The A-subclass of ATP-binding cassette (ABC) transporters comprises 12 structurally related members of the evolutionarily highly conserved superfamily of ABC transporters. ABCA transporters represent a subgroup of “full-size” multispan transporters of which several members have been shown to mediate the transport of a variety of physiologic lipid compounds across membrane barriers. The importance of ABCA transporters in human disease is documented by the observations that so far four members of this protein family (ABCA1, ABCA3, ABCA4, ABCA12) have been causatively linked to monogenetic disorders including familial high-density lipoprotein deficiency, neonatal surfactant deficiency, degenerative retinopathies, and congenital keratinization disorders. Recent research also point to a significant contribution of several A-subfamily ABC transporters to neurodegenerative diseases, in particular Alzheimer’s disease (AD). This review will give a summary of our current knowledge of the A-subclass of ABC transporters with a special focus on brain lipid homeostasis and their involvement in AD.

Keywords: ATP-binding cassette transporter, Alzheimer’s disease

ABC TRANSPORTERS

The superfamily of ATP-binding cassette (ABC) transporters constitutes a large group of highly conserved, multispan transmembrane transport proteins which can be found in all organisms from bacteria to man (Higgins, 1992; Holland et al., 2002). In most species, ABC transporters are abundantly represented (Linton and Higgins, 1998). In the human genome, 48 functional, protein-coding ABC transporter genes (Dean, 2005), and several ABC pseudogenes (Piehler et al., 2006, 2008) have been identified. All ABC proteins share a common global configuration and are composed of four specific core domains; two highly conserved ABCs and two transmembrane domains (TMDs; Figure 1; Higgins et al., 1986; Linton and Higgins, 1998). These four domains can be encoded in a single polypeptide chain, which is then called a “full-size” transporter (Figure 1). Alternatively, two homo- or heterodimers (“half-size” transporters), each containing one ABC and one TMD, attach to form the functional transporter (Dean, 2005). Based on phylogenetic analyses of the ABCs, human ABC transporters are divided into seven subfamilies, denoted ABC A–G (Dean, 2002). ABC transporters are primary active transporters using the energy from ATP-binding and -hydrolysis to translocate a wide variety of substrates including lipids, ions, sugars, peptides, amino acids, carbohydrates, vitamins, steroid hormones (Higgins, 1992; Holland et al., 2002), and xenobiotics, such as anticancer drugs (Gottesman et al., 2002). On a subcellular level, ABC transporters are located in eukaryotes in the plasma membrane and in the lipid membranes of the Golgi apparatus, endosomes, multivesicular bodies, endoplasmic reticulum, peroxisomes, and mitochondria (Kaminski et al., 2006). The function of ABC transporters in a broad range of physiological systems is also reflected by the fact that mutations in several ABC proteins result in monogenetic disorders affecting diverse physiological systems (Wenzel et al., 2007).

Outstanding experts in the field have recently contributed with reviews of single members or subsets of ABC transporters covering diverse aspects of ABC transporters and their role in health and disease, including brain lipid metabolism and Alzheimer’s disease (AD; Kim et al., 2008; Mack et al., 2008; Hirsch-Reinshagen et al., 2009; Koldamova et al., 2010). In the present review, we focus on the A-subfamily of ABC transporters and their role in brain lipid transport and neurodegeneration.

THE A-SUBCLASS OF ABC TRANSPORTERS

In 1994, in an effort to clone members of the ABC transporter superfamily, Luciani et al. (1994) identified two novel ABC transporter genes, named ABC1 (ABCA1) and ABC2 (ABCA2), in close proximity to each other on chromosome 9. Due to their structural features that clearly set them apart from other ABC transporters, Luciani et al. suggested that these transporters define a novel subgroup of ABC transporters, the A-subfamily of ABC transporters. Altogether, the human ABCA subfamily comprises 12 protein-coding genes, ABCA1–ABCA13, with “ABCA11” representing a transcribed pseudogene (Kaminski et al., 2006; Piehler et al., 2008). All ABCA proteins are full-size transporters (Tusnady et al., 2006).

At least three characteristics define the members of the A-subfamily of ABC transporters: (i) the A-subfamily contains the largest members of the ABC transporter superfamily. According to their predicted primary structure, ABCA transporters...
ABCA8, ABCA9, and ABCA10 and represent subgroup I (Piehler et al., 2002; Prades et al., 2002; Kaminski et al., 2006). The remaining seven ABCA transporters (ABCA1, ABCA2, ABCA7; Kaminski et al., 2006) are polypeptides ranging from 1543 aa (ABCA10) to 5058 aa (ABCA13) in size with a calculated molecular weight between 176 and 576 kDa (Kaminski et al., 2006). (ii) The extracellular domain between the first and second membrane spanning helix of each predicted TMD is particularly large in this subfamily (Kaminski et al., 2006). (iii) A highly hydrophobic domain in ABCA transporters interrupts the cytosolic linker that connects the two halves of an ABC transporter (Bungert et al., 2001; Vulevic et al., 2001; Peelman et al., 2003; Albrecht and Viturro, 2007). Most ABCA transporters show a broad tissue-specificity, including expression in brain (Kaminski et al., 2006), beside ABCA4, which is mainly expressed in the eye (Allikmets et al., 1997), and ABCA13 with detectable expression in only a small variety of tissues (Prades et al., 2002; Table 1).

Table 1 lists some of the biological properties of the members of the ABCA subfamily.

Phylogenetic analyses suggest that all ABCA subfamily transporters have evolved from a common ancestor gene (Kaminski et al., 2006) and can be further divided into two subgroups. The so-called “ABCA6-like” transporters comprise ABCA5, ABCA6, ABCA8, ABCA9, and ABCA10 and represent subgroup I (Piehler et al., 2002). These transporters form a compact gene cluster on chromosome 17q24 and are characterized by a strikingly high, mutually amino acid sequence identity and a significantly smaller size (between 1543 aa and 1642 aa) compared to the other ABCA proteins (Arnould et al., 2001; Piehler et al., 2002; Kaminski et al., 2006). The remaining seven ABCA transporters (ABCA1, ABCA2, ABCA3, ABCA4, ABCA7, ABCA12, and ABCA13) are included in subgroup II of the ABCA transporter subfamily and dispersed on six chromosomes (Dean, 2002).

