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Apolipoprotein E4 targets mitochondria and the mitochondria-associated membrane complex in neuropathology, including Alzheimer's disease

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Abstract

Apolipoprotein (apo) E4 sets the stage for neuropathology in Alzheimer's disease (AD) by causing mitochondrial dysfunction and altering mitochondria-associated membranes. Contact and apposition of mitochondrial-endoplasmic reticulum membranes are enhanced in brain cells in AD and associated with increases in tethering and spacing proteins that modulate many cellular processes. Contact site protein levels are higher in apoE4 cells. In apoE4 neurons, the NAD^+/NADH ratio is lowered, reactive oxygen species are increased, and NAD/NADH pathway components and redox proteins are decreased. Oxidative phosphorylation is impaired and reserve ATP generation capacity is lacking. ApoE4 neurons have ~50% fewer respiratory complex subunits (e.g., ATP synthase) and may increase translocase levels of the outer and inner mitochondrial membranes to facilitate delivery of nucleus-encoded complex subunits. Respiratory complex assembly relies on mitochondrial cristae organizing system subunits that are altered in apoE4 cells, and apoE4 increases mitochondrial proteases that control respiratory subunit composition for complex assembly.

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