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SULFUR AMINO ACID METABOLISM: Pathways for Production and Removal of Homocysteine and Cysteine

Martha H. Stipanuk
Division of Nutritional Sciences, Cornell University, Ithaca, New York 14853; email: mhs6@cornell.edu

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■ **Abstract** Tissue concentrations of both homocysteine (Hcy) and cysteine (Cys) are maintained at low levels by regulated production and efficient removal of these thiols. The regulation of the metabolism of methionine and Cys is discussed from the standpoint of maintaining low levels of Hcy and Cys while, at the same time, ensuring an adequate supply of these thiols for their essential functions. *S*-Adenosylmethionine coordinately regulates the flux through remethylation and transsulfuration, and glycine *N*-methyltransferase regulates flux through transmethylation and hence the *S*-adenosylmethionine/*S*-adenosylhomocysteine ratio. Cystathionine β-synthase activity is also regulated in response to the redox environment, and transcription of the gene is hormonally regulated in response to fuel supply (insulin, glucagon, and glucocorticoids). The H_2S-producing capacity of cystathionine γ-lyase may be regulated in response to nitric oxide. Cys is substrate for a variety of anabolic and catabolic enzymes. Its concentration is regulated primarily by hepatic Cys dioxygenase; the level of Cys dioxygenase is upregulated in a Cys-responsive manner via a decrease in the rate of polyubiquitination and, hence, degradation by the 26S proteasome.

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INTRODUCTION

In the past decade much of the interest in methionine (Met) metabolism has focused on the possible role of homocyst(e)ine in cardiovascular disease, adverse pregnancy outcomes, and Alzheimer's and other neurological diseases (80, 99, 174). More recently, cyst(e)ine has also been implicated as a possible agent or indicator of oxidative damage (46–48, 145). Among the physiological thiols, homocysteine (Hcy) and cysteine (Cys) are readily oxidized compared to glutathione (GSH); they have the highest reduction potentials, readily reduce Cu^{+2} to Cu^{+1}, and exist largely in oxidized forms in plasma (32, 101, 102, 150, 225).

It is clear that tissue concentrations of both Hcy and Cys are maintained at low levels by regulated production and efficient removal of these thiols. Nevertheless, Hcy is an essential intermediate in Met oxidation and in Cys synthesis and is necessary for utilization of methyl groups from betaine or N^5-methyl-tetrahydrofolate (N^5-methyl-THF). Cys is itself a precursor amino acid for synthesis of proteins, coenzyme A, and γ-glutamylcysteinylglycine, as well as Cys's catabolic products taurine and inorganic sulfur, and tissue levels of Cys must be high enough to support these synthetic processes. The body's capacity to function with low concentrations of Hcy and Cys is facilitated by its ability to store Cys as GSH, which may be hydrolyzed to generate Cys as needed; the reliance on GSH as the major cellular thiol or redox buffer; and the ability of cells to regenerate Met from Hcy. When sulfur amino acids are in excess, the enzymes involved in their catabolism are rapidly upregulated, mainly in response to *S*-adenosylmethionine (SAM) in the case of transsulfuration and Cys in the case of Cys oxidation.

SOURCES OF SULFUR-CONTAINING AMINO ACIDS IN THE FREE AMINO ACID POOL

Uptake of Dietary Sulfur-Containing Amino Acids

Met and Cys are metabolically linked via the unidirectional transsulfuration pathway that allows Met to serve as the source of sulfur for Cys synthesis. In mammals, Met is an essential amino acid, whereas Cys is considered a semiessential amino

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acid because it can by synthesized from Met sulfur and serine via transsulfuration. The sulfur amino acids, Met and Cys, are normally consumed as components of dietary proteins. Based on the Third National Health and Nutrition Examination Survey (NHANES III 1988–1994), the average intakes of methionine and cysteine are 2.3 and 1.3 g/day (15.4 and 10.7 mmol/day) for men and 1.6 and 0.9 g/day (10.7 and 7.4 mmol/day) for women in the United States (93a). Thus total sulfur amino acid intake averages 26 mmol/day for men and 18 mmol/day for women. The estimated average requirement of adults for Met plus Cys is $\sim$15 mg $\cdot$ kg^{-1} $\cdot$ day^{-1}, and the RDA is 19 mg $\cdot$ kg^{-1} $\cdot$ day^{-1} (43, 93a, 194, 232).

