Evidence of Muscle Mitochondrial Dysfunction in Type 1 Diabetic Patients

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Results: Skeletal muscle mitochondrial dysfunction occurs in insulin resistant states such as in type 2 diabetes, obesity and aging. Mitochondrial dysfunction has been proposed as the cause of insulin resistance. Insulin has been shown to enhance muscle mitochondrial biogenesis and therefore we determined whether insulin deficiency causes muscle mitochondrial dysfunction. We investigated 7 type 1 diabetic patients (T1D) (age= 27.1±2.5 yr, BMI=24.8±0.79 kg/m^2) during insulin deprivation (I-) and during insulin replacement (I+). Muscle biopsies from the vastus lateralis were obtained from T1D patients following 8-12 hours of insulin withdrawal (plasma glucose=289±14mg/dl) and while maintained on insulin replacement (plasma glucose= 98±3mg/dl). Indirect calorimetry showed resting VO_2 was higher during I- (325±24 ml/min) than I+ (267±11 ml/min, $p<0.01$), as was resting VCO_2 (237±21 ml/min in I- vs 208±14 ml/min in I+, $p=0.03$). The respiratory quotient, however, was lower during I- (0.73±0.02) than during I+ (0.78±0.03, $p=0.04$), indicating an accelerated fuel oxidation during I-. In contrast to higher oxygen consumption, muscle mitochondrial ATP production rate (MAPR), measured with a bioluminescent assay from muscle biopsy samples, was lower during I- (using glutamate+malate as substrate:10.6±1.3 µmol/min/g in I+ vs 7.8±1.1 µmol/min/g in I-, $p=0.008$, with similar 20-25% differences confirmed by 5 other substrates) than during I+. It is demonstrated that insulin deprivation in T1D patients results in an increased O_2 consumption but reduced muscle ATP production rate. These findings indicate an uncoupling of oxidative phosphorylation and fuel oxidation causing energy wasting. We conclude that muscle mitochondrial dysfunction results from of lack of insulin action on muscle, thus supporting that reduced insulin action in insulin resistant states causes muscle mitochondrial dysfunction.