The A-subfamily of ABC transporters has gained special focus over the last years as mutations in four members were identified as the underlying causes of monogenic diseases in humans, including mutations in ABCA1 [high-density lipoprotein (HDL)-deficiency/Tangier disease (TD)], ABCA3 (neonatal surfactant deficiency), ABCA4 (several forms of autosomal recessive macular dystrophies), and ABCA12 (two forms of hereditary keratinization disorders; Kaminski et al., 2006). The phenotypes of these loss-of-function mutations have resulted in valuable information about the physiological function of ABCA transporters and identified them as lipid transporters. Over the last years, evidence has accumulated that members of the A-subfamily of ABC transporters are also involved in more complex diseases like atherosclerosis (ABCA1), pediatric interstitial lung diseases (ABCA3), age-related macular degeneration (ABCA4), and AD (ABCA1, ABCA2, ABCA7; Kaminski et al., 2006).

**A-SUBFAMILY ABC TRANSPORTERS IN BRAIN LIPID HOMEOSTASIS AND NEURODEGENERATION**

**ABCA1**

**Molecular properties of ABCA1**

ABCA1 is the prototypic member of the A-subfamily of ABC transporters. It has been extensively studied since its identification in 1994. In particular, the discovery in 1999 that mutations in this ABCA subfamily transporter compromise cellular cholesterol export has attracted a lot of interest from researchers worldwide. The role of ABCA1 in cholesterol transport, HDL particle formation and atherosclerosis has been reviewed previously (Kaminski et al., 2006; Wenzel et al., 2007; Kang et al., 2010; Nagao et al., 2011b), and detailed reports on the implication of ABCA1 in AD and neurodegeneration have been published recently (Kim et al., 2008; Hirsch-Reinhagen et al., 2009; Koldanova et al., 2010).

The gene encoding ABCA1 is located on chromosome 9q31.1 and comprises 50 exons which span 147 kb DNA. The 254 kDa protein of ABCA1 consists of 2261 amino acids and displays the typical structure of a full-size ABC transporter with two ATP-bindings cassettes and two TMDs. ABCA1 shows a broad expression pattern with highest expression levels in smooth muscle, whole blood, placenta, liver, lung, adrenal glands, fetal organs, and brain (Langmann et al., 1999). The identification of mutations in ABCA1 causing HDL-deficiency syndromes, including TD, confirmed the role of ABCA1 as a key regulator in cellular HDL metabolism (Bodzioch et al., 1999; Brooks-Wilson et al., 1999; Lawn et al., 1999; Rust et al., 1999). To date, more than 80 mutations within the ABCA1 gene have been described (for an overview see The Human Gene Mutation Database at http://www.hgmd.org). In TD patients, cholesterol accumulates in peripheral tissues like tonsils, spleen, liver, and the artery wall leading to premature atherosclerosis and hepatosplenomegaly. This accumulation is due to an impaired efflux of cellular cholesterol to its extracellular acceptor.
Table 1 | Biological characteristics of A-subfamily ABC transporters.

| Gene symbol | Genomic localization (Gene size) | Protein size and weight | Major site of expression* | Expression in brain tissue* | Functionally involved in | Association with AD |
|-------------|---------------------------------|-------------------------|---------------------------|-----------------------------|--------------------------|---------------------|
| ABCA1       | 9q31.1 (147 kb)                 | 2261 aa 254 kDa         | Diverse (smooth muscle, blood cells, placenta, liver, lung, adrenal glands, fetal organs and brain; Langmann et al., 2003) | +                          | Phospholipid and cholesterol transport | Inhibition of Aβ production and amyloid formation |
| ABCA2       | 9q34.3 (21 kb)                  | 2436 aa 270 kDa         | Brain (Zhao et al., 2000; Kim et al., 2008) | +++                        | Cellular cholesterol and myelin lipid transport | Induction of Aβ production |
| ABCA3       | 16p13.3 (65 kb)                 | 1704 aa 191 kDa         | Lung (Yamano et al., 2001) | ++                         | Phosphatidylcholine and -glycerol trafficking, surfactant production | Unknown |
| ABCA4       | 1p22.1 (128 kb)                 | 2273 aa 256 kDa         | Retina (Allikmets et al., 1997) | (++)                       | N-retinylidene-phosphatidy-ethanolamine transport in rod cells | Unknown |
| ABCA5       | 17q24.3 (83 kb)                 | 1642 aa 187 kDa         | Diverse (Skeletal muscle, kidney, liver, placenta); (Petry et al., 2003) | +                          | Unknown | Unknown |
| ABCA6       | 17q24.2-3 (83 kb)               | 1617 aa 184 kDa         | Diverse (Liver, lung, heart, and brain; Kaminiski et al., 2001b) | ++                         | Unknown | Unknown |
| ABCA7       | 19p13.3 (25 kb)                 | 2146 aa 235 kDa         | Blood (precursor) cells (Kaminski et al., 2000; Tanaka et al., 2011b) | +                          | Phospholipid transport, phagocytosis | Inhibition of Aβ-production |
| ABCA8       | 17q24.2 (88 kb)                 | 1581 aa 179 kDa         | Diverse (Heart, skeletal muscle, liver; Tsuruoka et al., 2002) | ++                         | Unknown | Unknown |
| ABCA9       | 17q24.2 (86 kb)                 | 1624 aa 184 kDa         | Diverse (Heart, brain, and fetal tissues; Piehler et al., 2002) | ++                         | Unknown | Unknown |
| ABCA10      | 17q24.3 (97 kb)                 | 1543 aa 176 kDa         | Diverse (Heart, brain, and gastrointestinal tract; Wenzel et al., 2003) | ++                         | Unknown | Unknown |
| ABCA12      | 2q35 (207 kb)                  | 2595 aa 293 kDa         | Diverse (Keratinocytes, stomach; Annino et al., 2002) | +                          | Unknown | Unknown |
| ABCA13      | 7p12.3 (476 kb)                 | 5058 aa 576 kDa         | Diverse (Trachea, testis, bone marrow, submaxillary gland, epididymus, ovary, and thymus; Prades et al., 2002; Barros et al., 2003) | (++)                       | Unknown | Unknown |

*According to the Genome Reference Consortium built 37 (hg19, February 2009).

Expression information retrieved from GNF Expression Atlas 2 Data (http://biogps.org) and the cited studies.

aa, amino acids; AD, Alzheimer’s disease.

apolipoprotein A-I (apoA-I), the main apolipoprotein in HDL particles, by ABCA1 leading to a lack of HDL in the patient’s plasma (Bodzioch et al., 1999; Brooks-Wilson et al., 1999; Lawn et al., 1999; Rust et al., 1999). Further studies documented that both hepatic and intestinal ABCA1 contributes to HDL metabolism and that the liver is the predominant source of plasma HDL (Orso et al., 2000; Basso et al., 2003; Wellington et al., 2003; Timmins et al., 2005; Brunham et al., 2006).