Absorption of the products of protein digestion across the intestinal epithelium is highly efficient ($\sim$95%–99%). Dietary Met is transported by neutral amino acid transport systems ($B^{0,+}$, ASC, and L) and as Met-containing peptides by peptide transport systems. Dietary Cys is absorbed as Cys, cystine (CySSCy), and as Cys-containing peptides by a variety of L-amino acid and peptide transport systems in the small intestinal mucosa (131, 147, 173, 177). Transport of Cys is accomplished by neutral amino acid transporters including system B in the apical (brush border) membrane and system ASC in both the apical and basolateral plasma membranes of the intestinal mucosal cells; Cys uptake is largely Na^+-dependent. Cystine is transported by system $b^{0,+}$, a Na^+-independent system that is present in the apical membranes of the intestinal mucosa and serves cationic amino acids as well as zwitterionic amino acids. The Na^+-independent transporter LAT-2 (a subtype of system L) is responsible for the movement of cystine across the basolateral membrane of enterocytes.

Amino acids enter the plasma and circulate as free amino acids until they are removed by tissues. The liver removes a substantial proportion of the sulfur-containing amino acids from the portal circulation and utilizes them for synthesis of protein and GSH or for catabolism to taurine and sulfate (74, 184). GSH is exported into plasma, and this Cys-containing tripeptide, as well as its metabolites, CysGly and γ-GluCys, can be a source of Cys to tissues via the action of γ-glutamyl transpeptidase and dipeptidases. Only negligible amounts of Hcy are present in the diet (169).

The reabsorptive epithelium of the renal proximal tubule has transport systems similar to those of the absorptive epithelium of the intestine, and the kidney efficiently reabsorbs amino acids from the filtrate. Renal reabsorption of Cys and Met is normally very high ($\geq$94%), and the loss of amino acids in the urine is normally negligible (146, 184). Urinary Met excretion has been reported to be 22 to 41 μmol per day, and urinary cyst(e)ine excretion by adults has been reported as 63 to 285 μmol per day (128, 157).

Turnover of Sulfur-Containing Amino Acids in Body Protein and GSH Pools

In addition to the intake of dietary protein, turnover of body protein and peptide pools releases free Met and Cys into the body pools. Turnover of body protein

involves a flux of approximately 38 mmol of Cys and 32 mmol of Met per day (73, 126, 156). Most of the endogenous protein turnover occurs intracellularly, but a considerable amount of the turnover is due to hydrolysis of endogenous proteins that are secreted into the gastrointestinal tract, where they are subsequently digested to amino acids and peptides that are absorbed along with those from dietary proteins. In adults, essentially an equivalent amount of Met and Cys are utilized for resynthesis of the degraded proteins and peptides. Formation of amino acyl tRNAs for protein synthesis effectively competes with other pathways using Met or Cys as substrate because the amino acyl tRNA synthetases have high affinities for amino acids. Catabolism of Met/Hcy and Cys is quite restricted at low intakes of sulfur amino acids with remethylation of Hcy back to Met and incorporation of Cys into GSH, along with incorporation of both into protein, having high priority (72, 187, 232).

The breakdown of GSH also contributes to the free amino acid flux. GSH serves as a reservoir of Cys, which can be released when Cys supply is low. Tissue GSH levels become depleted at sulfur amino acid intakes that are marginal but adequate for protein synthesis, demonstrating that protein synthesis has a higher priority for Cys than does GSH synthesis (123, 187). The normal turnover of GSH in adults has been estimated to be ~40 mmol per day, which is slightly greater than estimates of the magnitude of Cys turnover in the body protein pool (72, 73, 122, 193, 194).

