ABCA1 Is Required for Normal Central Nervous System ApoE Levels and for Lipidation of Astrocyte-secreted apoE*

Suzanne E. Wahrle†, Hong Jiang‡, Maia Parsadanian§, Justin Legleiter¶, Xianlin Han†, John D. Fryer‡†, Tomasz Kowalewski‡‡, and David M. Holtzman**††§§§§§

From the †Program in Neuroscience, ‡Department of Neurology, **Department of Molecular Biology and Pharmacology, ††Center for the Study of Nervous System Injury, §§Alzheimer’s Disease Research Center, Washington University, St. Louis, Missouri 63110 and the †§Department of Chemistry, Carnegie Mellon University, Pittsburgh, Pennsylvania 15213

ABCA1 is an ATP-binding cassette protein that transports cellular cholesterol and phospholipids onto high density lipoproteins (HDL) in plasma. Lack of ABCA1 in humans and mice causes abnormal lipidation and increased catabolism of HDL, resulting in very low plasma apoA-I, apoA-II, and HDL. Herein, we have used Abca1+/− mice to ask whether ABCA1 is involved in lipidation of HDL in the central nervous system (CNS). ApoE is the most abundant CNS apolipoprotein and is present in HDL-like lipoproteins in CSF. We found that Abca1+/− mice have greatly decreased apoE levels in both the cortex (80% reduction) and the CSF (98% reduction). CSF from Abca1+/− mice had significantly reduced cholesterol as well as small apoE-containing lipoproteins, suggesting abnormal lipidation of apoE. Astrocytes, the primary producer of CNS apoE, were cultured from Abca1+/+, +/−, and −/− mice, and nascent lipoprotein particles were collected. Abca1+/− astrocytes secreted lipoprotein particles that had markedly decreased cholesterol and apoE and had smaller apoE-containing particles than particles from Abca1+/+ astrocytes. These findings demonstrate that ABCA1 plays a critical role in CNS apoE metabolism. Since apoE isoforms and levels strongly influence Alzheimer’s disease pathology and risk, these data suggest that ABCA1 may be a novel therapeutic target.

ABCA1 is the founding member of the ATP-binding cassette (ABC) family of transporters, which is the largest group of transmembrane transporters with 48 known family members in humans (1). All ABC transporters share homology in their ATP-binding domain and use ATP to translocate a wide variety of substrates across extra- and intracellular membranes (2). Defects in ABC transporters cause at least 14 known genetic diseases (3).

ABCA1 transports cellular cholesterol and phospholipids from cells onto high density lipoproteins (HDL) in plasma (4, 5). In humans, loss-of-function mutations in ABCA1 cause Tangier’s disease (6–9), which is characterized by accumulation of cholesterol in lymphatic tissues and increased catabolism of abnormally lipidated HDL, resulting in very low levels of plasma HDL and HDL-associated apolipoproteins A-I (apoA-I) and A-II (apoA-II) (10, 11). ABCA1 knock-out mice (Abca1−−−−) have been produced, and the mice have a similar phenotype as patients with Tangier’s disease (12).

However, neither Tangier’s disease patients nor Abca1−−−− mice have been examined to determine whether ABCA1 plays a role in lipidation or metabolism of lipoproteins in the central nervous system (CNS). The most abundant apolipoprotein in the CNS is apolipoprotein E (apoE), which is produced within the CNS, primarily by astrocytes and to some extent microglia (13–17). ApoE is present in brain tissue and in the cerebrospinal fluid (CSF), where it is present in HDL-like particles (18–20). By analyzing brain tissue, CSF, plasma, and primary astrocyte cultures from Abca1+/+, +/−, and −/− mice, we determined that deletion of ABCA1 markedly affects metabolism of apoE and cholesterol in the CNS and in nascent lipoprotein particles secreted by cultured astrocytes. These findings have implications for neurological diseases involving apoE, such as Alzheimer’s disease.