Despite extensive efforts, the molecular mechanisms by which ABCA1 modulates the cellular cholesterol efflux and HDL biogenesis are still unclear. A current model suggests that the initial step is binding of small amounts of apoA-I, the main protein component of HDL particles, to the large, first extracellular domain of ABCA1 that leads to stabilization and activation of the transporter. Activation of ABCA1 triggers increased translocation of phospholipids from the cytosolic to the exofacial leaflet of the plasma membrane which subsequently bends and reveals high affinity binding sites for apoA-I in so-called exovesiculated lipid domains. Membrane bound apoA-I then passively accepts membrane phospholipids and cholesterol to form discoidal HDL particles (Vedhachalam et al., 2007a,b, 2010; Kang et al., 2010; Nagao et al., 2011a,b). An alternative model postulates that apoA-I is internalized after binding to ABCA1 and the resulting apoA-I/ABCA1 complex is then targeted to late endosomes where apoA-I binds lipids. These apolipoprotein–lipid complexes are subsequently released to the extracellular space by exocytosis (Oram, 2008; Yvan-Charvet et al.,...
Evidence has accumulated to suggest that both mechanisms of ABCA1-dependent apoA-I loading with lipids exist. However, there is still an ongoing controversy as to which one is the dominant mechanism in HDL biogenesis.

**ABCA1 in the CNS and Alzheimer's disease**

The expression of ABCA1 in the brain was already noted by Luciani et al. (1994) describing the identification and cloning of ABCA1 from embryonic mouse brain RNA. Subsequent studies reported highest expression of ABCA1 in the brain regions of the olfactory bulb, hippocampus, cerebellar cortex, choroid plexus, and in germinatal regions of embryonic and early postnatal brains (Fukumoto et al., 2002; Tachikawa et al., 2005). Experiments on isolated brain cells showed expression of ABCA1 in neurons, astrocytes, microglia, and oligodendrocytes, with highest expression levels in neurons and microglia (Koldamova et al., 2003; Kim et al., 2006). ABCA1 expression in brain capillary endothelial cells has also been reported (Pansenboeck et al., 2002; Ohtsuki et al., 2004).

Several observations led to the investigation of a potential link between ABCA1 and apoE: (i) ABCA1 is a major regulator of HDL biogenesis outside the CNS by facilitating cholesterol and phospholipid loading onto apoA-I (Kaminski et al., 2006). (ii) ApoE is the most abundant apolipoprotein in the CNS and present in HDL-like particles in the cerebrospinal fluid (Hayashi, 2011). (iii) The major apoE isoforms (apoE2, apoE3, and apoE4) are highly associated with disposition to and onset of AD (Hirsch-Reinshagen et al., 2009). (iv) Membrane cholesterol is known to regulate processing of amyloid precursor protein (APP) and generation of beta-amyloid (Aβ)-fibrils (Simons et al., 1998; Puglielli et al., 2003). Initial clues for an interdependency between apoE and ABCA1 came from experiments showing that Abca1 expression induced by liver X receptor (LXR) and retinoid X receptor (RXR) agonists increases efflux of cholesterol to lipid-free apoA-I and apoE3 in isolated mouse neurons, astrocytes, and microglia (Koldamova et al., 2003). Despite the fact that apoE is mainly secreted from astrocytes (Hayashi, 2011), further studies identified ABCA1-dependent loading of apoE with cholesterol as a mechanism by which cholesterol is targeted to neurons (Kim et al., 2007). Importantly, ABCA1 also appears to enhance the reverse process, the removal of cholesterol from neurons. Studies in Abca1−/− mice finally documented the central role of ABCA1 in apoE lipiddation and that intact ABCA1 is required for normal CNS apoE concentrations (Hirsch-Reinshagen et al., 2004; Wahrle et al., 2004). These studies demonstrated that Abca1−/− mice had significantly reduced (about 80% reduction) apoE levels in the brain, CSF, and plasma. In addition, they revealed that the observed apoE reduction is specific as levels of apoI, another major apolipoprotein in the brain, were unchanged (Hirsch-Reinshagen et al., 2004; Wahrle et al., 2004). Moreover, endogenous apoE particles secreted from ABCA1-deficient glia showed poor lipiddation (Hirsch-Reinshagen et al., 2004; Wahrle et al., 2004). Interestingly, several independent groups were able to demonstrate that these poorly lipiddated apoE particles enhance Aβ deposition in offsprings from Abca1−/− mice crossbred with four different murine models of AD (Hirsch-Reinshagen et al., 2005; Koldamova et al., 2005; Wahrle et al., 2005). Unexpectedly, the Abca1 null mutant offsprings exhibited increased Aβ immunoreactivity and amyloid load demonstrating that the poorly lipiddated apoE particles from ABCA1-deficient glia enhance beta-amyloid deposition. None of these studies, however, found evidence for a significant contribution of Abca1 deficiency to APP processing or Aβ production in vivo strongly suggesting that Abca1 enhances amyloid formation indirectly via facilitation of apoE lipiddation. Conversely, ABCA1 overexpression studies revealed that robust (>6-fold over endogenous expression) but not weak overexpression (about 50%) of ABCA1 results in decreased amyloid deposition (Hirsch-Reinshagen et al., 2007; Wahrle et al., 2008). Based on the findings that ABCA1 depletion results in increased amyloid deposition and ABCA1 induction shows a reciprocal effect and the fact that APP processing or Aβ production is not influenced by Abca1 depletion in vivo, the concept of the ABCA1–apoE pathway of Aβ clearance has been put forward. In this model, nascent apoE particles are secreted from astrocytes and microglia and are subsequently lipiddated by ABCA1 forming discoidal lipid–apoE complexes. In a second step, these are further loaded with lipids by ABCG1 (and likely other ABC transporters) to form spherical, mature apoE-containing lipid particles present in the CNS. Finally, mature apoE–lipid particles bind Aβ and facilitate the cellular uptake and clearance of Aβ via a functional apoE-receptor (Figure 2: Hirsch-Reinshagen et al., 2009).

Of note, a most recent study reports that transient expression of ABCA1 TD mutants in CHO cells stably expressing APP reduces Aβ production to a similar degree as wild-type ABCA1 but independently of cholesterol efflux (Kim et al., 2011). These findings,
which challenge the proposed model of Aβ clearance via ABCA1-lipidated apoE, rather suggest a direct effect of the ABCA1 protein on Aβ production and amyloid formation.

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. In light of this, ABCA1 may be a promising candidate for therapeutical interventions aiming at the prevention and treatment of AD.