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Sulfur Balance

Adult human subjects remain in sulfur balance, with sulfur excretion being essentially equivalent to sulfur intake (18 to 26 mmol per day). This means that the amount of sulfur amino acids being catabolized per day is essentially equal to the intake per day. The transsulfuration pathway is essentially the sole pathway of Met catabolism under normal conditions. Transsulfuration results in transfer of the sulfur of Met to serine to form Cys (158). Thus, the sulfur from either Met or Cys ends up being oxidized via the Cys catabolic pathways to the end products sulfate and taurine, which are excreted in the urine. In studies of urinary sulfur excretion of children and adults, free sulfate accounted for about 77%–92%, ester sulfate for about 7%–9%, taurine for about 2%–6%, and cyst(e)ine for about 0.6%–0.7% of the total sulfur excreted (127, 139, 233). Taurine excretion varies greatly with differences in taurine intake and can make up as much as 10% of total urinary sulfur. Other sulfur-containing compounds found in urine in trace amounts (less than 0.2% of total sulfur) include Met, Hcy, cystathionine, N-acetylcysteine, mercaptolactate, mercaptoacetate, thiosulfate, and thiocyanate (127, 128, 139). In a study of young Japanese women, Nakamura et al. (233) found that free sulfate, but not ester sulfate or taurine, was significantly correlated with urea excretion, which suggests that free sulfate excretion is a good index of sulfur amino acid intake.

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METABOLISM OF METHIONINE/HOMOCYSTEINE AND CYSTEINE FORMATION

Transmethylation

ACTIVATION OF Met BY FORMATION OF SAM The essential amino acid, Met, is activated by ATP to form SAM in a reaction catalyzed by Met adenosyltransferase (EC 2.5.1.6). Liver-specific and nonliver-specific Met adenosyltransferases (MATs) are products of two different genes, *MAT1A* and *MAT2A*, respectively (29). Mature liver expresses *MAT1A*, whereas expression of *MAT2A* occurs in all tissues and is induced during liver growth and dedifferentiation. MAT2 (α_2), encoded by gene *MAT2A*, has a low K_m for Met ($\sim$8 μM) and is inhibited by SAM (116, 197). The *MAT2B* gene encodes a regulatory subunit (β_γ) that associates with the α_2 subunit in an unknown stoichiometry (116); the regulatory subunit is needed for optimal activity (124). The liver-specific isozyme (α_1), encoded by gene *MAT1A*, exists as a tetramer (MAT1) or dimer (MAT3). MAT1 has a moderate K_m for Met ($\sim$40 μM) and is slightly inhibited by SAM. In contrast, MAT3 has a high K_m for Met ($\sim$200 μM) and demonstrates strong positive cooperative modulation by SAM at physiological Met and SAM concentrations. MAT3 is the predominant isozyme in rat liver. MAT3 allows the liver to uniquely respond to an influx of excess Met with increased SAM formation, permitting rapid clearance of excess Met by the liver. In contrast, the velocity of SAM synthesis in extrahepatic tissues would be expected to be nearly maximal, relatively unaffected by an increase in Met concentration, and sensitive to feedback/product inhibition by SAM.

Hereditary MAT1/3 deficiency due to mutations in the *MAT1A* gene causes persistent hypermethioninemia and, in some cases, unusual breath odor or neurological problems including neural demyelination (25, 213). In general, the neurological symptoms correlate with the severity of the hypermethioninemia that results from various mutations. Patients with the most markedly elevated levels of plasma Met also had elevated plasma total Hcy and often mildly elevated plasma cystathionine concentrations (181). Targeted disruption of the *MAT1A* gene in mice resulted in elevated plasma methionine and decreased hepatic SAM and GSH levels (125, 129). These mice spontaneously developed nonalcoholic steatohepatitis and were susceptible to choline-deficient diet-induced fatty liver, hepatic hyperplasia, and hepatocellular carcinoma.

