5th Amino Acid Assessment Workshop

Mammalian Cysteine Metabolism: New Insights into Regulation of Cysteine Metabolism[1,2]

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ABSTRACT The mammalian liver tightly regulates its free cysteine pool, and intracellular cysteine in rat liver is maintained between 20 and 100 nmol/g even when sulfur amino acid intakes are deficient or excessive. By keeping cysteine levels within a narrow range and by regulating the synthesis of glutathione, which serves as a reservoir of cysteine, the liver addresses both the need to have adequate cysteine to support normal metabolism and the need to keep cysteine levels below the threshold of toxicity. Cysteine catabolism is tightly regulated via regulation of cysteine dioxygenase (CDO) levels in the liver, with the turnover of CDO protein being dramatically decreased when intracellular cysteine levels increase. This occurs in response to changes in the intracellular cysteine concentration via changes in the rate of CDO ubiquitination and degradation. Glutathione synthesis also increases when intracellular cysteine levels increase as a result of increased saturation of glutamate-cysteine ligase (GCL) with cysteine, and this contributes to removal of excess cysteine. When cysteine levels drop, GCL activity increases, and the increased capacity for glutathione synthesis facilitates conservation of cysteine in the form of glutathione (although the absolute rate of glutathione synthesis still decreases because of the lack of substrate). This increase in GCL activity is dependent on up-regulation of expression of both the catalytic and modifier subunits of GCL, resulting in an increase in total catalytic subunit plus an increase in the catalytic efficiency of the enzyme. An important role of cysteine utilization for coenzyme A synthesis in maintaining cellular cysteine levels in some tissues, and a possible connection between the necessity of controlling cellular cysteine levels to regulate the rate of hydrogen sulfide production, have been suggested by recent literature and are areas that deserve further study. J. Nutr. 136: 1652S–1659S, 2006.

KEY WORDS: • *cysteine* • *cysteine dioxygenase* • *glutathione* • *glutamate-cysteine ligase* • *hypotaurine* • *taurine* • *coenzyme A* • *cysteamine* • *hydrogen sulfide*

The mammalian liver tightly regulates its intracellular free cysteine pool. In rats, for instance, intracellular cysteine is narrowly maintained between 20 and 100 nmol/g even when dietary protein or sulfur amino acid intake is varied from subrequirement to above-requirement levels for this species (1). The effect of diet on plasma and hepatic cysteine levels is illustrated by the data shown in **Figure 1**. Rats that had been adapted to a high-protein diet and then fed a low-protein diet supplemented with cysteine had, at 6 h after the diet was introduced, a large increase in the portal plasma cysteine concentration but no increase above the fasting value for cysteine in the arterial plasma or in the liver. On the other hand, the plasma cysteine concentration was not significantly decreased, compared with fasting levels, in rats fed a low-protein diet, whereas the hepatic cysteine concentration was markedly decreased. Thus, in rats, the liver allows its own cysteine concentration to vary about 5-fold (from 20 to 100 nmol/g) while regulating cysteine degradation to maintain the plasma cysteine concentration within a 2.5-fold range (between 80 and 200 μmol/L). By keeping cysteine levels within a very narrow range, the liver addresses 2 opposing homeostatic requirements. Cysteine levels must be sufficiently high to meet the needs of protein synthesis and the production of other essential molecules that include glutathione, coenzyme A, taurine, and inorganic sulfur. At the same time, however, cysteine concentrations must also be kept below the threshold of cytotoxicity. The potent toxicity of excess cysteine has been demonstrated in several animal models (2–4), and chronically high levels of cysteine have been closely associated with rheumatoid arthritis (5), Parkinson's disease (6), Alzheimer's disease (6), systemic lupus erythematosus (7), increased risk of cardiovascular disease (8), and adverse pregnancy outcomes in humans (9).

The central role of hepatic cysteine dioxygenase in regulation of cysteine levels. An important enzyme that contributes to the regulation of steady-state intracellular cysteine levels is cysteine dioxygenase (CDO,[4] EC 1.13.11.20). Expressed at

[1] Published in a supplement to *The Journal of Nutrition*. Presented at the conference "The Fifth Workshop on the Assessment of Adequate Intake of Dietary Amino Acids" held October 24–25, 2005 in Los Angeles. The conference was sponsored by the International Council on Amino Acid Science (ICAAS). The organizing committee for the workshop and guest editors for the supplement were David H. Baker, Dennis M. Bier, Luc Cynober, Yuzo Hayashi, Motoni Kadowaki, and Andrew G. Renwick. Guest editors disclosure: all editors received travel support from ICAAS to attend workshop.

[2] The work reported here was supported by National Institutes of Health Grants DK-056649 and DK- 0664303.

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[4] Abbreviations used: CDO, cysteine dioxygenase; CSD, cysteinesulfinate decarboxylase; GCL, glutamate-cysteine ligase; GCLC, GCL catalytic subunit; GCLM, GCL modifier subunit; GSH, glutathione; PKAN, pantothenate kinase-associated neurodegeneration.