ABSTRACT

Patients with Alzheimer's Disease (AD) exhibit substantial cerebrovascular damage, including the accumulation of β-amyloid (Aβ) peptides within the vessel wall. Mid-life vascular risk factors increase the risk of AD potentially via the loss of beneficial or gain of toxic functions in circulating high density lipoprotein (HDL). Low plasma levels of apolipoprotein A-I (apoA-I), the primary protein component of HDL, increase AD risk and correlate with cognitive decline, and preliminary preclinical evidence supports a role of apoA-I in mediating removal of cerebrovascular Aβ, suppressing neuroinflammation, and enhancing cognitive function. Our strategy was to perturb peripheral and central nervous system (CNS) apoA-I levels through genetic modification of proteins known to regulate apoA-I metabolism and via indirect and direct pharmacological manipulation of apoA-I to delineate its CNS transport, regulation and therapeutic potential in AD.

Loss of ATP binding cassette transporter A1 (ABCA1), which effluxes cholesterol onto lipid-poor apoA-I to generate immature pre-β-HDL, lead to significant parallel decreases of circulating and CNS apoA-I, while stimulation of ABCA1 activity with an Liver-X-Receptor (LXR) agonist substantially increased apoA-I levels selectively in the CNS, solubilized Aβ and improved cognitive function in AD mice. Although apoA-I was increased independent of ABCA1, ABCA1 was required to observe LXR-mediated cognitive benefits, suggesting lipidation of apolipoproteins is a critical regulator of their function. Pre-β-HDL appear to be the more biologically relevant species regarding CNS health, as loss of lecithin-cholesterol acetyl transferase (LCAT), which esterifies free cholesterol to generate mature α-HDL, does not impact AD pathology *in vivo*. Intravenously injected human apoA-I gains access to the CNS predominantly via the blood cerebrospinal fluid barrier, where it is bound, internalized, and transported by the epithelial cells of the choroid plexus in a specific receptor mediated fashion. Weekly injection of reconstituted HDL, formulated to enrich the pre-β pool, into symptomatic AD mice transiently decreased plasma Aβ levels but was unable to modulate brain Aβ, neuroinflammation, or endothelial activation in the experimental paradigm used. Collectively, these data identified ABCA1 generated apoA-I pre-β-HDL species as a key population of HDL subspecies for modulating AD pathology *in vivo*.