The high-energy sulfonium compound SAM serves primarily as a methyl donor via reactions catalyzed by a variety of methyltransferases and involving a variety of acceptors. These SAM-dependent methylations are essential for biosynthesis of a variety of cellular components including creatine, epinephrine, carnitine, phospholipids, proteins, DNA, and RNA. In fact, SAM serves as the methyl donor for essentially all known biological methylation reactions, with the notable exception of those involved in methylation of Hcy (see below). The coproduct of transmethylation, S-adenosylhomocysteine (SAH), is hydrolyzed to yield adenosine and Hcy, which can be remethylated to Met or condensed with serine to form

cystathionine. An alternative fate of SAM is decarboxylation to form dSAM, which is the donor of aminopropyl groups for synthesis of spermidine and spermine (151, 183). Polyamine synthesis also results in the formation of 5′-methylthioadenosine from dSAM. Although decarboxylation of SAM by SAM decarboxylase competes with the methyltransferases for SAM, the decarboxylase reaction typically consumes less than 10%–30% of available SAM (77, 93), and Met is efficiently resynthesized from the sulfur and methyl group of 5′-methylthioadenosine formed as a by-product in the polyamine synthetic pathway (3, 154, 183, 211) (see Figure 1).

SAM-DEPENDENT TRANSMETHYLATION The methyl group of SAM is transferred to a nitrogen, oxygen, or sulfur atom of a wide range of compounds in reactions catalyzed by numerous methyltransferases. Mudd et al. (136) estimated that the total daily utilization of Met methyl groups in transmethylation reactions was ~13–14 meq per day for a female patient. The largest requirement for methyl group transfer was for formation of creatine from guanidinoacetate, which was estimated to be ~10 mmol per day in women (138). Intake of labile methyl groups (Met or choline) beyond the apparent requirement of ~14 meq per day resulted in nearly equimolar increases in sarcosine synthesis via the glycine *N*-methyltransferase (EC 2.1.1.20) reaction.

Despite both the diversity of the methyl acceptors and the specificity of the individual SAM-dependent methyltransferases, essentially all of these enzymes share the properties of relatively high affinity for the common substrate, SAM, as well as inhibition by SAH, the common product. The actual inhibitory constants vary over a wide range (22, 87, 107). Thus, the ratio of substrate to product (SAM to SAH) may have a large effect on methyltransferase reactions, and the intracellular levels of both SAM and SAH must be regulated. The physiological ratios of SAH/SAM are generally lower than those required for inhibition of the methyltransferases, and changes in these ratios are minimized because inhibition of methyltransferases by SAH will be accompanied by increases in SAM due to decreased transmethylation (49, 51, 65, 87, 220).

GLYCINE *N*-METHYLTRANSFERASES Observations in individuals deficient in glycine *N*-methyltransferase, which catalyzes the methylation of glycine, have indicated that this enzyme plays a unique regulatory role. Normal individuals will exhibit an increase in plasma sarcosine (*N*-methylglycine) in response to a Met load, but individuals with defects in glycine *N*-methyltransferase exhibit hypermethioninemia and markedly elevated levels of plasma SAM, but no increase in sarcosine level (135). Glycine *N*-methyltransferase mRNA was abundant in adult liver and pancreas and found in lesser amounts in prostate (27). Glycine *N*-methyltransferase activity was found in liver and pancreas and, in lower amounts, kidney (231).

The kinetic parameters of glycine *N*-methyltransferase are quite different from those observed for most SAM-dependent methyltransferases. Glycine *N*-methyltransferase is a homotetramer that is weakly inhibited by its product SAH, has a relatively high K_m for SAM, and shows cooperative rate behavior with respect

