Enhanced De Novo Arginine Synthesis And Protein Turnover In Pediatric Cystic Fibrosis Patients With Nutritional Failure

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RATIONALE: Nitric oxide (NO) deficiency and muscle wasting commonly occurs in Cystic Fibrosis (CF), negatively influencing outcome. Besides an amino acid substrate for protein synthesis, arginine (ARG) is a precursor for NO synthesis, which plays an important role in inflammatory conditions such as CF. As plasma arginine levels are still preserved in stable CF patients, we propose that an upregulated de novo arginine synthesis (from Citrulline (CIT) via conversion of glutamine) is present in clinically stable CF patients to meet the increased demand for Arginine and NO production. We hypothesize that in CF this is related to enhanced protein wasting for provision of CIT precursors, predominantly in those with nutritional failure.
METHODS: We examined in 15 pediatric patients with CF (FEV1: 86 ± 32 % pred, age: 15.8 ± 4.2 y) and 16 healthy young controls, whole body protein synthesis (PS) and breakdown (PB), and net PB (=PB-PS) by the combined infusion of the stable isotopes L-[ring-2H5]phenylalanine and L-[ring-2H2]tyrosine. Arginine and Citrulline turnover were assessed by simultaneous infusion of L-[guanidine-15N2]arginine and L-[ureido-15N-2H2]citrulline; de novo ARG production and NO synthesis were calculated. In arterialized-venous plasma, the isotope enrichment values and amino acid concentrations were measured by LC-MS. Fat-free mass was assessed using Dual-energy X-ray absorptiometry. Presence of nutritional failure in the CF group was defined according to the criteria: BMIp ≤ 10 and/or FFMIp ≤ 5. Statistics was done using ANOVA.
RESULTS: An increased whole body CIT turnover, de novo ARG synthesis and ARG clearance was found in CF patients with nutritional failure (n=7) as compared to the CF patients without nutritional failure and the healthy control subjects ($p<0.05$). Concomitantly, elevated values for whole body PS and PB were present in CF patients ($p<0.001$ vs. healthy controls), with the highest values being present in the group with nutritional failure. In contrast, plasma ARG concentration, NO synthesis and net PB were not different between the groups ($p>0.05$).
CONCLUSIONS: Nutritional failure in CF is associated with elevated whole body CIT production and protein turnover possibly to adapt for the enhanced de novo ARG production in order to maintain NO synthesis. This suggests increased arginine and protein requirements in CF with nutritional failure.
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