**EXPERIMENTAL PROCEDURES**

*Animals and Tissue Preparation—Mice heterozygous for the Abca1 null allele on a DBA background were obtained from the Jackson Laboratory, Bar Harbor, ME (strain name: DBA/1-Abca1+/−). These mice have similar abnormalities to those found in humans with Tangier’s disease, such as greatly reduced plasma HDL (12). The heterozygous mice were bred to one another to generate littermates with all Abca1 genotypes: wild type (Abca1+/+), heterozygous (Abca1+/−), and knock-out (Abca1−−−−). All animals used for in vitro experiments were between 10 and 14 weeks old. For fluid and tissue analysis, animals were anesthetized with pentobarbital, CSF was collected from the cisterna magna as described (21), blood was collected by cardiac puncture, and animals were perfused with PBS-heparin (3 units/ml). Regional brain dissection was performed, and brain samples were frozen on dry ice.

*ApoE ELISA—A sandwich ELISA for mouse apoE was developed with a sensitivity of ~1 ng/ml. 96-well plates were coated overnight with 0.5 µg/well of a mouse monoclonal antibody (WU E-4) raised against apoE (22), washed with PBS, blocked with 1% milk in PBS, and then washed again. Brain samples were sonicated in 0.05% TWEEN in PBS with 1× Complete protease inhibitor mixture (1× protease inhibitors) (Roche Applied Science), debris was pelleted by a 10,000 g min spin, and the supernatant was diluted in 0.1% bovine serum albumin, 0.025% Tween in PBS. Conditioned medium, plasma, and CSF were diluted directly into 0.1% bovine serum albumin, 0.025% Tween in

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Primary Astrocyte Cultures—Primary cultures of forebrain astrocytes (~95% pure) were prepared from individual neonatal (1-3-day-old) mice as described previously (28). Astrocytes were grown in Dulbecco’s modified Eagle’s medium:F-12 containing 10% fetal bovine serum, 10% heat-inactivated horse serum, 1 mM sodium pyruvate, 100 units/ml penicillin, 100 µg/ml streptomycin, 250 ng/ml Fungizone, and 10 ng/ml epidermal growth factor (Sigma).

To obtain ACM, confluent astrocyte cultures were washed twice with sterile PBS. Serum-free medium was added (Dulbecco’s modified Eagle’s medium:F-12, 1% N2 supplement (Invitrogen), 1 mM sodium pyruvate, 100 units/ml penicillin, 100 µg/ml streptomycin, 250 ng/ml Fungizone), and cells were incubated for 3 days. Media were then collected and spun at 2,000 × g for 10 min to remove cellular debris. 0.1% sodium azide and 1× protease inhibitors were added, and the ACM was stored at -4°C until analysis. Following harvesting of ACM, astrocytes were scraped from the flasks, washed with PBS, pelleted, and sonicated in PBS.

Fractionation of ACM—ACM was concentrated 40-fold with a 10-kDa molecular mass cut-off spin concentrator (Millipore, Billerica, MA). 1 ml of concentrated ACM was subjected to gel filtration chromatography using a BioLogic system (Bio-Rad) with tandem Superose 6 HR 10/30 columns (Amersham Biosciences) in 0.15 NaCl, 0.001 EDTA, 0.02% sodium azide as described previously (29).

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Lipids in CSF and Cortex of Abca1<sup>+/−</sup> Mice—Since the major function of ABCA1 outside the CNS is transport of cholesterol and phospholipids onto HDL, we examined whether ABCA1 deficiency altered the levels of cholesterol and phospholipids within the CNS. We found that total cholesterol in CSF was reduced by 24% in Abca1<sup>+/−</sup> mice as compared with wild type littermates (Fig. 2A). This is likely because ABCA1 deficiency results in decreased levels of HDL, the lipoprotein class that normally carries some proportion of cholesterol in the CSF. In contrast to CSF, total cholesterol levels in brain tissue (cortex) were not significantly different between Abca1<sup>+/−</sup>, Abca1<sup>+/+</sup>, and Abca1<sup>−/−</sup> mice (Fig. 2B). Cholesterol esters in cortex represented less than 5% of the total cholesterol and were also not significantly different (data not shown). Anionic phospholipids, choline glycerophospholipids, sphingomyelins, and ethanolamine glycerophospholipids were measured in cortex by electrospray ionization mass spectrometry and did not vary significantly between Abca1<sup>+/−</sup> and Abca1<sup>−/−</sup> mice (n = 5 in each group, data not shown).

