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## Blunting of insulin-mediated proteolysis in leg muscle of elderly subjects may contribute to age-related sarcopenia

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Sarcopenia is common in the elderly, with a loss of muscle mass of 0.5–2%/year after 50 years of age<sup>(1)</sup>. However, although the mechanisms must involve some disturbance of the normal processes of maintenance of muscle protein, available data suggest that basal post-absorptive muscle protein synthesis (MPS) is not decreased and muscle protein breakdown (MPB) not elevated. However, it has been shown previously that the response of MPS to essential amino acids is less sensitive and of lower capacity in elderly men (approximately 70 years of age) than in young men (approximately 25 years of age). Now the hypothesis has been tested that the normal insulin-mediated blunting of MPB, which accompanies feeding, is blunted in elderly subjects compared with younger subjects. Five young subjects (three men, two women, age 19–33 years, BMI 24 kg/m<sup>2</sup>) and eight elderly subjects (four men, four women, age 61–72 years, BMI 26 kg/m<sup>2</sup>) were studied in the post-absorptive state. Cannulas were inserted to allow sampling of arterialised hand blood and femoral venous blood and infusion of [1,2-<sup>13</sup>C]leucine and [<sup>2</sup>H<sub>5</sub>]phenylalanine (0.75 mg/kg prime, 1.0 mg/kg per h and 0.3 mg/kg prime, 0.6 mg/kg per h respectively). Blood flow in the femoral artery was measured by Doppler ultrasound. Insulin and octreotide were infused to achieve plasma insulin concentrations at approximately 4 mU/l and approximately 15 mU/l respectively, each for 1.5 h. Glucose was infused to maintain euglycaemia (approximately 5 mM) together with sufficient mixed amino acids (AA; Glamin; Fresenius, Runcorn, Cheshire, UK) to allow maintenance of the post-absorptive plasma AA concentration. Leg exchange of leucine, phenylalanine and unlabelled AA were measured using GC-MS and ion-exchange chromatography at both insulin concentrations. In all subjects the post-absorptive state was characterized by a net efflux of AA, as a result of the predominance of MPB over MPS. In the young subjects infusion of insulin to approximately 15 mU/l reduced MPB by approximately 60% from 296 (SD 47) nmol leucine/100 ml leg per min ( $P < 0.01$ ) and by approximately 52% from 97.5 (SD 14.2) nmol phenylalanine/100 ml leg per min. However, in the elderly this effect was markedly blunted, the suppression from 153 (SD 30) nmol leucine/100 ml leg per min and 70.2 (SD 11.6) nmol phenylalanine/100 ml leg per min not reaching statistical significance in either case. Thus, it appears that insulin-induced suppression of MPB is blunted in the elderly, which may contribute to the progressive inability of older individuals to maintain their muscle mass.

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2. Cuthbertson D, Smith K, Babraj J, Leese G, Waddell T, Atherton P, Wackerhage H, Taylor PM & Rennie MJ (2005) *FASEB J* **19**, 422–424 (Epublication 13 Dec 2004).