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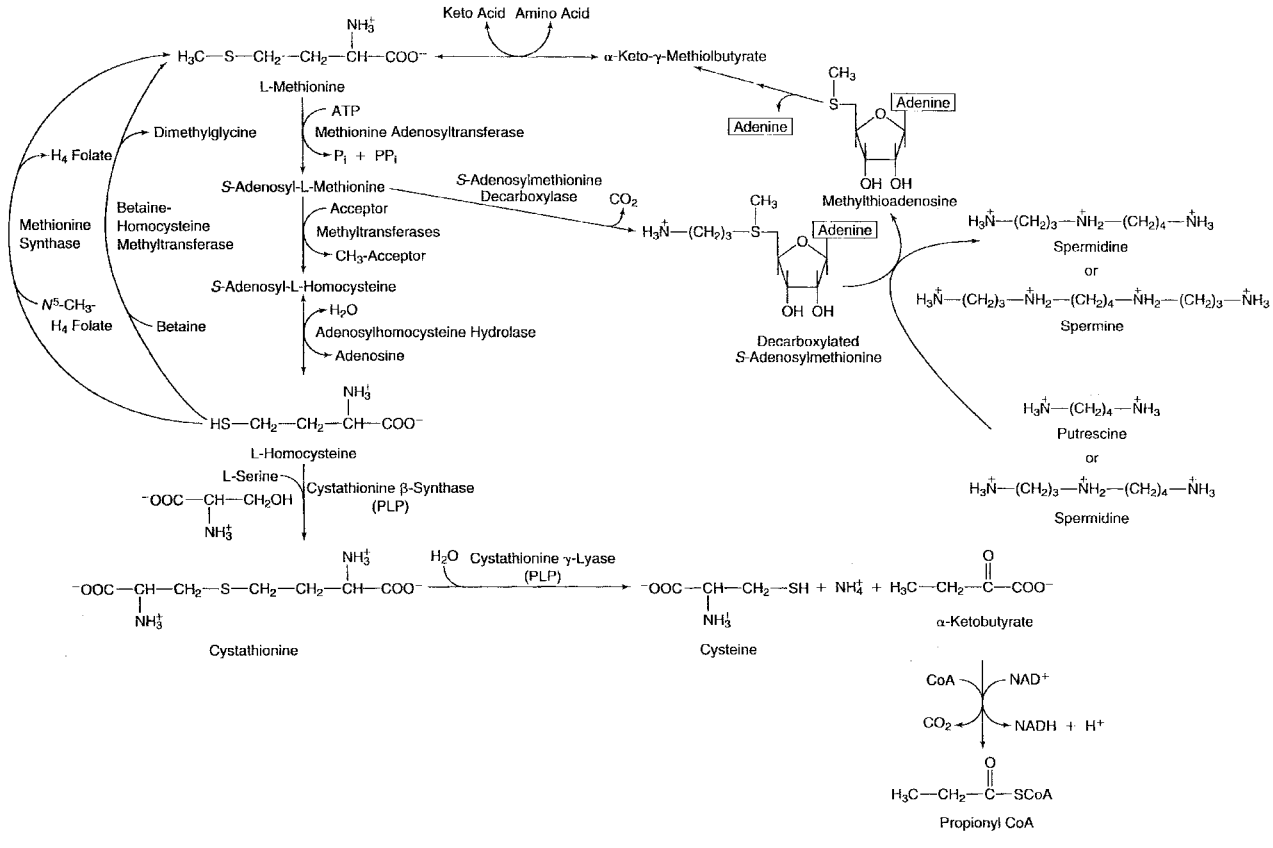

Figure 1 Pathways of methionine transmethylation, remethylation, transsulfuration, and polyamine synthesis. From Reference 192a, p. 266.

to SAM (130, 202). Glycine *N*-methyltransferase is inhibited by N^5-methyl-THF (229, 230). When SAM concentrations are elevated and $N^{5,10}$-methylene-THF reductase activity is thereby inhibited, the concentration of N^5-methyl-THF would be expected to decrease, and inhibition of glycine *N*-methyltransferase by N^5-methyl-THF would be relieved. Thus, glycine *N*-methyltransferase appears to serve as a benign high-capacity SAM-dependent methyltransferase that integrates regulation of transmethylation and de novo methyl group synthesis. It is able to convert excess methyl groups to a nontoxic product (sarcosine) from which glycine can be regenerated and methyl groups (via N^{5-10}-methylene-THF) can be oxidized or recycled as one-carbon units. By regulating the SAM level and the SAM/SAH ratio, glycine *N*-methyltransferase optimizes methyl group supply and activity of methyltransferase enzymes. Inappropriate activation of glycine *N*-methyltransferase by glucocorticoids or retinoid compounds was associated with impairment of methylation reactions and the hypomethylation of DNA (164–166).

