ABCA7 is expressed in the brain and is present primarily in microglia and macrophages, and also neurons. GWAS studies indicate an association of ABCA7 with Alzheimer’s disease (AD); however, ABCA7 function in the AD context is unclear. In the present studies we focused on the function of ABCA7 in AD. Our data indicate that transient expression of ABCA7 in human embryonic kidney cells moderately stimulated [3H]cholesterol efflux (four-fold) to apolipoprotein E (apoE) discoidal lipid complexes (that resemble brain lipoproteins) but not to lipid-free apoE. As membrane lipid composition modulates amyloid precursor protein (APP) processing to form toxic Abeta peptides, we investigated the impact of ABCA7 on Abeta generation. Transient ABCA7 expression inhibited Abeta secretion (by 50%) from Chinese hamster ovary cells stably expressing human APP when compared with mock-transfected cells. To probe for a function of ABCA7 in vivo, we crossed ABCA7 null mice with J20 amyloidogenic AD mice. We found that ABCA7 loss doubled insoluble Abeta levels and amyloid plaques in the brain. This did not appear to be related to changes in APP processing (APP C-terminal fragment analysis). Interestingly, the capacity for bone marrow-derived macrophages derived from ABCA7 null mice to degrade Abeta was reduced by 51% compared with wild-type mice. Our results suggest ABCA7 plays a role in the regulation of Abeta homeostasis in the brain and that this may be related to Abeta phagocytic clearance.