**Association studies of ABCA1 and Alzheimer’s disease**

Besides these efforts to explore the functional implication of ABCA1 in amyloid deposition and development of AD, 11 studies have thus far investigated associations between single nucleotide polymorphisms (SNP) in the ABCA1 gene and the development of AD in various populations. Among the allelic variants identified in the ABCA1 gene, the SNPs rs2230806 (R219K), rs4149313 (I883M), and rs2230808 (R1587K) have been most extensively studied. At this point, however, the data from available association studies are inconclusive. This sobering resume is likely the result of major variations in the genetic and ethnic background of the cohorts investigated and varying experimental power of the studies. The 219K allele of the coding SNP rs2230806, for example, has been associated with both predisposition to AD (Rodriguez-Rodriguez et al., 2007; Sundar et al., 2007) and the opposite, a protective effect for the development of AD (Wollmer et al., 2003; Katzov et al., 2004; Wang and Jia, 2007; Wawrant-De et al., 2007; Reynolds et al., 2009). Other studies were unable to identify an association between common ABCA1 sequence variants and AD or delayed onset of AD (Li et al., 2004; Kolsch et al., 2006; Shibata et al., 2006; Wahrle et al., 2007). Although an anti-Alzheimer effect of the ABCA1 219K variant cannot be excluded at this point, further studies that rely on stringent design and strictly defined cohorts are necessary to explore the potential association between ABCA1 allelic variants and AD.

**ABCA2**

**Molecular properties of ABCA2**

Originally, ABCA2 was co-identified with ABCA1 in mice and is the second member of the A-subfamily of ABC transporters (Luciani et al., 1994). The human gene comprises 48 exons, is located on chromosome 9q34 and shows an extreme compact structure within a genomic region of only 21 kb (Kaminski et al., 2001a; Vulevic et al., 2001; Ile et al., 2004). The ABCA2 full-length cDNA is 7.3 kb in size and codes for a 270 kDa protein consisting of 2436 aa (Kaminski et al., 2001a; Vulevic et al., 2001). ABCA2 is mainly expressed in brain and nervous tissues with particularly high expression in cells facilitating myelin production in the brain (oligodendrocytes) and peripheral nerves (Schwann cells), respectively (Luciani et al., 1994; Zhao et al., 2000; Vulevic et al., 2001; Zhou et al., 2001, 2002; Langmann et al., 2003; Tanaka et al., 2003b; Su et al., 2004; Wang et al., 2005; Kim et al., 2006; Saito et al., 2007; Wahrle et al., 2008). Based on comparison of ABCA2 expression in astrocytic tumors and oligodendrogliomas, and in schwannomas and healthy Schwann cells, respectively, ABCA2 has also been proposed as a molecular marker for oligodendrogliomas and vestibular schwannomas (Wang et al., 2005; Soichi et al., 2007). However, ABCA2 has also been detected in a variety of other brain cells including neurons and brain endothelial cells (Ohtsuki et al., 2004; Broccardo et al., 2006; Kim et al., 2006; Warren et al., 2009; Shawahna et al., 2011), and other tissues outside the CNS including monocytes, macrophages, T-cells, thyroid gland, kidney, liver, thymus, heart, ovary, lung, and various tumor cells, respectively (Zhao et al., 2000; Kaminski et al., 2001a; Vulevic et al., 2001; Zhou et al., 2001, 2002; Ile et al., 2004; Broccardo et al., 2006). On a subcellular level, both electron microscopy and immunocolocalization experiments indicate a localization of ABCA2 around lysosomes and in the Golgi apparatus (Vulevic et al., 2001; Zhou et al., 2001, 2002). Ile et al. (2004) identified a novel 5′-localized exon of ABCA2 encoding an alternative N-terminus. Using Laser scanning confocal microscopy, the authors found that this novel isoform also co-localizes with lysosome-associated proteins-1 and -2 (LAMP1 and 2) and shows highest expression in peripheral blood leukocytes. In addition to this alternative exon 1-transcript, ABCA2 is transcriptionally expressed at least into five alternative transcripts which are differentially expressed in different brain regions (Piehler et al., unpublished data).

**ABCA2 and lipid transport in the CNS**

Although the intracellular localization of ABCA2 is in agreement with the finding that ABCA2 overexpressing HEK293 cells do not stimulate cholesterol efflux to apoA-I, apoE, or apoE disks (Kim et al., 2007), several observations suggest a role of ABCA2 in brain cholesterol metabolism: (i) the putative promotor sequence of ABCA2 contains multiple potential transcription factor binding sites for neural cell differentiation (Kaminski et al., 2001a). (ii) ABCA2 transcription displays cholesterol–responsive regulation (Kaminski et al., 2001a; Davis, Jr. et al., 2004; Davis, Jr., 2011) and (iii) ABCA2 is coordinately expressed with other sterol-dependent genes (Davis, Jr. et al., 2004). (iv) ABCA2 overexpression in CHO cells leads to an increase in LDL receptor expression and other genes involved in cholesterol metabolism (Davis, Jr. et al., 2004). (v) This results in a reduction of LDL-derived free cholesterol esterification and an accumulation of un-esterified LDL-cholesterol in the endosomal/lysosomal pathway (Davis, Jr. et al., 2004), which is part of the processing of APP to Aβ. A recent study by Davis using N2a neuroblastoma cells, however, reported a decrease of the LDL receptor in response to ABCA2 overexpression and thus a decrease in the uptake of a fluorescent LDL analog (Davis, Jr., 2011). In this work, the author also shows that ABCA2 overexpression leads to a reduction in total, free- and esterified cholesterol levels in the neuronal cells overexpressing ABCA2 (Davis, Jr., 2011). In addition, a decrease in plasma membrane cholesterol was noted, but not in other organelles or lipid raft compartments. Moreover, de novo cholesterol synthesis or trafficking of cholesterol to the plasma membrane or the endoplasmic reticulum were unaffected (Davis, Jr., 2011). Together, these results clearly indicate a regulatory role of ABCA2 cholesterol metabolism within the cell.

