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Randomized control trials

Enhanced anabolic response to milk protein sip feeding in elderly subjects with COPD is associated with a reduced splanchnic extraction of multiple amino acids☆

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SUMMARY

Background & aims: We previously observed in elderly subjects with Chronic Obstructive Pulmonary Disease (COPD) an enhanced anabolic response to milk protein sip feeding, associated with reduced splanchnic extraction (SPE) of phenylalanine. Milk proteins are known for their high Branched-chain Amino Acids (BCAA) content, but no information is present about splanchnic extraction and metabolism of the individual BCAA in COPD.
Objective: To investigate whether BCAA metabolism and SPE of the individual BCAA are altered in COPD during milk protein sip feeding.
Design: In elderly subjects with COPD and in healthy age-matched elderly SPE, endogenous rate of appearance (Raendo) of the leucine (LEU), isoleucine (ILE) and valine (VAL) were measured before and during sip feeding of a Whey protein meal. To study the effect of aging, the healthy elderly were compared to a group of healthy young subjects. Stable isotopes of L-[$^2H_3$]-LEU, L-[1-^{13}C]-ILE and L-[1-^{13}C]-VAL were given on two separate test days orally or intravenously. Simultaneously, L-[ring-$^2H_5$]-phenylalanine (PHE) and L-[ring-$^2H_2$]-tyrosine (TYR) were given to determine the whole body protein breakdown (WbPB), synthesis (WbPS) and NetPS.
Results: SPE of all BCAA, TYR, and PHE ($p < 0.01$) were lower in the COPD group, and the increase in netPS during feeding was higher in the COPD group ($P < 0.01$) due to higher values for PS ($P < 0.001$). Raendo of all BCAA, PHE and TYR were higher in the COPD than the healthy elderly group ($P < 0.05$) before and during feeding ($P < 0.001$). Sip feeding resulted in a reduction of Raendo of PHE, ILE and VAL ($P < 0.05$). Postabsorptive Raendo was not different for any of the measured amino acids between the healthy elderly and young group, while sip feeding resulted in a reduction of Raendo of PHE. Only SPE of TYR was higher in the elderly ($P < 0.05$) and the increase in netPS during sip feeding was independent of aging.
Conclusion: The enhanced anabolic response to milk protein sip feeding in normal-weight COPD patients is associated with a reduced splanchnic extraction of multiple amino acids including all branched-chain amino acids.
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1. Introduction

Milk proteins (casein and whey) have been used as therapeutic modality to conserve muscle mass in chronic wasting diseases such as Chronic Obstructive Pulmonary Disease (COPD). Milk proteins are known for their high branched-chain amino acids (BCAA) content, which include leucine (LEU), isoleucine (ILE) and valine (VAL). BCAA are playing critical roles in protein structure, metabolism and regulation.[1] Furthermore, there is evidence that BCAA can improve respiratory function in neonates[2] and attenuate ratings of perceived exertion during exercise.[3]

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BCAA are essential amino acids. We previously observed in patients with COPD an elevated anabolic response to sip feeding of a casein protein meal.[4] Moreover, we found that adding free BCAAs to a BCAA-low soy protein sip meal was able to enhance anabolism in COPD patients, but not in healthy elderly.[5] We realize that sip feeding is a model of continuous enteral feeding in contrast to bolus meals as practiced by patients in daily life. On the other hand, sip feeding excludes modifying effects of differences in absorption kinetics between proteins. Therefore, sip feeding gives important insight whether differences in the amino acid composition of the protein play a role to its anabolic capacity in COPD. In both studies with sip feeding,[4,5] a reduced splanchnic extraction (SPE) of the essential amino acid phenylalanine was observed in the COPD group. Moreover, the COPD patients were characterized by higher values for phenylalanine turnover, suggesting that alterations in splanchnic extraction and metabolism of phenylalanine might play a role in the mechanism in which anabolism was stimulated in COPD. Whether the reduced SPE in COPD during protein feeding specifically involves PHE or also other amino acids including the BCAA is not known.

Patients with COPD with a deprived nutritional state are often characterized by reduced plasma BCAA levels in the postabsorptive state[6,7] without significantly elevated leucine turnover levels.[8] Low plasma BCAA levels in COPD are associated with disturbances in muscle energy metabolism during exercise,[9] suggesting that preservation of BCAA levels is of importance in COPD. In contrast, COPD patients with preserved body weight have increased leucine turnover[8] and preserved plasma leucine levels.[6] These data suggest that a reduced splanchnic BCAA extraction from a meal might be an adaptive mechanism to preserve the plasma BCAA levels in normal weight COPD. It is unclear whether there is a discrepancy in turnover rate and splanchnic extraction between the individual BCAAs in response to feeding in COPD patients and healthy subjects. As different extraction patterns of the individual BCAAs during milk protein feeding will result in modified delivery of BCAAs to muscle, this information might be important to determine the optimal composition of the individual BCAAs in milk protein to optimize anabolism in COPD.

