Targeting Mitochondria in Duchenne Muscular Dystrophy

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Duchenne muscular dystrophy (DMD) is a rare genetic muscle disease that is characterized by severe wasting of muscle (known as atrophy), impaired mobility and death in males by early 20s. Mitochondria, commonly known as the power house of the cell, are dysfunctional and associated with muscle weakness in DMD. Currently there is no cure for DMD, so treating secondary impairments in the disease may improve quality of life and mobility. Olesoxime, a mitochondrial targeting drug, has shown benefits in other neurodegenerative diseases and thus the purpose of this study is to examine the effect of olesoxime in a mouse model of DMD. We hypothesize that olesoxime will improve mitochondrial function in DMD and improve disease pathology (i.e. muscle damage & force production). To assess this, male D2.mdx mice received a daily oral gavage of olesoxime or a vehicle control (corn oil) from 10 days of age to day 28. We also assessed healthy (wildtype) mice as a control. Olesoxime treatment improved mitochondrial respiration, or the ability of mitochondria to make ATP, compared to vehicle control in both the quadriceps and diaphragm muscles, but not to the extent of wildtype mice. Corresponding to this improvement, quadricep to bodyweight ratios, hindlimb muscle volume and whole-body lean volume (measured by microCT) were also improved. Olesoxime also improved the recovery from fatigue in the quadriceps but had no effect in the diaphragm. Serum creatine kinase, a marker of muscle damage, was lower with olesoxime treatment compared to the vehicle group. Olesoxime did not alter mitochondrial hydrogen peroxide (a reactive oxygen species) emission and mitochondrial-derived death pathways, measured by calcium retention capacity and caspase activity. Given these results, olesoxime improved some aspects of mitochondrial function, force and increased muscle mass. However, the mechanisms by which these improvements occur are unknown and will be examined in additional analyses. The results of this work highlight that olesoxime mildly improve muscle mass and function in D2.mdx mice and targeting mitochondria might be considered a therapeutic target in males with DMD.