Metabolism as a target for ALS therapy

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Despite intense preclinical and clinical research over the last decades, Amyotrophic Lateral Sclerosis (ALS, a neurodegenerative disease characterized by the loss of upper and lower motor neurons) is still invariably fatal over a short period following diagnosis and thus any breakthrough in this area would clearly help to solve urgent unmet medical needs.

Mitochondrial damage and alterations of energy metabolism in motor neurons have been widely demonstrated in ALS patients and models. However, cell types within the nervous system distinct from motor neurons (e.g. astrocytes or microglial cells) or muscle cells have also been shown to participate in the disease progression, which is characterized by increased fuel metabolism and decreased fat stores in ALS patients and animal models. These changes are seen as a switch from glycolysis (use of glucose as the main energy source) to □-oxidation (use of lipids as main energy source). This change in fuel usage can in turn account for the hypermetablism (increased oxygen consumption required to produce the same amount of ATP from lipids than from glucose) observed in both patients and mice models. Furthermore, decreased ATP production and/or decreased glucose metabolism may underlie neuron hyperexcitability, selective degeneration of upper and lower motor neurons and muscle pathology.

Overall, these “loss of metabolic flexibility” may well represent a target for therapeutic intervention.