Severe Protein Restriction Activates Liver Protein Catabolism and ATF4-CHOP-TRB3 Pathway to Comprensate for Amino Acid Deficiency

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Objectives: Severely low-protein diets (LP) induce behavioral and metabolic changes including a decrease in body weight, an increase in relative food intake (FI) and alterations in hepatic metabolism. During such protein restriction, changes in hepatic anabolic and catabolic protein pathways could transitory participate to compensate for amino acid (AA) deficiency. In the present study, liver expression of gene involved in proteosynthesis and proteolysis pathways, were related to FI, blood AA levels and body composition in rats fed LP diet.

Methods: Growing rats were fed for three weeks different diets containing 3-5-8-12-15 or 20% energy of milk protein. Body weight and FI were measured daily. At the end of the experiment, tissues and biological fluids were removed for gene expression measurement and blood AA UPLC analysis. Statistical analysis was done by 1- or 2-factor ANOVA, when data were repeated.

Results: Despite an increase in relative food intake under P3 and P5% diets, P3, P5 and P8% diets resulted in significant growth retardation compared to other groups. Lean mass was significantly decreased in rats under P3, P5 and P8% compared to P12, P15 and P20% diets, while there was no difference in fat mass between all groups. P3, P5 and P8% diets induced a decrease in essential amino acid concentrations in portal vein, whereas there was no significant difference between groups in veina cava. Severely protein restricted P3% and P5% diets induced an increase in hepatic gene expression involved in proteolysis as calpain 2 and ubiquitin, and an activation of ATF4-CHOP-TRB3 pathway.

Conclusions: These results suggested that under severe protein restriction, hepatic protein catabolism became a source of plasma amino acid that could partially compensate for the AA not provided by the diet. These observations confirm that liver plays a major role in the adaptation of the body to dietary protein restriction and highlight that severe dietary protein restriction induced liver protein catabolism by inducing an activation of ATF4-CHOP-TRB3 pathway in order to provide amino acids to body tissues.

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