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Editorial

Branched-chain amino acids antagonism in patients with cirrhosis and a simulated upper GI bleed ☆

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The interorgan nitrogen exchange and the metabolism of amino acids are profoundly altered in patients with liver disease, which results in an imbalanced amino acid composition of the blood characterized by low levels of glutamate, branched-chain amino acids (BCAA), e.g., valine, isoleucine and leucine, while the concentrations of most other amino acids are elevated. This disturbance in protein and amino acid metabolism decreases both the clearance of toxic metabolites and the protein synthesis, which often results in a negative nitrogen balance. The prevalence of protein–energy malnutrition in patients with cirrhosis is high-reaching as much as 60–90%, depending upon the severity and etiology of the disease [1]. By now it is also evident that the incidence of complications, that often end up with the development of hepatic encephalopathy and multiorgan dysfunction increases with malnutrition in patients with chronic liver disease [1].

Because cirrhosis is associated with insulin resistance and altered fuel substrate utilization the changes in the BCAA composition are of interest as ingested BCAA, which may escape metabolism can be used simply as fuel substrates (as they do not need the intermediate step of conversion to glucose) by an increased oxidation of BCAA. Although the metabolism of the three BCAA result in different products, the initial steps in their metabolism are similar. The activity of the BCAA aminotransferase, that exists in three isozymes, result in three 2-oxoacids that all are oxidatively decarboxylated by an inner mitocondrial membrane enzyme complex, i.e., the branched-chain 2-oxoacid dehydrogenase (BCOD). This event produces NADH and $CO_2$and is the rate-limiting step in BCAA oxidation. The resulting CoA compounds are next acted on by an enzyme that resemples the first dehydrogenase of fatty acid β-oxidation and ends up in the Krebs-cycle for energy production. Under conditions with low levels of BCAA the BCOD complex activity is suppressed [2] preserving as much BCAA as possible for protein synthesis. As mentioned before the BCAA in patients with chronic liver disease is reduced and the activity of the BCOD complex could be expected to be low, at least under stable, uncomplicated conditions.

Unfortunately complications often occur in patients with cirrhosis with development of hemodynamic instability with tissue hypoperfusion. Especially episodes of upper GI bleeding, a common complication in cirrhotic patients has been shown to further imbalance the plasma amino acids composition. Indeed, variceal bleeding is well known to be an important initial trigger event for acute deterioration in patients with cirrhosis with development of hepatic encephalopathy and renal failure, which cannot solely be explained by the hemodynamic instability this causes.

Dr. Olde Damink and colleagues have previously suggested that another explanation may be of importance due to the fact that ingested blood contains only small amounts of isoleucine, while the concentration of the two other BCAA, i.e., leucine and valine are severalfold higher [3]. In other words, an upper GI bleed from

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Abbreviations: BCAA, branched-chain amino acids; BCOD, branched chain 2-oxoacid dehydrogenase.

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varices seems to decrease the blood concentration of isoleucine, while most of the other amino acids increase. So the question arises if an isolated decrease in the isoleucine concentration together with an increase in that of leucine (and valine) may cause problems that calls for closer clinical attention? To answer this question it may be of value first to recall the concept of BCAA antagonism, as this is the focus in another important paper by Dr. Olde Damink in this issue of Journal of Hepatology [4].

Harper et al. [5] showed already in 1954 that feeding with a low-protein diet with excess of leucin prevents growth in rats. This was not the case when leucine was added to a diet less restricted in protein or when the low-protein diet was added isoleucine and valine, which suggested that leucine interfere with growth through mechanisms causing a defective utilization of BCAA. In the following years subsequent studies showed that leucine decreases the concentrations of valine and isoleucine because excess dietary leucine causes accelerated catabolism of these amino acids. The reason for this excess "use" of valine and isoleucine during a high plasma leucine concentration has until now been unclear, but is here hypothesized [4] to simply rely on the fact that all BCAA share the same transport and degradation pathways that's include the BCOD. In other words an isolated elevated leucine concentration may induce oxidation of all the BCAA's via activation of the BCOD complex even if the plasma and tissue concentration of isoleucine and valine are already subnormal. In this context, the paper in this issue of *Journal of Hepatology* by Dr. Steven Olde Damink et al. [4] is a particularly timely publication, where they simulated an upper GI bleed in a non-randomised, controlled, design that included only five patients with stable, compensated cirrhosis. The aim of this elegant study [4] was to determine the isoleucine turnover and oxidation, using state-of-the-art techniques both during an intragastric placebo infusion (i.e., saline) and during administration of an amino acid solution mimicking hemoglobin.

The obtained data show that the studied patients developed profound hypoisoleucinemia, and that the whole body isoleucine flux decreased by ~70% during exposure to such a simulated upper GI bleed. Since, isoleucine oxidation and the non-oxidative fraction of isoleucine flux decreased similarly this indicates, as also concluded by the authors [4], that the rate of protein synthesis decreases. At the same time the fraction of isoleucine flux used for oxidation did not decrease, which indicates that an upper GI bleed in patients with cirrhosis induces BCAA antagonism, and the authors suggest that the resulting hypoisoleucinemia is of pathophysiological importance for complications such as muscle waste, malnutrition, recurrent infections, renal failure, and hepatic encephalopathy.

If BCAA antagonism is induced in patients with cirrhosis complicated by variceal bleeding what can we then possibly do to counteract the imminent complications that follow? An interesting possibility here [4] and previously [3] suggested by the authors is to initiate i.v. infusion of isoleucine to help correct the imbalanced BCAA composition and thereby prevent catabolism, hepatic encephalopathy and other complications [3]. Though so simple and appealing in theory, the data and conclusions here presented will likely require a considerable amount of resources (and hard work), to be demonstrated in large cohort of cardiovascular unstable cirrhotic patients experiencing a real upper GI bleed.

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