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APOE and Brain Lipid Metabolism in Aging and Alzheimer's Disease

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The apolipoprotein E (*APOE*) gene is the strongest genetic risk factor for Alzheimer's disease (AD), with the *APOE4* allele increasing the risk and the *APOE2* allele providing protection compared to the reference *APOE3* allele. Physiologically, the apoE protein functions as a lipid carrier, transporting cholesterol and other lipids in both the periphery and the brain by binding to cell surface apoE receptors. Using human *APOE* allele-specific targeted replacement mice, we found that apoE2 reduces cholesterol levels in the brain parenchyma but increases them in the cerebrospinal fluid. Both changes correlate with improved memory performance and longevity compared to apoE3 and apoE4. Increased lipid association and metabolism are also observed with the AD-protective variant *APOE3*-Jacksonville, which reduces apoE self-aggregation, thereby enhancing its function as a superior lipid acceptor. Using human induced pluripotent stem cell (iPSC)-derived cerebral organoid models, we found that apoE deficiency leads to the intracellular accumulation of lipids and α-synuclein, highlighting apoE's critical role in promoting lipid efflux to maintain cellular homeostasis. The impaired function of apoE4 in brain lipid metabolism is evident in multiple brain cell types, particularly microglia, where lipid accumulates as lipid droplets in both amyloid and demyelination mouse models. Collectively, our studies underscore the critical role of apoE in brain lipid metabolism, which is essential for brain health, and reveal isoform-specific effects that impact AD pathogenesis.