Human sarcopenia reveals an increase in SOCS-3 and myostatin and a reduced efficiency of Akt phosphorylation

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Introduction. Sarcopenia is the general term for a reduction in muscle quality and function due to aging. This can be seen by an increase in muscle atrophy, often in type II fibres, which is related to the reduction of maximal voluntary strength. Sarcopenia has an important socio-economic consequence as falls are a major source of morbidity and mortality in the increasing population of the elderly. Findings in the literature have prompted us to hypothesise that human sarcopenia may be linked to increased levels of in TNFα and SOCS3; the latter causing perturbations in GH signalling and increasing myostatin. Consequently, this would result in a reduced phosphorylation and activation of Akt signalling and therefore inhibit and activate respectively, muscle hypertrophy and atrophy signalling cascades. The aims of the present study were to determine if age-related sarcopenia in humans was linked with perturbations in TNFα, SOCS3, GH, STAT5 and IGF levels as well decreases in the Akt/GSK/mTOR and increases in the Akt/FKHR/atrogene signalling pathways.

Methods. This study investigated the regulation of several genes and proteins involved in the activation of key signaling pathways promoting muscle hypertrophy including GH/STAT5, IGF-1/Akt/GSK-3β/4E-BP1 and muscle atrophy including TNFα/SOCS3 and Akt/FKHR/atrogene, in muscle biopsies from 13 young (20 ± 0.2 years) and 16 older (age, 70 ± 0.3 years) males.

Results. In the older, when compared with the young subjects, muscle fibre cross sectional area was reduced by 40-45% in the type II muscle fibres. TNFα and SOCS-3 were increased by 2.8 and 1.5 fold respectively. Growth hormone receptor protein (GHR) and IGF-1 mRNA were decreased by 45%. Total Akt, but not phosphorylated Akt, was increased by 2.5 fold. This corresponded to a 30% reduction in the efficiency of Akt phosphorylation in the older subjects. Phosphorylated and total GSK-3β was increased by 1.5 and 1.8-fold respectively, while 4E-BP1 levels were not changed. Nuclear FKHR and FKHRL1 were decreased by 73 and 50%, with no changes in their atrophy target genes, atrogin-1 and MuRF1. Myostatin mRNA and protein levels were significantly elevated by 2 and 1.4 fold.

Conclusion. This is the first study to compare the regulation of several key signalling pathways, known to control skeletal muscle hypertrophy, including GH/STAT5, IGF-1/Akt/GSK/4E-BP1, and skeletal muscle atrophy, including TNFα/SOCS3 and Akt/FKHR/atrogene, in muscle biopsies from young and old men. It appears that human sarcopenia is associated with an increase in TNFα and SOCS-3 which may result in a reduction of GHR levels or sensitivity. The significant increase in total Akt protein content, but not in Akt phosphorylation, in muscle from the older subjects, suggests an inefficiency in Akt activation and by analogy reduced protein synthesis. The observed increase in myostatin mRNA and protein levels in the older subjects, combined with recent observations in cardiac and rodents cells (refs), suggest that myostatin is a prime candidate inhibiting Akt phosphorylation in the elderly. Establishing if this is the case should be a priority for future investigations aimed at reducing human sarcopenia.

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