprecipitation and LC-MS need to be performed.

Non-invasive molecular imaging methods such as PET possess a great potential to directly study the functional activity of ABC transporters in the brains of patients with neurodegenerative disorders. PET imaging may help to clarify the role of ABC transporters in the pathophysiology of these diseases and may also qualify as a tool for early diagnosis in a region-specific pattern. Moreover, PET imaging of ABC transporter function may be indispensable in the development of new therapeutic approaches, which induce ABC transporter activity at the blood–brain barrier to promote Aβ clearance from brain. However, the use of PET to measure ABC transporter function relies on the availability of suitable and selective PET radiotracers. It is hoped that future efforts in radiotracer development will provide new and improved ABC transporter-specific radiotracers to fully exploit the potential of this powerful imaging method.

In conclusion, ABC transporters have been proven to be involved in the process of the excretion of toxic peptide species and location-specific impairment of these export mechanisms may lead to proteopathies of the brain including AD, PD, HD, and other. Exploiting molecular and imaging techniques with regard to ABC transporters will result in the discovery of new diagnostic options and activation of these transporters in new preventive and/or therapeutic treatment options.

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