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Unraveling the evolutionary marathon: improved mitochondrial bioenergetics in CMP-Neu5Ac hydroxylase gene deleted (Cmah-/-) mouse skeletal myofibers.

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Text:

Objective: Humans are unique among hominids in that they are endurance athletes. Inactivation of the CMP-Neu5Ac hydroxylase (CMAH) gene, which encodes a hydroxylase converting sialic acid Neu5Ac to Neu5Gc, is thought to contribute to this exceptional capacity for endurance running. Recently, our group demonstrated improved fatigue resistance and preserved intracellular O_2, estimated by NAD(P)H levels in contracting mouse Cmah-/- flexor digitorum brevis (FDB) single fibers under low oxygen tension. Hypothesis: Efficient regulation of mitochondrial oxygen consumption contributes to improved skeletal myofiber fatigue resistance in Cmah-/- mice. Methods: The mitochondrial bioenergetic potential of permeabilized FDB and soleus fiber bundles from wild type (WT) and Cmah-/- mice was evaluated using a physiological creatine kinase clamp method and high-resolution respirometer. Experiments were conducted with pyruvate and malate with or without branched chain amino acids (BCAAs) as the substrates. Respiratory chain conductance and maximal respiration were measured. Results: FDB Cmah-/- fibers from male but not female mice revealed an increase conductance above WT fibers independent of substrate (male: genotype, p=0.006, substrate, ns; female: genotype, ns, substrate, ns). Maximal respiration was also increased only in male FDBs fibers and was even greater when BCAAs were included in the respiration media. (male: genotype, p=0.003, substrate, p=0.0007, interaction, p=0.002.; female: genotype, ns, substrate, ns). Soleus Cmah-/- fibers from male and female mice revealed an increase conductance above WT fiber bundles that was also greater in the presence of BCAAs but only for male mice (male: genotype, p=0.003, substrate, p=0.05.; female: genotype, p=0.009, substrate, ns). Maximal respiration was increased only in male Cmah-/- soleus fibers independent of substrate. (male: genotype, p=0.002, substrate, ns.; female: genotype, ns, substrate, ns). Summary: Fibers from both the FDB and soleus of male Cmah-/- mice have a greater capacity for mitochondrial respiration under a metabolically active state that is similar to myofibers stimulated to repeatedly contraction in a hypoxic environment. Conclusion: These data suggest that efficient regulation of mitochondrial respiration utilizing BCAAs as a substrate, particularly in males, could contribute to an elite endurance phenotype.

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