Anabolic signaling deficits underlie amino acid resistance of wasting, aging muscle

Daniel Cuthbertson,*,† Kenneth Smith,*,§ John Babraj,*, Graham Leese,† Tom Waddell,*, Philip Atherton,*,‡ Henning Wackerhage,*, Peter M Taylor,* and Michael J Rennie*,§,1

*Division of Molecular Physiology, School of Life Sciences, University of Dundee, Dundee, Scotland; †Department of Medicine, Ninewells Hospital and Medical School, Tayside NHS Trust, Dundee, Scotland; ‡Department of Biological Sciences, University of Central Lancashire, Preston, UK; §University of Nottingham, School of Biomedical Sciences, Division of Clinical Physiology, Graduate Entry Medical School, City Hospital, Derby, UK

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SPECIFIC AIMS

Healthy aging is associated with wasting of skeletal muscle of unknown cause. We hypothesized that, for lack of good evidence of derangements of muscle protein turnover in the basal, post-absorptive state, the deficit in the muscle maintenance must lie elsewhere, possibly in a diminished response to amino acids, the most anabolically potent of nutrients. We aimed to test this by measuring the responses to mixed oral essential amino acids (EAA) of 1) skeletal muscle protein synthesis (MPS) and 2) components of anabolic signaling pathways in healthy young and elderly men.

PRINCIPAL FINDINGS

We studied 44 young and elderly men (means±sd, respectively: age, 28±1, 70±1 y; body mass index, (BMI), 24±3, 26±4 kg.m⁻²; skeletal muscle mass, 33±4, 28±4 kg, P<0.01). We measured the fractional synthetic rates (FSR) of protein in their m. vastus lateralis as the rate of incorporation of [13C] leucine from a primed, constant infusion of [1-13C]a-ketoisocaproic acid, over 3 h after they drank solutions of 0–40 g of mixed essential amino acids (EAA) to obtain dose-response relationships, while clamping plasma insulin and glucose at basal concentrations. Muscle biopsies were taken before and 3 h after EAA.

1. Rates of muscle protein synthesis

Basal rates (MPS) were indistinguishable between the young and elderly (myofibrillar FSR, 0.030±0.005%,h⁻¹, sarcoplasmic FSR, 0.055±0.007%,h⁻¹, grand means±sd) but the elderly showed decrements in the anabolic sensitivity of MPS to EAA (Fig. 1), which occurred in both groups without any increase in insulin as a result of the clamp. On relating rates of MPS to the plasma availability (i.e., the area under the time curve of its concentration) rather than the dose of leucine, (the possibly regulatory EAA), the differences were magnified (P<0.001).

2. Protein synthetic capacity

Both RNA: Protein ratio and the ratio of MPS to RNA after ingestion of 10 g of EAA (P<0.001), were less in the elderly, suggesting both reduced capacity and efficiency of MPS.

3. Signaling capacity and activation by EAA and index of inflammation

The concentrations and degree of activation (phosphorylation state) of components of the amino acid sensing/signaling anabolic pathways (mTOR, p70S6 kinase, eIF4BP-1) were significantly less (~30 to 50%, P<0.01) in the elderly (Fig. 2). The concentration of NF-κB, a transcription factor associated with inflammation, was 4-fold greater (P<0.01).

CONCLUSIONS AND SIGNIFICANCE

These results demonstrate 1) EAA stimulate MPS independent of an increase in insulin availability; 2) in the elderly, a deficit in MPS in the basal state is unlikely; and 3) the decreased sensitivity and responsiveness of MPS to EAA, associated with decrements in the concentrations and excitability of components of anabolic signaling pathways, are probably major contributors to the failure of muscle maintenance in the elderly, possibly following an increased inflammatory state. These findings provide an explanation

1 Correspondence: University of Nottingham, School of Biomedical Sciences, Division of Clinical Physiology, Graduate Entry Medical School, City Hospital, Derby DE22 3DT, UK. E-mail: michael.rennie@nottingham.ac.uk
Figure 1. Relationships in healthy men and elderly men between rates of A) myofibrillar and B) sarcoplasmic protein synthesis in vastus lateralis (determined on the basis of intracellular leucine labeling and time profile of leucine) and dose of essential amino acids (EAA) given orally; and relationships between increase of C) myofibrillar and D) sarcoplasmic protein synthesis above baseline against increase of AUC of plasma leucine above baseline (Δ AUC); (values are means±se; *P<0.05, **P<0.005).

Figure 2. Quantification after Western analysis of components of anabolic signaling pathways in muscle from young vs. elderly and effects of 10 g EAA on their phosphorylation; (means±sd; *different from basal). Differences after EAA are significantly different between young and old (P<0.05).

Figure 3. The effect of aging on human muscle maintenance and development of sarcopenia.
for the apparent paradox of ongoing sarcopenia in individuals in whom no apparent deficit of muscle protein synthesis or breakdown could be discerned in the postabsorptive basal state. There is no likely benefit to elderly people of simply increasing daily protein intake (because of their decreased anabolic capacity); nevertheless, a good case exists for consuming foods with a high protein:energy ratio, with most dietary protein being taken during a main meal (ideally after vigorous exercise) to maximize availability in the sensitive range of EAA concentration.