To determine whether there was any lipid buildup in brain, we stained 3-month-old Abca1<sup>+/−</sup> and Abca1<sup>−/−</sup> brain sections with oil red O. There was no evidence of abnormal lipid deposition in the Abca1<sup>−/−</sup> mice (Fig. 2C). Standard histological staining methods including cresyl violet for nuclei and Luxol fast blue for myelin also revealed no abnormalities in the brains of Abca1<sup>−/−</sup> mice (data not shown).

Lipoprotein Particles from CSF and Astrocyte Conditioned Media of Abca1<sup>+/−</sup> Mice—In addition to evaluating the effects of ABCA1 deficiency on the levels of lipids and apoE in the CNS in vivo, we studied apoE- and apoA-I-containing lipoproteins in CSF and nascent apoE-containing lipoproteins produced by astrocytes to examine how ABCA1 deficiency affected their properties. We determined the size distribution of apoE- and apoA-I-containing lipoproteins in mouse CSF by non-denaturing gradient gel electrophoresis. As we have described previously (21), apoE in CSF of wild type mice was in HDL-like particles 10–17 nm in diameter with the most abundant sizes being between 13 and 16 nm (Fig. 3A). ApoE particles from...
Abca1<sup>−/−</sup> CSF were similar in size to wild type. However, in addition to apoE levels in CSF from Abca1<sup>−/−</sup> being markedly reduced, apoE was present within particles that had a size distribution that was different from wild type mice. In addition to having a population of particles between 13 and 16 nm in diameter, CSF from Abca1<sup>−/−</sup> mice also had a population of smaller apoE-containing particles that were 7–8 nm in diameter, suggesting that they were poorly lipidated. ApoA-I was also greatly reduced in CSF from Abca1<sup>−/−</sup> mice, and the small amount that was there was present in particles of ~7.3 nm as compared with particles of 8–11 nm in CSF from Abca1<sup>+/+</sup> mice (Fig. 3B).

Because Abca1<sup>−/−</sup> mice have both very low CSF apoE levels and altered particle size distribution, this led us to investigate whether there was a primary alteration of nascently produced apoE-containing HDL from astrocytes, the cells that produce the majority of apoE in the CNS. We compared total cholesterol and apoE in ACM derived from primary astrocyte cultures from Abca1<sup>+/+</sup>, <sup>−/−</sup>, and <sup>−/−<sup>−/−</sup> mice and found that total levels of apoE in ACM did not vary by Abca1 genotype (Fig. 3E). However, the levels of total cholesterol were significantly lower in Abca1<sup>−/−</sup> ACM (Fig. 3D). This suggests that apoE is secreted at normal levels by Abca1<sup>−/−</sup> astrocytes, but the apoE is not normally lipidated in the absence of ABCA1.

To examine the extent of lipidation of apoE-containing particles, ACM was subjected to size analysis by non-denaturing gradient gel electrophoresis followed by Western blotting for apoE. This demonstrated apoE-containing lipoprotein populations of ~12, 11, and 8 nm in ACM from Abca1<sup>+/+</sup> mice but much smaller lipoproteins in ACM from Abca1<sup>−/−</sup> mice of ~7.3 and <7 nm (Fig. 3C). These data suggested that apoE-containing particles from Abca1<sup>−/−</sup> ACM were likely very lipid-poor.