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SAH HYDROLYSIS TO Hcy Removal of SAH, the by-product of these methyl transfer reactions, is mainly accomplished by SAH hydrolase (EC 3.3.1.1), which hydrolyzes SAH, forming adenosine and Hcy (50, 52). SAH hydrolase is present in all cells, contains tightly bound NAD^+, which participates in the catalytic process, and has a K_m for SAH that is much above normal tissue concentrations (53, 111). Although the equilibrium of SAH hydrolase actually favors formation of SAH, the reaction is normally driven forward by rapid removal of the products. If the hydrolase is insufficient for removal of SAH, intracellular binding of SAH to specific (and saturable) protein sites or export of SAH from the cell may be used as additional means to lower the cellular SAH level. As predicted, inhibition of SAH hydrolase is accompanied by accumulation of SAH and inhibition of intracellular transmethylation reactions (22, 88, 117, 172). Inhibition of SAH hydrolase also results in alterations in remethylation reactions and altered folate metabolism due to the methyl trap process (15, 21) and to inhibition of adenosine kinase (71).

The adenosine generated by SAH hydrolase is removed by adenosine deaminase (EC 3.5.4.4) or adenosine kinase (EC 2.7.1.20), whereas the Hcy generated by hydrolysis of SAH is removed by remethylation or transsulfuration. In remethylation, Hcy acquires a methyl group from N^5-methyl-THF or from betaine to form Met, thus conserving the homocysteinyl moiety. In transsulfuration, the sulfur is transferred to serine to form Cys, and the remainder of the Hcy molecule is catabolized to α-ketobutyrate and ammonia. Met synthase(N^5-methyl-THF–Hcy methyltransferase; EC 2.1.1.13), betaine–Hcy methyltransferase (EC 2.1.1.5), and cystathionine β-synthase (EC 4.2.1.22) carry out these reactions using Hcy as substrate. Thus, Hcy is located at an important regulatory branch point. Hcy may be used for resynthesis of SAH by reversal of SAH hydrolysis, undergo remethylation to Met, undergo conversion to cystathionine (which commits it to transsulfuration), or be exported from the cell. Normal plasma homocyst(e)ine may therefore represent the amino acid in transit from the site of production to a site of catabolism such as the kidney.

Remethylation and Its Role in Hcy Removal

Hcy METHYLTRANSFERASES: Met SYNTHASE AND BETAINE–Hcy METHYLTRANSFERASE The remethylation pathway allows Met to be regenerated from Hcy using new methyl groups synthesized in the folate coenzyme system or using preformed methyl groups, both of which may subsequently be transferred to acceptors via SAM-dependent methyltransferase reactions. The remethylation of Hcy by transfer of a methyl group from N^5-methyl-THF is catalyzed by Met synthase. Met synthase is widely distributed in mammalian tissues and contains methylcobalamin as an essential cofactor. The methyl group of N^5-methyl-THF is synthesized de novo in the folate coenzyme system. The final step of N^5-methyl-THF synthesis is the irreversible reduction of $N^{5,10}$-methylene-THF, which is catalyzed by the flavoenzyme $N^{5,10}$-methylene-THF reductase (EC 1.1.1.68), using NADH as the electron donor. This reaction is under regulation by SAM and SAH, with SAM inhibiting the conversion of $N^{5,10}$-methylene-THF to N^5-methyl-THF, and SAH reversing the inhibition (14, 118). The 3-carbon of serine is the major donor of one-carbon units for the de novo synthesis of methyl groups in most human tissues (36, 39, 81). Oltean & Banerjee (143) recently reported that the 5′-UTR of Met synthase mRNA contains a B_{12}-responsive element that allows translational upregulation of Met synthase by vitamin B_{12} by shifting the mRNA from the ribonucleoprotein to the polysome pool.

