Mitochondrial Aging in Human Muscle in Vivo: Causes, Prevention, and Reversibility

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Our goal is to evaluate the cellular factors leading to mitochondrial dysfunction with age, how life-long physical activity can prevent loss of mitochondrial function and whether endurance training in elderly human muscle can reverse age-related dysfunction. The mitochondrial theory of aging proposes that reactive oxygen species (ROS) cause damage that generates defects in oxidative phosphorylation. Our new data point to substantial mitochondrial dysfunction with age – reduced mitochondrial capacity, uncoupling of ATP supply from O_2 uptake, and loss of cellular ATP – in human muscle in elderly subjects. To evaluate the cellular factors leading to this dysfunction, we use new optical and magnetic resonance spectroscopic methods to non-invasively measure ATP synthesis and O_2 uptake in vivo. Parallel analysis of muscle biopsies allows us to determine the cellular basis of the defects in mitochondrial oxidative phosphorylation. We make these measurements in human subjects from a range of ages and in muscles differing in susceptibility to age-related dysfunction based on fiber type content. A new series of experiments will focus on senior athletes to determine whether chronic endurance activity preserves mitochondrial function. These athletes allow us to test whether chronic activity into old age preserves mitochondrial function. We are also investigating the reversibility of mitochondrial dysfunction. Endurance training of elderly subjects is used to induce muscle adaptations to test for reduction in age-related cellular damage and improvement in mitochondrial function. The clinical implication of this research is the development of a non-invasive measurement that is diagnostic of mitochondrial dysfunction. Such an in vivo measurement would permit targeting interventions to individuals with the most affected muscles to reverse the functional loss that is a leading cause of disability in the elderly.