To analyze the lipid composition of astrocyte-secreted lipoproteins, ACM was fractionated by size exclusion chromatography. ApoE ELISAs and cholesterol assays of the different fractions demonstrated that lipoproteins from Abca1<sup>−/−</sup> ACM contain less apoE, are smaller, and have markedly less cholesterol than Abca1<sup>+/+</sup> ACM (Fig. 4, A and B). Lipoprotein-associated apoE was reduced in Abca1<sup>−/−</sup> ACM by 80% as compared with Abca1<sup>+/+</sup> ACM. As expected, ~75% of the apoE in the Abca1<sup>+/+</sup> ACM was in fractions 31–41, corresponding to the HDL size range. However, ~75% of the lipoprotein-associated apoE in the Abca1<sup>−/−</sup> ACM was in fractions 45–55, which corresponds to much smaller particles. These smaller lipoprotein particles derived from Abca1<sup>−/−</sup> astrocytes were very cholesterol-poor as compared with Abca1<sup>+/+</sup> particles (0.69 µg of total cholesterol/µg of apoE for Abca1<sup>−/−</sup> versus 2.3 µg of total cholesterol/µg of apoE for Abca1<sup>+/+</sup>).

To confirm the size and shape of the abnormal Abca1<sup>−/−</sup> particles, AFM was performed on the size exclusion chromatography fractions from Abca1<sup>+/+</sup> and Abca1<sup>−/−</sup> ACM with the highest apoE levels. AFM is a tool of choice because it allows for characterization of the three-dimensional shape of nanoparticles under nearly physiological conditions. Its use to study lipoprotein particles and the protocols needed to obtain reliable volume measurements were recently described elsewhere (31).
The AFM images obtained demonstrate that the most abundant apoE-containing particles in Abca1/H11002/H11002 ACM are significantly smaller than in Abca1/H11001/H11001 ACM (Fig. 4C).

DISCUSSION

In this study, we have analyzed brain tissue, CSF, plasma, and primary astrocyte cultures from Abca1/H11001/H11001, H11001/H11002, and H11002/H11002 mice to determine whether deletion of ABCA1 affects metabolism of apoE, cholesterol, and phospholipids in the CNS and in nascent lipoprotein particles secreted by astrocytes. We found that Abca1−/− mice have greatly decreased apoE levels in the plasma (96% reduction), CSF (98% reduction), and cortex (80% reduction) as compared with Abca1+/+ mice. The decreased apoE levels in plasma and brain that we observed are similar to those seen by others. The decreased apoE levels in the CNS are not related to Apoe gene expression but likely result from increased catabolism of abnormally lipidated apoE-containing HDL lipoproteins produced in the CNS, as occurs with abnormally lipidated apoA-I and apoA-II that are secreted by the liver and are rapidly catabolized in the plasma of Tangier’s disease patients (10, 11).

Although the alterations in CNS apoE levels were profound, differences in total CNS lipids were more subtle and present only in CSF. Brain tissue from Abca1+/+, −/−, and −/− mice had no differences in free cholesterol, esterified cholesterol, and phospholipids and showed no evidence of lipid deposition by histological staining. These results suggest that ABCA1 does not play a major role in regulating global cellular lipid levels in brain tissue in vivo and that this regulation is performed by additional molecules. However, CSF from Abca1−/− mice had significantly reduced cholesterol, showing that ABCA1 is important in regulating extracellular lipid levels in the CNS.

Conditioned media collected from primary cultures of astrocytes derived from Abca1+/+, −/−, and −/− mice showed that although total levels of apoE secreted by astrocytes are not affected by Abca1 genotype, secretion of cholesterol into the media is markedly reduced in Abca1−/− cultures, which is consistent with ABCA1 having a role in transporting astrocyte-derived cellular cholesterol onto lipoproteins. This function may occur in the astrocyte secretory pathway or extracellularly. Analysis of nascent lipoprotein particles isolated from conditioned media of primary astrocyte cultures demonstrated