The other Hcy methyltransferase, betaine−Hcy methyltransferase, is present only in liver, kidney, and lens of humans and requires betaine as the methyl donor (41, 63, 198). Betaine−Hcy methyltransferase is a zinc metalloenzyme (10, 20, 58). This enzyme uses preformed methyl groups from dietary betaine (169) or from betaine derived from either dietary choline (235) or choline synthesized through successive SAM-dependent methylations of phosphatidylethanolamine. The enzyme is feedback-inhibited by its product, *N,N*-dimethylglycine (63, 68, 69, 180).

The sequential oxidative demethylation of *N,N*-dimethylglycine and sarcosine (*N*-methylglycine) yields N^5-methylene-THF. Thus the use of Met methyl groups to synthesize choline via SAM-dependent methylation of phosphatidylethanolamine, the oxidation of choline to betaine, the utilization of a betaine methyl group for remethylation of Hcy, and the funneling of the remaining methyl groups back to the folate coenzyme system can be seen as an additional methyl group cycle. Although nearly all of the one-carbon units used for remethylation appear to originate from the 3-carbon of serine via folate-dependent remethylation in folate-replete tissues, betaine may be an important methylating agent when the folate-dependent methylating pathway is impaired by ethanol ingestion, drugs, nutritional imbalances, or when betaine or choline levels are high (64, 69, 210). Rat liver betaine-Hcy methyltransferase mRNA content and enzyme activity increased when rats were fed Met-deficient diets with adequate choline, and increased further when the diet was supplemented with betaine (148, 149).

A gene (*BHMT2*) that codes a 40-kDa protein with 73% identity to betaine-Hcy methyltransferase has been identified in humans (24). The BHMT2 transcript is most abundant in adult liver and kidney and is found at lower levels in brain,

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heart, and skeletal muscle. Whether this putative Hcy methyltransferase plays a physiological role in Hcy remethylation remains to be determined.

Met SYNTHASE AND $N^{5,10}$-METHYLENE-THF DEFICIENCIES Inborn errors of Met synthase or of methyl-THF or methylcobalamin synthesis result in homocysteinemia, homocystinuria, and hypomethioninemia (200). Patients with Met synthase deficiency suffer from megaloblastic anemia with or without some degree of neural dysfunction and mental retardation. Also, polymorphisms in Met synthase reductase, which catalyzes the conversion of the inactive form of human Met synthase to the active state of the enzyme, have been associated with mild homocysteinemia (144). Mice that were heterozygous for a disrupted Met synthase gene had slightly elevated levels of plasma Hcy and Met compared to wild-type mice but were otherwise indistinguishable (200). Homozygous knockout embryos survived through implantation but died soon thereafter; nutritional supplementation with folinate, Met, choline, or betaine during pregnancy was unable to rescue the embryos. It is presumed that human patients with Met synthase deficiency either have residual Met synthase activity or a compensatory mechanism that is absent in mice.

Chen et al. (28) reported elevated plasma Hcy in both heterozygous and homozygous $N^{5,10}$-methylene−THF reductase knockout mice. These $N^{5,10}$-methylene−THF reductase-deficient mice also had low SAM and elevated SAH levels and exhibited global DNA hypomethylation. Heterozygous knockout mice appeared normal, whereas the homozygotes were smaller and exhibited developmental retardation with cerebellar pathology. Abnormal lipid deposition in the aorta was observed in older heterozygous and homozygous mice.

Kvittingen et al. (119) reported an interesting case of Met synthase deficiency without megaloblastic anemia. A child presented with neonatal homocystinuria, hypomethioninemia, and severe neurological symptoms including developmental delay and seizures, and was found to have a defect in methylcobalamin synthesis. In addition, the child was homozygous for the C677T polymorphism in the $N^{5,10}$-methylene-THF reductase gene. It was assumed that the concomitant existence of this mutation with the Met synthase defect might have prevented folate trapping and thus the megaloblastic anemia. Given recent reports of a dissociation between hematological and neurological symptoms in a number of patients with vitamin B_{12} deficiency and the relatively high frequency of the C677T polymorphism in the $N^{5,10}$-methylene-THF reductase gene, further exploration of the interaction of Met synthase deficiency and $N^{5,10}$-methylene-THF reductase polymorphisms might provide additional insight into the mechanisms underlying the clinical symptoms (23).

