Methionine metabolism in liver diseases\textsuperscript{1,2}

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The detailed study by Bosy-Westphal et al (1) in this issue of the Journal echoes and significantly extends observations that have been made in numerous laboratories during the past half century. However, despite the clarity of the conclusion that both hypermethioninemia and hyperhomocysteinemia are frequent in patients with chronic liver diseases, the basis for these abnormalities remains obscure.

Methionine metabolism in mammals consists of 2 pathways, the methionine cycle and the transsulfuration sequence, that have in common the first 3 reactions (2). Thus, both include the conversion of methionine to S-adenosylmethionine (AdoMet), the utilization of AdoMet in diverse transmethylation reactions yielding a methylated product plus S-adenosylhomocysteine, and the cleavage of S-adenosylhomocysteine to yield homocysteine and adenosine. Whereas these 3 reactions occur in all mammalian cells, postnatal liver alone contains a form of methionine adenosyltransferase (MAT I/III; EC 2.5.1.6) with a high Michaelis constant ($K_m$) for methionine. The extrahepatic form, MAT II, has different kinetic properties, being both inhibited by AdoMet and near saturation at normal intracellular methionine concentrations. Consequently, only the liver can respond to increased availability of methionine by significantly increasing the synthesis of AdoMet.

The methionine cycle is completed by the remethylation of homocysteine. The methionine synthase (EC 2.1.1.3) reaction, which requires methylcobalamin as a cofactor and uses methyltetrahydrofolate as the methyl donor, is present in all mammalian cells. A second remethylation reaction, catalyzed by betaine–homocysteine S-methyltransferase (BHMT; EC 2.1.1.5), has a more restricted distribution, being found in humans only in liver, kidney, and lens (2).

The reaction catalyzed by cystathionine-β-synthase (CBS; EC 4.2.1.22) is the first unique reaction in the transsulfuration pathway. This pyridoxal phosphate–requiring enzyme couples homocysteine with serine to form cystathionine. AdoMet activates CBS. Hydrolysis of cystathionine by γ-cystathionase (EC 4.4.1.1), also a pyridoxal enzyme, to yield α-ketobutyrate and cysteine completes the transsulfuration sequence. In mammals, the total pathway occurs only in liver, kidney, small intestine, and pancreas. The brain, and possibly adipose tissue, contains CBS but lacks cystathionase (2).

Given this metabolic structure, several explanations for the accumulation of both homocysteine and methionine in chronic liver disease are possible. One, based on studies of specific inborn errors of metabolism, is impaired cystathionase synthesis. Increased concentrations of methionine would result from the methylation of homocysteine that could not enter the transsulfuration sequence. However, a recent study by Look et al (3) that reported increased cystathionine in cirrhosis refutes this hypothesis, unless there is an additional impairment at the cystathionase reaction. A more likely explanation is that dedifferentiated and transformed hepatocytes lack cystathionase. During the perinatal period, hepatic cystathionase increases with age and cystathioninuria has been reported in patients with hepatoblastoma (4). These observations suggest that the appearance of increased cystathionase may be a marker for regeneration or neoplastic transformation in patients with cirrhosis.

On the basis of a series of elegant studies, Mato and his co-workers (5) reported that the high-$K_m$ MAT is defective in cirrhosis. They use this finding to explain the increase in methionine and hypothesize that the reduced synthesis of AdoMet results in a reduced activation of CBS with a consequent increase in homocysteine. This hypothesis is supported by the report of hyperhomocysteinemia and hypermethioninemia in subjects with inherited defects in MAT I/III (6). In the latter situation, increases in cystathionase may result from inhibition of cystathionase, but only in subjects with elevations of plasma methionine far above that seen in chronic liver disease.

I see no reason to reject the possibility that the abnormalities in methionine metabolism reflect impairment at multiple enzyme sites. Avila et al (5) found reduced messenger RNA for MAT I/III, methionine synthase, BHMT, and CBS in cirrhotic livers. Although they measured gene expression and not enzyme content, which might be a function also of the rates of protein synthesis and degradation, this observation highlights the blunt, nonselective nature of the pathology. In addition, studies in humans are subject to marked variability reflecting the differing etiologies of the liver diseases as well as patient-specific genetic and environmental factors. Consequently, we could have anticipated the observed variation between individual patients and between laboratories.

The difficulty of the search for an explanation should not obscure the importance of this quest because abnormalities of methionine metabolism may serve to perpetuate the hepatic pathology that was initiated by inherited defects, viral infection, alcohol and other toxic exposures, or autoimmunity. Consequently, reversal of the defects may mitigate the illness. Several possibilities merit attention.

1) Deficient synthesis of AdoMet might contribute to hepatocyte dedifferentiation with consequent increases in regeneration and malignant transformation. Reduced tissue AdoMet may facilitate the synthesis and release of tumor necrosis factor and

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other cytokines (7). Therapeutic AdoMet is available, although its efficacy in liver diseases continues to be debated.

2) A defect in transsulfuration, effectively making cysteine an essential nutrient, might impair the synthesis of glutathione necessary for both an effective response to oxidative stress and an adequate mechanism for xenobiotic detoxification (8). Both nutritional supplements of cysteine and preparations of metabolic surrogates are available.

3) Increased concentrations of homocysteine may potentiate both necrosis and fibrogenesis (9). In this situation, optimal therapy awaits definition. Bosy-Westphal et al (1) confirm the frequent failure of high dosages of folate, cobalamin, and pyridoxine to normalize plasma total homocysteine concentrations in patients with chronic liver disease. The studies of Look et al (3) may provide insight. Although confounded by the frequent concomitant renal insufficiency, plasma concentrations of both dimethylglycine and sarcosine were increased in those subjects. The BHMT reaction is the only metabolic source of dimethylglycine. Furthermore, flow through this reaction is determined in large measure by the availability of betaine, which is derived from dietary choline. Future studies should focus on the dietary content of choline and the possibility that supplementation with choline or betaine will restore the intracellular concentrations of betaine necessary for homocysteine methylation.

REFERENCES