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that Abca1−/− astrocytes secrete apoE-containing particles of markedly smaller size with reduced cholesterol and apoE, demonstrating that ABCA1 is required by the main cellular producer of apoE in the CNS to normally lipidate apoE. Of the apoE produced by CNS cells such as astrocytes that reach the CSF of Abca1−/− mice, a fraction of the particles present were also abnormally small, although some were of normal size. Thus, there appears to be a mechanism that does not require ABCA1 to lipidate some apoE that reaches the CSF. However, the fact that CSF apoE levels in Abca1−/− were 2% of normal suggests that the non-ABCA1 mediated pathway is inefficient and that most apoE particles produced in the absence of ABCA1-mediated lipidation are rapidly metabolized in the CNS.

ApoE and apoJ are the two major apoproteins produced by astrocytes, and each is secreted into unique apoE- or apoJ-only containing particles (33). ApoE secreted by astrocytes is present in particles that contain approximately an equal mass of apoE, cholesterol, and phospholipids (21). Furthermore, virtually all cholesterol and phospholipids secreted by astrocytes are associated with apoE (33). In contrast, apoJ secreted by astrocytes has very little associated cholesterol or phospholipids (21) and we found that it was present at normal levels in the brains of Abca1−/− mice. Thus, apoJ particles are stable in the absence of ABCA1, possibly because they are normally lipid-poor and do not require extensive lipidation for stability.

These data demonstrate that complete loss of ABCA1 profoundly affects apoE levels in the CNS. Additionally, since Abca1+/− mice had intermediate apoE levels, more subtle alterations in ABCA1 gene dosage and/or functionality may affect apoE metabolism. The Apoe genotype is a major risk factor for both Alzheimer’s disease (AD) and cerebral amyloid angiopathy (CAA) (34–36). The Apoe genotype may also influence neurologic prognosis after intracerebral hemorrhage (37), traumatic brain injury (38), and multiple sclerosis (39). The effects of apoE on AD and CAA are likely to be mediated in large part by the role of apoE as an amyloid-β (Aβ) chaperone that influences Aβ clearance and fibrillogenesis (40). In amyloid precursor protein transgenic mice that develop many of the pathological changes seen in AD and CAA, the level of apoE, regardless of species or genotype, markedly influences the time of onset, conformation, and amount of the Aβ peptide that accumulates in the brain with age (41–45). For example, when amyloid precursor protein transgenic mice were crossed to Apoe−/− mice, animals lacking apoE had almost no fibrillar Aβ deposition, neuritic plaques, or CAA, and Apoe−/− mice had less than 50% as much Aβ-related pathology as Apoe+/+ mice (41–44). These results show that alterations in CNS apoE levels by as little as 50% have massive effects on AD-like pathology in the CNS. Since ABCA1 regulates both the level of apoE as well as its state of lipidation, modulation of ABCA1 levels or function is likely to directly influence apoE/Aβ interactions along
with Aβ deposition and its negative consequences in the brain. In addition to the effects of ABCA1 on apoE, recent studies also suggest that ABCA1 can influence cellular Aβ production (46–48). These effects are likely independent of apoE since alterations in ABCA1 expression levels affect Aβ in some cell types that do not express apoE. Several studies also suggest a direct link between ApoE polymorphisms and risk for AD (32, 49, 50).

In summary, we have shown that ABCA1 is required for normal CNS apoE levels as well as production of normally lipidated apoE-containing lipoproteins by astrocytes. Since apoE levels in the CNS profoundly influence AD and CAA pathology in vivo, modulation of ABCA1 function and levels may be a novel therapeutic target for AD, CAA, and other diseases of the CNS.

Acknowledgments—We thank Ravi Rajaram, Kirsten Jansen, Mike Spinner, Dr. Anne Cross, Dr. Anne Fagan, and Hua Cheng for technical assistance and helpful advice.

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J. Biol. Chem. 2004, 279:40987-40993.
doi: 10.1074/jbc.M407963200 originally published online July 21, 2004

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