Next to the studies documenting highest expression of ABCA2 in oligodendrocytes and Schwann cells, which facilitate myelination of neurons in the CNS and the peripheral nervous system, several experiments point to a role of ABCA2 in myelin lipid transport.
in addition to cholesterol homeostasis. Analysis of maturing central and peripheral nervous tissues revealed that temporal and spatial expression of ABCA2 was closely correlated with that of myelin sheath-associated proteins (Zhou et al., 2002; Tanaka et al., 2003b). To date, two independent groups have reported the generation of Abca2 deficient mice. In both studies, Abca2-null mice phenotypically displayed reduced body weight and an obvious distinct tremor of their limbs and were reported to be easily startled (Mack et al., 2007; Sakai et al., 2007a). In the study by Mack and colleagues, Abca2−/− mice exhibited ultrastructurally abnormal myelin sheaths with increased myelin sheath thickness in the spinal cord and a reduced periodicity of the myelin membrane both in the spinal cord and cerebrum. In contrast, no apparent change in total, esterified or free plasma cholesterol, or in total CNS tissue lipid composition (ceramide, sphingosine, or sphingomyelin species) were observed in the Abca2 deficient mice. Because female Abca2-null mice had a lower body weight compared to their male littermates, the authors suggest a hormone-dependent role of Abca2 in neurological development (Mack et al., 2007). Sakai et al. (2007a) observed no abnormalities in the cytoarchitectonic or compact myelin structure in their Abca2 knock-out mice, but significant differences in lipid concentrations of both total brain tissue and myelin fractions compared to wild-type animals. From 4 to 64 weeks of age, Abca2-null mice brains exhibited an accumulation of gangliosides along with reduced sphingomyelin, and an accumulation of cerebrosides and sulfatides at 64 weeks of age. Analysis of the brain of Abca2 knock-out mice revealed reduced sphingomyelin and a significant increase of the major ganglioside GM1. The latter finding is of particular interest as it has been shown that raised levels of gangliosides in brain tissue induce beta-amyloid fibril formation (Yanagisawa, 2007). In conclusion, functional studies from the past years corroborate an involvement of ABCA2 in brain lipid metabolism. However, further work is required to define in detail the molecular involvement of ABCA2 in neuronal cholesterol homeostasis and myelin lipid metabolism.

ABCA2 in Alzheimer’s disease

Most recently, functional studies indicate a link between ABCA2 and the central molecular process in AD: beta-amyloid production. Using amplified differential gene expression, Chen et al. (2004) showed that overexpression of ABCA2 results in upregulation of genes commonly associated with oxidative stress and the pathogenesis of AD, including seladin-1, amyloid b (A4) precursor protein, vimentin, LDL receptor-related protein 3, Slc23a1, and calसarscinar-1. Using confocal microscopy, the authors showed that increased ABCA2 levels impact the expression of Aβ and APP, and that ABCA2 co-localizes with both Aβ and APP in discrete intracellular vesicles that also stained positively for the endolysosome markers LAMP1 and LAMP2 (Chen et al., 2004). Further evidence for ABCA2 as a key regulator of APP metabolism has recently been provided by Davis showing that overexpression of ABCA2 in neuronal N2a cells increased both the transcription of APP and the amount of APP holoprotein, and promoted amyloidogenic processing of APP (Davis, Jr., 2010). These findings are in line with a most recent report demonstrating that knock-down/knock-out of ABCA2 in mammalian cells in vitro, in Drosophila melanogaster and in mice results in reduced production of Aβ (Michaki et al., 2011). In this study, ABCA2 depletion led to a relative shift from β- to α-secretase dependent cleavage of APP resulting in increased levels of APPsβ and a relative decrease in APPsββ production. This observation computes well with the results by Davis reporting enhanced β-secretase cleavage of APP at the alternative cleavage site Glu11 (β′-site; Davis, Jr., 2010) which is increasingly used alternatively to the canonical Asp1 amino acid site (β-site) under conditions of β-secretase excess (Fluhrer et al., 2002; Liu et al., 2002). As ABCA2 is a likely regulator of cellular homeostasis and β-secretase acts within the detergent resistant domains (DRMs) of membranes (Wahrl et al., 2002; Ehehalt et al., 2003; Abad-Rodriguez et al., 2004; Vetrivel et al., 2004), depletion of ABCA2 may change DRM stabilization and thus the relative amount of APP processed by α- and β-secretase. Of note, Michaki et al. also found in their study that ABCA2 depletion leads to a reduction of APP processing by γ-secretase. This was due altered γ-secretase complex formation which in turn was caused by aberrant glycosylation of Nicastrin, one of the components of γ-secretase (Michaki et al., 2011). Interestingly, the reduction of γ-secretase cleavage of APP by ABCA2 depletion occurred in a substrate-selective manner since processing of Notch, another important substrate of γ-secretase, was unaffected (Michaki et al., 2011).

Association studies of ABCA2 and Alzheimer’s disease

In an effort to explore a potential association between genetic variation within ABCA2 and AD, two groups reported a strong correlation between a synonymous SNP (rs908832) and early-onset and sporadic AD in a Caucasian and a Western European population, respectively (Mace et al., 2005; Wollmer et al., 2006). In one study, however, the association was ethnicity-dependent and not present in a Southern European and an Asian population (Wollmer et al., 2006). In the same study, the authors reported an association of this SNP with cholesterol levels in the cerebrospinal fluid, a known determinant of AD (Wollmer et al., 2006). In contrast, Minster et al. (2008) could not confirm the observed association of rs908832 with early onset AD (EOAD) or sporadic AD. Despite the rather limited cohort size of the EOAD cohort (137 EOAD patients, 1006 controls), the study had a power of >90% to detect the odd-ratios reported by Mace et al. and Wollmer et al. respectively. At this point, more work is required to establish whether a clinically relevant association does exist between AD and genetic ABCA2 variants.

Taken together, evidence has accumulated through the past years to suggest important roles of ABCA2 in intracellular brain cholesterol homeostasis and APP processing. Although the molecular basis of the interdependency of ABCA2 and cholesterol traffic and Alzheimer disease are currently not fully understood, the knowledge of altered secretase activity due to changes in ABCA2 activity and cholesterol homeostasis may represent a starting point for developing therapeutical approaches to AD.

ABCA7

Molecular properties of ABCA7

ABCA7 is a 220 kDa A-subfamily ABC transporter that exhibits highest sequence similarity to ABCA1 (54%) and ABCA4 (49%; Kaminski et al., 2000, 2006; Broccardo et al., 2001). Initially, ABCA7 was cloned from human macrophages (Kaminski et al.,
ABCA7 siRNA and from heterozygous ABCA7 shares highest sequence identity with ABCA1, the main ABCA7 promoter contains sterol responsive elements and is regulated by SREPBs (Iwamoto et al., 2006), and shows highest ABCA7 expression in the densely packed neurons of the hippocampus (Kim et al., 2005). Results from studies investigating apoA-I mediated cholesterol efflux from macrophages and in peritoneal macrophages (Linsel-Nitschke et al., 2005). Several studies have thus far reported both intracellular detection of ABCA7 and its localization in the plasma membrane (Ikeda et al., 2003; Sasaki et al., 2003; Abe-Dohmae et al., 2004; Iwamoto et al., 2006). The putative presence of ABCA7 both in the cell and on the cell surface may be explained by the observation that ABCA7 is transcribed into several alternative variants (Ikeda et al., 2003; Kaminski et al., 2006).

