Lipid Dysregulation in ALS: Mechanistic Insights and Pathways to Homeostasis

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Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder marked by progressive motor neuron loss, muscle atrophy, and systemic energy imbalance. To investigate the neurometabolic alterations underlying ALS, we performed untargeted quantitative metabolomic profiling of brain tissue from transgenic mice expressing ALS-linked FUS R521G and littermate controls. Mass spectrometry revealed significant elevations in multiple acylcarnitines, key intermediates in mitochondrial β-oxidation. Importantly, excessive accumulation of acylcarnitines is increasingly recognized as cytotoxic, contributing to mitochondrial dysfunction, oxidative stress, and inflammation. Complementary cytohistological analyses of hFUSR521G mouse brain revealed pronounced lipid droplet (LD) accumulation and elevated peroxidized lipid levels in both neurons and astrocytes—findings corroborated by post-mortem spinal cord samples from ALS patients harboring FUS R495X or K510E mutations. Treatment with arimoclomol, a compound shown to ameliorate ALS-associated phenotypes, significantly reduced LDs, acylcarnitines, and lipid peroxidation in hFUSR521G mice and in primary neurons and astrocytes expressing FUS R521G. Mechanistically, we show that arimoclomol enhances LD-mitochondrial contacts and promotes LD catabolism through mitochondrial β-oxidation. This effect is abrogated by etomoxir, an irreversible inhibitor of CPT1, the rate-limiting enzyme of the carnitine shuttle, highlighting a CPT1-dependent mechanism for lipid mobilization. Together, these findings reveal a previously unrecognized role for mitochondrial lipid metabolism in ALS pathogenesis and identify a therapeutic pathway for mitigating the cytotoxic consequences of lipid and acylcarnitine accumulation in FUS-associated ALS.

Sponsored By: This work was supported by Canadian Institute of Health (202309PJT-506236) and the ALS Canada-Brain Canada Discovery Grant

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