Therefore, in the present study, we examined whole body turnover and splanchnic extraction of the individual BCAAs; LEU, VAL and ILE in the postabsorptive state and during whey sip feeding using stable isotope methodology. In addition, whole body protein breakdown and (net) protein synthesis rate were studied to determine the anabolic response to whey protein sip feeding in COPD. In this way we were able to compare these data with the previously obtained data using casein and soy protein, taking into account differences in absorption kinetics. As COPD commonly occurs in the elderly, normal-weight COPD patients and a healthy elderly age-matched control group were studied to carefully examine the effects of the disease on protein and BCAA metabolism without a potential direct effect of a deprived nutritional state. Besides a group of healthy elderly, also a group of young individuals were studied to investigate the direct effect of aging.

2. Subjects and methods

2.1. Subjects

A group of eight patients with moderate airflow obstruction (FEV_1: 50 ± 4% of predicted), 8 healthy elderly (age-matched) volunteers, and 8 healthy young subjects, all men, were studied. The patients were in clinically stable condition and suffered from moderate COPD (stage 2 + 3) according to the established GOLD guidelines.[10] The patients were outpatients, attending the hospital for routine pulmonary control every 6 or 12 months. Exclusion criteria for all groups were malignancy, cardiac failure, recent surgery, and endocrine, hepatic or renal disorders. Also, subjects who were using systemic corticosteroids within 3 months before the study were excluded. Maintenance treatment of the studied COPD patients consisted of inhaled β_2-agonists, inhaled anticholinergics, inhaled corticosteroids, oral theophylline, or a combination. 25% and 62% of the COPD patients and healthy elderly controls were present vs. former smokers resp. 37% of the healthy young subjects were current smokers. Written informed consent was obtained from all subjects and the study was approved by the medical ethics committee of the University Hospital Maastricht.

2.2. Pulmonary function tests

Before the study, the healthy elderly and COPD patients underwent spirometry for determination of forced expiratory volume in 1 s (FEV_1), as a marker of disease severity, with the highest value from at least 3 technically acceptable maneuvers being used. The diffusion capacity for carbon-monoxide (DLCO) as an indirect indicator of emphysema was measured using the single-breath method (Masterlab; Jaeger; Würzburg, Germany). All values obtained were related to a reference value and expressed as percentages of the predicted value.[11] The COPD patients had lower values for FEV_1 (COPD vs. healthy elderly patients: 50 ± 4%pred vs. 110 ± 5%pred, $P < 0.01$) and DLCO (COPD vs. healthy elderly: 78 ± 7%pred vs. 104 ± 9%pred, $P < 0.05$).

2.3. Study design

On 2 test days which were at least 3 days apart, subjects came to the metabolic ward of the University Hospital Maastricht after an overnight fast. All subjects were instructed to continue their habitual dietary intake for at least 3 days preceding the study.

2.4. Body composition measurements

Body weight was measured using an electronic beam scale with digital readout to the nearest 0.1 kg (model 708; Seca) with the subjects standing barefoot and wearing light indoor clothing. Body height was measured to the nearest 0.1 cm (model 220, Seca). Whole-body fat-free mass (FFM) was measured in each subject using bioelectrical impedance analyses (Xitron 4000B, Xitron Technologies) to express metabolic data per kilogram of FFM. FFM was calculated using a specific regression equation described by Dey et al.[12]

2.5. Study protocol

The protocol started at 07:15 AM, after an overnight fast from 00:00 AM. All subjects were in supine position for 3.5 h. On the 1st test day, a catheter was placed in an antecubital vein of the arm for infusion of the tracer (85 mL/h), according to a primed constant continuous infusion protocol. Primed and constant infusion of the stable isotopes L-[ring-$^2H_5$]-Phenylalanine (PHE; $^2H_5$-phe; prime: 2.19 μmol/kg bw, infusion: 2.26 μmol/kg bw/h), L-[ring-$^2H_2$]-Tyrosine (TYR; $^2H_2$-tyr; prime: 0.31 μmol/kg bw, infusion: 0.77 μmol/kg bw/h), L-[5,5,5,-$^2H_3$]-Leucine (LEU; $^2H_3$-leu; prime: 2.19 μmol/kg bw, infusion: 2.4 μmol/kg bw/h, L-[1-^{13}C]-Isoleucine (ILE; ^{13}C-ile; prime: 0.61 μmol/kg bw, infusion: 1.26 μmol/kg bw/h) and L-[1-^{13}C]-Valine (VAL; ^{13}C-val; prime: 8.85 μmol/kg bw, infusion: 8.85 μmol/kg bw/h) were infused IV via the antecubital vein catheter to be able to measure and compare whole body rate of appearance of PHE, TYR, LEU, ILE and LEU. In addition, a prime was given of L-[ring-$^2H_4$]-TYR, (prime: 0.31 μmol/kg bw). The stable isotopes were purchased from Cambridge Isotopic Laboratories