The elusive function of ABCA7

Despite its identification more than 10 years ago, the definite molecular function of ABCA7 still needs to be elucidated. Several lines of evidence point to a role in cellular lipid transport: (i) ABCA7 shares highest sequence identity with ABCA1, the main molecule for cholesterol export to apoA-I to produce HDL particles (Kaminski et al., 2006), (ii) ABCA7 is up-regulated upon cholesterol load of macrophages and down-regulated upon cholesterol efflux from these cells (Kaminski et al., 2000), (iii) the ABCA7 promoter contains sterol responsive elements and is regulated by SREBP1s (Iwamoto et al., 2006) and (iv) other A-subfamily members, of which the substrate has been identified, serve as transporters of lipids (ABCA1, ABCA3, ABCA4, ABCA12; Kaminski et al., 2006). Results from studies investigating apoA-I mediated release of phospholipids and cholesterol by ABCA7 under different conditions, however, are conflicting. Whereas some reports suggest that cells overexpressing ABCA7 exhibit increased apolipoprotein-mediated efflux of both phospholipids and cholesterol (Ikeda et al., 2003; Abe-Dohmae et al., 2004; Hayashi et al., 2005), data from other experiments could not confirm that ABCA7 facilitates the release of cholesterol from cells (Wang et al., 2003; Abe-Dohmae et al., 2004; Linsel-Nitschke et al., 2005). The situation is complicated by the observations that peritoneal macrophages treated with ABCA7 siRNA and from heterozygous ABCA7+/− mice showed unaffected apoA-I mediated cellular cholesterol and phospholipid release (Linsel-Nitschke et al., 2005). Moreover, Abca7 null mice, which have been reported to be lethal by one group (Iwamoto et al., 2006), showed unchanged cholesterol and phospholipid efflux levels in bone marrow-derived macrophages investigated by another group (Kim et al., 2005). Abca7 knock-out mice showed no obvious phenotypic abnormalities, but surprisingly exhibited a gender dependent reduction in serum total cholesterol, HDL concentration and visceral fat (Kim et al., 2005). At this point, further work is required to establish how and to which degree ABCA7 contributes to human lipid trafficking.

ABCA7 in CNS lipid transport and Alzheimer’s disease

Based on the notion that ABCA7 is expressed in the brain and potentially functions as a lipid transporter, Chan et al. (2008) investigated whether ABCA7 regulates cholesterol efflux to apoE, the major apolipoprotein in the brain, and whether it influences beta-amyloid production. They found that overexpression of ABCA7 stimulated cholesterol efflux to discoidal apoE-lipid complexes independent of the apoE isoform. Lipid-free apoE did not accept cholesterol suggesting that apoE disks present in the CNS may function as acceptors for ABCA7-mediated cholesterol efflux. Moreover, the authors noted that ABCA7 significantly inhibited beta-amyloid secretion from human amyloid precursor protein expressing cells. Using fluorogenic substrates and GFP-tagged APP they demonstrated that the observed inhibition was due to an apparent retention of APP in a perinuclear location rather than an inhibitory effect on α-, β-, or γ-secretase activity (Chan et al., 2008).

Along with the sustained efforts to elucidate the role of ABCA7 in cellular lipid transport, evidence has accumulated during the past years that links another potential function of this transporter to neurodegenerative disease. Recent reports indicate a central role of ABCA7 in phagocytosis and the engulfment of apoptotic cells (Iwamoto et al., 2006; Jehle et al., 2006; Tanaka et al., 2010, 2011ab). In addition to the finding that ABCA7 mRNA and protein is up-regulated during phagocytosis via the SREBP2 pathway (Iwamoto et al., 2006), these studies showed that knock-down of ABCA7 results in a decreased phagocytic activity (Iwamoto et al., 2006) and that heterozygous ABCA7+/− mice exhibit a defective clearance of apoptotic cells (Jehle et al., 2006). Both the phagocytic rate and the expression of ABCA7 are increased in ABCA1-deficient fibroblasts (Bared et al., 2004; Iwamoto et al., 2006). In contrast, the phagocytic activity is reduced in the peritoneal cavity of ABCA7−/− mice compared to wild-type animals (Tanaka et al., 2010). These studies also indicate that apoA-I and apoA-II both stabilize and increase surface ABCA7 and thus increases the phagocytic rate rather than contribute to lipid efflux from the cell. This stimulation of phagocytosis was sustained in ABCA1 siRNA treated J774 macrophages and in the peritoneal macrophages from ABCA1−/− mice (Tanaka et al., 2010). Another study by the same group also demonstrated that statin treatment of J774 cells induces ABCA7 expression by its cholesterol-lowering effect and simultaneously enhances phagocytosis. This increase in phagocytic activity was abolished by ABCA7 siRNA treatment of the statin stimulated cells (Tanaka et al., 2011a).

The finding that ABCA7 promotes Fc receptor-independent phagocytosis is of particular interest taking into account that human microglia cells contribute to the phagocytic removal of apoptotic debris from the brain (Stolzing and Grune, 2004; Napoli and Neumann, 2009) and given that among brain cells microglia displays highest ABCA7 expression. Based on this, it is tempting to speculate that microglial ABCA7 has an active role in the...
Fc receptor-independent phagocytic uptake of debris and plaques generated in the process of neurodegenerative disorders.

Moreover, the recent demonstration of a T cell receptor (TCR)-based machinery for specific immune recognition in macrophages that functions as a modulator of phagocytic capacity (Beham et al., 2011) raises the intriguing possibility of a functional link between ABCA7 and the novel variable macrophages immune system. It will be most challenging to investigate whether and to which degree an interdependencies exists between ABCA7 and the macrophage TCR-like immunoreceptors in the pathogenesis of macrophage-dependent neurodegenerative diseases such as multiple sclerosis and HIV dementia.

**Association studies of ABCA7 and Alzheimer’s disease**

Next to functional studies, independent evidence for roles of ABCA7 in brain lipid homeostasis and neurodegeneration comes from a recent genome-wide association study (GWAS) and reanalysis of combined GWAS datasets which identified a candidate locus for AD in the ABCA7 gene (Jones et al., 2010; Hollingworth et al., 2011). The hot spot, which is defined by a common genetic variant in the ABCA7 gene (rs3764650) located in intron 13, exhibited a strong association with this disease. Also a non-synonymous SNP in ABCA7 exon 32 (rs3752246) which showed the highest linkage disequilibrium with rs3764650 was found to be significantly associated with LOAD (Hollingworth et al., 2011). However, as rs3752246 encodes a glycine to alanine substitution at position 1527 of the protein, which is regarded as a benign change, this SNP is unlikely to be the relevant functional variant. The authors also excluded an association between rs3764650 and the expression of ABCA7 analyzing data from two expression quantitative trait loci (eQTL) datasets. Although these studies present compelling evidence for an association of ABCA7 with AD, the genetic mechanisms that define a causative interrelationship still await elucidation.

