Restoring mitochondrial creatine metabolism can partially improve muscle health in a mouse model of Duchenne Muscular dystrophy


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Duchenne muscular dystrophy (DMD) is a fatal disease characterized by muscle loss and weakness with no cure. Mitochondria have previously been shown to be dysfunctional in association with muscle weakness in DMD. We recently reported that mitochondrial creatine metabolism is impaired in the D2.mdx mouse model of DMD. This finding is important given mitochondrial creatine is important for providing energy to muscle cells and preventing increases in reactive oxygen species production. As such, rescuing this pathway might improve muscle health in DMD. We determined whether the mitochondrial-targeted drug Olesoxime (TRO19622) improves mitochondrial creatine-dependent bioenergetics and muscle health in D2.mdx mice. Male D2.mdx mice received a daily oral gavage of olesoxime (DRUG) (30mg/kg b.w.) or corn oil (VEH, vehicle) from days 10-28 of age. Age-matched wildtype (WT) animals served as healthy controls. The ability of creatine to stimulate ATP production in WT quadriceps (+37-62% across 100-500µM ADP) and diaphragm (+39-55%) was lost in VEH only for quadriceps but rescued by DRUG (+18-28%). Likewise, the ability of creatine to attenuate mitochondrial H2O2 emission in WT quadriceps (-30 to -38%) and diaphragm (-33 to -34%) was lost in VEH but was rescued by DRUG in quadriceps (-42 to -43%) and diaphragm (-23 to -26%). These improvements in creatine metabolism were related to significantly lower serum creatine kinase (-58%, DRUG vs VEH; muscle damage marker), longer cage hang time (+53%), and small increases in whole body lean volume (+3.0%) and hindlimb muscle volume (+6.5%) as assessed by microCT. Decreases in grip strength, voluntary wheel running distance, maximal force or recovery from fatigue in quadriceps (in situ) and diaphragm (in vitro) observed in VEH vs WT were not altered by DRUG. In summary, short-term treatment with olesoxime rescued mitochondrial creatine metabolism which was related to early partial improvements in some indices of muscle health in D2.mdx mice.