Muscle response to insulin is impaired in diabetic humans, in association with a defect in signaling pathway

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Purpose: Aging is associated with decrements in insulin sensitivity and increased incidence of Type 2 Diabetes. The exacerbation of insulin resistance involves defects in skeletal muscle which accounts for the bulk of insulin-mediated glucose uptake. Aging is also associated with a diminution in the size and strength of skeletal muscle. However, in understanding the pathogenesis of these processes little is known at the molecular level regarding interactions between insulin resistances and declining muscle performance. To determine whether there was a relationship between insulin resistance and regulation of genes involved in muscle contraction, we studied human skeletal muscle biopsies from 20 insulin sensitive individuals, 20 insulin resistance individuals, and 17 diabetic individuals, obtained before (basal) and during euglycemic insulin clamps (insulin-stimulated).

Methods and Results: Gene expression was assessed using the Affymetrix Hu95A-E microarrays to identify alterations in gene expression in response to insulin stimulation among these subgroups. In insulin sensitive individuals, we have identified 827 insulin responsive genes (at \( p < 0.01 \) and true positive rate >80%) with 371 being up-regulated and 456 down-regulated when compared before and after insulin stimulation. Microarray data were validated using reverse transcription quantitative PCR. Bioinformatics analyses using Gene Ontology software identified genes involved in muscle development (criteria = 21 genes regulated out of 74 total; at \( p < 0.001 \), myoblast differentiation (criteria = 2 genes regulated out of 3 total; at \( p < 0.001 \), and striated muscle contraction (criteria = 5 genes regulated out of 15 total; at \( p < 0.001 \) as the most pronounced functional class of genes regulated by insulin. Unexpectedly, almost all genes were down-regulated (with the notable exception of MyoG up-regulation); indicating that acute insulin stimulation is directing the muscle towards substrate metabolism and de-emphasizing contractile function. However, in insulin resistant and diabetic subgroups, 30 muscle-related genes among 86 lost the down-regulated response to acute insulin stimulation. These genes included: myosin heavy polypeptide 7, myosin heavy polypeptide 2, myosin light polypeptide 1, myosin binding protein C, myosin light polypeptide 3, troponin T3, troponin T, tropomyosin 2, mitogen-activated protein kinase 12, muscle blind-like, calpain 3, interferon-related developmental regulator 1, integrin alpha 7, actin alpha 1 and actin beta. Similarly, insulin upregulation of MyoG was abrogated in the insulin resistant and diabetic subgroups.

Conclusions: Insulin resistance and Type 2 diabetes are associated with dysregulation of an extensive number of genes involved in muscle development and contraction. This strongly suggests that insulin resistance of aging could contribute to impaired muscle...
performance in aging. The specific functional impact of altered gene expression on muscle performance will require further study.

**Research Area:** Basic biology of aging  
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