**OTHER A-SUBFAMILY ABC TRANSPORTERS**

Beside the above ABC transporters, other A-subfamily members are expressed only to a limited degree in brain and nervous tissues. Anecdotal reports on potential functions of these are rare, but mainly point to an involvement in cellular lipid metabolism. Future detailed studies will help to determine whether these A-subfamily transporters are implicated in brain lipid homeostasis and the pathophysiology of neurodegenerative processes. The following subchapter provides a brief synopsis of our current knowledge on additional members of the A-subfamily of ABC transporters.

**ABCA3**

ABCA3 is mainly expressed in the human lung alveolar type II cells on the limiting membrane of lamellar bodies, which represent the storage form of lung surfactant. Mutations in ABCA3 have been shown to cause fatal surfactant deficiency in full-term newborns (Shulenin et al., 2004) and are associated with milder forms of interstitial lung disease as well (Bullard et al., 2005; Kunig et al., 2007; Karjalainen et al., 2008; Yokota et al., 2008). The phenotype of surfactant deficiency caused by mutations in ABCA3 has been confirmed in ABCA3 knock-out mice by several groups (Ban et al., 2007; Cheong et al., 2007; Fitzgerald et al., 2007; Hammel et al., 2007). Although the exact molecular contribution of ABCA3 to surfactant production is still unknown, an essential role of this transporter in lipid transport, in particular in phosphatidylcholine and phosphatidylglycerol trafficking, during lamellar body formation has been established. Expression of ABCA3 has also been detected in total brain tissue (Fitzgerald et al., 2007; Stahlman et al., 2007), oligodendrocytes, neurons, astrocytes, and microglia (Kim et al., 2006), a tissue expression pattern that is similar to that of ABCA2 in the developing mouse brain (Tachikawa et al., 2005). Given the expression of ABCA3 in the brain and the fact that phosphatidylcholine and phosphatidylglycerol are the lipid compounds mainly affected in the ABCA3-defective lung, it appears realistic to assume roles of ABCA3 in the transport of these lipids in the brain. However, studies investigating this function are currently unavailable. In detail examination of ABCA3 deficient mouse brains will help to gain further insight into a possible role of ABCA3 in brain lipid homeostasis.

**ABCA4**

ABCA4 is one of the best characterized A-subcell ABC transporters. Already in 1997 it was shown that mutations in this retina-specific transporter, also termed ABCR, cause Stargardt disease. This degenerative eye-disease is characterized by progressive impairment of central vision early in life, presence of lipofuscin deposits in the central retina, and bilateral photoreceptor atrophy in the macula (Allikmets et al., 1997; Molday, 2007). Also the rare, but more severe cone-rod dystrophy type 3 and retinitis pigmentosa type 19 have been shown to be caused by mutations in ABCA4 (Cremers et al., 1998; Martinez-Mir et al., 1998; Maugeri et al., 2000). Extensive studies of this transporter strongly suggest that ABCA4 facilitates the export of the phospholipid N-retinylidenephosphatidylethanolamine, a byproduct of the visual cycle, from the lumen to the cytoplasm of disk membranes in rod cells (Sun et al., 1999; Weng et al., 1999; Ahn et al., 2000; Mata et al., 2000; Beharry et al., 2004; Molday, 2007). Depletion of ABCA4 activity results in accumulation of retinoids in disk membranes and subsequent retinal pigment epithelial cell death and neurodegeneration of photoreceptors, a process that ultimately leads to severe vision loss in affected individuals (Weng et al., 1999; Mata et al., 2000; Molday, 2007). ABCA4 is also expressed outside the retina in rat choroid plexus epithelial cells and human brain capillary endothelial cells (Ohtsuki et al., 2004; Bhongsatiern et al., 2005; Tachikawa et al., 2005) suggesting a role of this ABC protein in blood-cerebrospinal fluid barrier function. Because ABCA4 dysfunction leads to accumulation of retinoids in the retinal pigment epithelium, it may be worthwhile investigating whether ABCA4 present in the choroid plexus is involved in the regulation of retinoid concentrations in the CNS which are associated with motor neuron disease and AD (Maden, 2007).

**ABCA6-like transporters**

Only little is known about the function of the subgroup of ABCA6-like transporters which form a compact gene cluster located on chr 17q24.2-3. This cluster comprises the transporters ABCA5, ABCA6, ABCA8, ABCA9, and ABCA10, respectively. Although
all ABCA6-like transporters are expressed at detectable levels in the brain (Nagase et al., 1998; Arnould et al., 2001; Kaminski et al., 2001b, 2006; Piehler et al., 2002; Tsuruoka et al., 2002; Langmann et al., 2003; Wenzel et al., 2003, 2007; Kim et al., 2006) and it is likely that they are involved in lipid transport processes, their potential implication in human brain lipid homeostasis and neurodegeneration remains purely speculative at this point.

Reports on ABCA5 expression and function are anecdotic and the sites of expression appear to be highly diverse. Interestingly, ABCA5 expression has been documented mainly in the context of epithelial malignancies including prostate cancer (Hu et al., 2007), adenocarcinoma (Ohitsuki et al., 2007), melanomas (Heimerl et al., 2007), esophageal carcinoma (Huang et al., 2009), mesothelioma (Shukla et al., 2010), and oral squamous cell carcinoma (Cha et al., 2011), respectively. Other studies report high ABCA5 expression in the brain, lung, heart, thyroid gland, and testis (Kubo et al., 2005; Petry et al., 2006). Upregulation of ABCA5 in human brain microvascular endothelial cells derived from the blood–brain barrier endothelium in response to tacrolimus treatment has also been reported (Quezada et al., 2008). On the subcellular level, ABCA5 localizes to lysosomes and late endosomes, and Abca5+/− mice exhibit exophthalmos and a collapse of the thyroid gland (Kubo et al., 2005). In adulthood, these animals develop a dilated cardiomyopathy-like heart and die due to cardiac insufficiency (Kubo et al., 2005). Despite its expression in the brain and its potential involvement in cholesterol metabolism (Ye et al., 2008, 2010), it appears unlikely that ABCA5 plays a crucial role in brain lipid homeostasis since overt abnormalities are not observed in the brain of ABCA5 deficient mice (Kubo et al., 2005).

ABCA6, ABCA9, and ABCA10 are also expressed at detectable levels in the brain and regulated during monocyte differentiation and cholesterol transport in human macrophages (Kaminski et al., 2001b, 2006; Piehler et al., 2002; Wenzel et al., 2003; Albrecht and Viturro, 2007) suggesting roles of these transporters in lipid transport. However, definitive evidence supporting an implication of these highly homologous transporters in brain lipid transport is still outstanding.

