Lactate dehydrogenase inhibition in astrocytes reverts the neurotoxic phenotype induced by an excess of fatty acids.

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Astrocytes play a major role on lipid metabolism in the central nervous system. Due to their morphological and functional characteristics, astrocytes can uptake fatty acids (FAs) from the bloodstream and extracellular space and store them into lipid droplets (LDs). LDs in neuronal and glial cells can react dynamically, and LDs accumulation in astrocytes has been shown to occur upon exposure to various stress stimuli. Different hypotheses proposed to explain motor neuron degeneration in amyotrophic lateral sclerosis (ALS) implicate mitochondrial dysfunction and oxidative stress. Mitochondrial dysfunction in astrocytes is associated with elevation of cytoplasmic lipids and lipid-binding proteins. We observed an increase in LDs content in the spinal cord of symptomatic ALS mice, as well as, in human transdifferentiated astrocytes obtained from ALS patients. Using a co-culture model, we examined the effect of FAs overload in astrocyte-motor neuron interaction. Our data show that LDs accumulation promotes an NF-κB-driven pro-inflammatory response in non-transgenic astrocytes, that ultimately is detrimental to motor neuron survival. These results provide additional evidence to the notion that altered energy balance may contribute to neuronal death in ALS. Furthermore, we show that metabolic reprograming of astrocytes, through the inhibition of lactate dehydrogenase, reverts LDs accumulation in mouse and human astrocytes expressing ALS-linked mutations. Together, out data highlights the potential implications of lipid metabolism in astrocyte-neuron interaction in ALS pathology and suggest that rather than solely function as a protective mechanism to neighboring neurons, LDs accumulation acts as a stressor that can induce a phenotypic transformation in astrocytes.

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