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Skeletal muscle gene transcript changes in type 1 diabetic patients following insulin deprivation

Helen Karakelides , Yan Asmann , Maureen Bigelow , Kevin R Short , Ketan Dhatariya and K. Sreekumaran Nair

Endocrinology, Metabolism, Diabetes and Nutrition, Mayo Clinic, 200 1st ST SW, Mayo, W-18, Rochester, MN, 55905

ABSTRACT

Insulin resistance is associated with skeletal muscle mitochondrial (mito) dysfunction in many conditions including type 2 diabetes (T2D). Poor glycemic control in T2D is associated with muscle mito gene transcript alterations. It is unknown whether muscle mito changes are related to reduced insulin action or vice versa. We obtained vastus lateralis muscle biopsies from 7 type 1 diabetic patients (T1D) following 8-12 hrs of insulin deprivation (I-) and replacement (I+) and measured skeletal muscle mito ATP production (MATP) and gene transcripts. I- and I+ changed glucose and glucagon levels (glucose=291±15mg/dl in I- vs 97±3 in I+ and glucagon=79.8±15.3 pg/mL in I- vs 47.3±5.9 in I+, $p<0.04$). Whole body O_2 consumption increased during I- by 15% ($p<0.05$) but maximal MATP decreased by 21.3-27.9% ($p<0.05$). Gene transcript profiling in skeletal muscle analyzed using Affymetrix GeneChip arrays showed alterations in 2355 transcripts. Pathway analysis showed down-regulation of oxidative phosphorylation and arachidonic acid metabolism, and up-regulation of VEGF and actin cytoskeleton signaling in I-. We conclude that the reduced insulin action that occurred during I- in T1D resulted in substantial changes in gene transcript levels of muscle mito genes and reduced maximal MATP, supporting that insulin is key regulator of muscle mito function by exerting its effect at various levels