Initial studies have indicated a role of ABCA8 in drug transport with a substrate specificity close to that of ABCG2 which is located at the blood–brain barrier (Tsuruoka et al., 2002). Moreover, Abca8a transcription is induced in the mouse liver upon acute digoxin intoxication (Wakaumi et al., 2005). A recent study by Reppe et al. (2010) also suggests an association between ABCA8 and bone mineral density in postmenopausal Caucasian women.

ABCA12

ABCA12 was co-identified with ABCA13 in 2002 and mapped to the locus linked to lamellar ichthyosis on chromosome 2q34 (Parmentier et al., 1999; Annilo et al., 2002). Subsequent studies revealed that mutations in this transporter cause three related hereditary skin diseases: lamellar ichthyosis type 2 (Lefevre et al., 2003), non-bullous congenital ichthyosiform erythroderma (Natsuga et al., 2007; Akiyama et al., 2008) and harlequin ichthyosis (HI; Akiyama et al., 2005; Kelsell et al., 2005; Akiyama, 2006). All three entities represent hereditary dyskeratinization disorders, but present with different clinical severity. Whereas lamellar ichthyosis type 2 is a relatively mild form of dyskeratinization with skin desquamation over the whole body and large, pigmented scales (Lefevre et al., 2003), HI presents with a distorting phenotype in which the patient’s body is covered with an enormous horny shell with deep fissures leading to water loss, electrolyte abnormalities, severe infections, and mostly death within the first days after birth (Unamuno et al., 1987; Akiyama et al., 2005; Akiyama, 2006). Analysis of the mutations identified in the different dyskeratinization entities suggests that the severity of the phenotype correlates with the remaining activity of the mutated ABCA12 protein product. The molecular correlate of these dyskeratinization disorders is the absence or malformation of so-called lamellar granules (LG; Akiyama et al., 2005; Kelsell et al., 2005) which physiologically contribute to assemble the skin barrier by extruding their lipid content into the extracellular space during the keratinization process (Wertz, 2000). Since mutations in ABCA12 result in an abnormal distribution pattern of glucosylceramide, a major lipid component of LG (Kelsell et al., 2005; Akiyama et al., 2008), and ABCA12 ultrastructurally co-localizes with glucosylceramide to LG on their way from the Golgi apparatus to the cell periphery (Sakai et al., 2007), it is realistic to assume an essential role of ABCA12 in intracellular sphingolipid transport processes (Akiyama, 2011). Of note, expression of ABCA12 has also been reported in fetal brain (Annilo et al., 2002). It remains to be established, however, whether ABCA12 exerts functions in the regulation of the sphingolipid metabolism in the developing brain.

ABCA13

ABCA13 is the largest known ABC transporter with a gene size of 450 kb comprising 62 exons which code for a 576-kDa polypeptide of 5058 aa and with an exceptionally large extracellular domain of more than 3500 aa (Prades et al., 2002; Barros et al., 2003). In normal tissues, highest mRNA expression was found in human trachea, testis, bone marrow, submaxillary gland, epididymis, ovary, and thymus (Prades et al., 2002; Barros et al., 2003). High expression in the brain tumor cell line SNB-19 has also been reported (Prades et al., 2002). The molecular function of ABCA13 is currently unknown. Intriguingly, a recent report points to an association between genetic variants of ABCA13 and schizophrenia, bipolar disorder, and depression (Knight et al., 2009). In this study, the population attributable risk of the identified mutations was 2.2% for schizophrenia and 4.0% for bipolar disorder. However, a more recent report failed to confirm this observation (Dwyer et al., 2011).

NON A-SUBFAMILY ABC TRANSPORTERS

Next to the A-subfamily ABC transporters reviewed above, several studies point to roles of ABC transporters outside this subfamily in brain lipid homeostasis and neurodegeneration (Kim et al., 2008). ABCB1, also known as MDR1 and P-glycoprotein, is one of the best characterized ABC transporters. It functions mainly as an exporter of amphipathic molecules such as anticancer drugs that confer multidrug resistance to tumor cells (Sarkadi et al., 2006).
Transport of lipids (phosphatidylcholine and ethanolamine, glycosylceramide, and sphingomyelin) by ABCB1 has also been reported (van Helvoort et al., 1996). Despite its overall low expression in human brain (Langmann et al., 2003), its presence and functional implication in the blood–brain barrier have been well documented (Cordon-Cardo et al., 1989; Tatsuta et al., 1992; Tishler et al., 1995; Seetharaman et al., 1998; ElAli and Hermann, 2011; Vogelgesang et al., 2011). Importantly, recent studies indicate a central role of ABCB1 in the efflux of Aβ from the brain (Lam et al., 2001; Vogelgesang et al., 2004, 2011; Cirrito et al., 2005; Kuhnke et al., 2007; Hartz et al., 2010) which is reduced by approximately 30% in AD patients compared to healthy individuals (Mawuenyega et al., 2010). In addition to ABCB1, additional studies strongly suggest the involvement of the ABC proteins ABCA1, ABCG1, and ABCG2, respectively, in the export of Aβ (Xiong et al., 2009; Koldomova et al., 2010; Krohn et al., 2011). Finally, another G-subfamily ABC transporter, designated ABCG1, has been implicated in the processing of APP to generate Aβ peptides (Sarkadi et al., 2006; Kim et al., 2007). Each of these transporters may represent a potential pharmaceutical target for therapeutic interventions aiming at the reduction of Aβ accumulation and the prevention of AD progression.

CONCLUSION

ATP-binding cassette transporters constitute an evolutionary ancient group of large proteins which mediate the transmembrane transport of a diverse spectrum of substrates. Specifically, the members of the recently identified A-subfamily of ABC transporters serve as key regulators of cellular lipid transport processes. Given that the central nervous system, next to adipose tissue, represents the second major lipid rich area in higher organisms, it is reasonable to assume that A-subfamily ABC transporters are of critical importance for the treatment of the CNS. In fact, recent evidence links A-subfamily transporters and also other members of the ABC protein family to the maintenance of brain lipid homeostasis and neurodegenerative diseases. In particular, the transporters ABCA1, ABCA2, and ABCA7 are promising research targets that bear significant therapeutic potential for the treatment of neurodegenerative disease. Whereas ABCA7 appears to inhibit Aβ production, a positive effect on Aβ production has been reported for ABCA2. Moreover, available evidence suggests that ABCA1 acts as a suppressor of Aβ production and deposition. Recent experiments involving ABCA1 inducing LXR agonists have shown promising, antiamyloidigenic effects and thus highlight the importance of ABCA1 as a promising drug target in combating AD.

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