Differences in Met synthase activity may be responsible for the Met dependence reported for some tumor cells (106). A Met-dependent rat liver tumor cell line (HTC) was found to contain low levels of Met synthase activity, have a lower Cys requirement, and contain higher concentrations of GSH and taurine compared to a rat liver tumor cell line (Phi-1) that was not Met-dependent. These observations

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suggest that Hcy was metabolized by transsulfuration rather than remethylation in the Met-dependent cells.

Transsulfuration and Its Role in Hcy Removal and Cys Production

TRANSSULFURATION PATHWAY The transsulfuration of Hcy to Cys is catalyzed by two pyridoxal 5′-phosphate (PLP)-dependent enzymes, cystathionine β-synthase and cystathionine γ-lyase (EC 4.4.1.1; cystathionase). Cystathionine β-synthase catalyzes the condensation of Hcy and serine to form cystathionine in an irreversible reaction, which explains the unidirectional flow in the transsulfuration sequence from Met to Cys (7, 61). The cystathionine is then hydrolyzed by cystathionine γ-lyase to form Cys and α-ketobutyrate plus ammonia. The α-ketobutyrate is further catabolized by oxidative decarboxylation to propionyl-CoA, which enters the tricarboxylic acid cycle at the level of succinyl-CoA; the oxidative decarboxylation of α-ketobutyrate can be catalyzed by pyruvate and branched-chain keto acid dehydrogenase complexes. Thus, the transsulfuration pathway is responsible both for the catabolism of the carbon chain of Met and for the transfer of Met sulfur to serine to synthesize Cys.

Although all cells are capable of transmethylation and remethylation, the catabolism of Hcy via transsulfuration is restricted to certain tissues. Tissues that are not capable of a sufficient rate of transsulfuration require an exogenous source of Cys and must export Hcy (or cystathionine) for further metabolism/removal by other tissues. Transsulfuration occurs in tissues that contain both cystathionine β-synthase and cystathionine γ-lyase (155).

Mudd et al. (137) reported that cystathionine β-synthase activity was highest in liver and pancreas of rats, with substantial activity also present in kidney, small intestine, brain, and adipose tissue (137). High levels of cystathionine β-synthase activity were also found in monkey liver and pancreas and in human liver (137). Of four tissues tested (liver, kidney, brain, and lung), the highest levels of cystathionine β-synthase mRNA were found in liver of human adult tissues and in liver and brain of human fetal tissues (155). The expression of cystathionine β-synthase in brain of adult mice or rats was predominantly observed in the Purkinje cells and the hippocampal neurons (114, 163). High levels of cystathionine γ-lyase were found in liver, pancreas, and kidney of rats (137). Cystathionine γ-lyase was absent from fetal liver and brain, and fetal liver contained a higher level of cystathionine than did adult liver (76). Maximal hepatic activity was obtained at about three months of age in human infants (238), and cystathionine γ-lyase activity was present in various regions of brain from a six-month-old infant at autopsy (76).

In the steady-state metabolic condition in normal individuals, the intake of Met sulfur is balanced by metabolism of an almost equivalent amount of Hcy sulfur through the transsulfuration pathway (136, 154, 183, 194). This must be true regardless of the extent of remethylation. Little sulfur is oxidized or lost

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during Met metabolism and essentially all Met sulfur is transferred to Cys prior to oxidation/excretion of the sulfur atom.

A lack of cystathionine β-synthase is known to cause Hcy accumulation as well as export of Hcy from the cell, leading to homocysteinemia. In cystathionine β-synthase knockout mice, plasma Hcy levels were about 40 times higher than normal in the homozygous mice and 2 times higher than normal in heterozygous mutants (223). Adenosylhomocysteine was elevated in all tested tissues of the homozygous mutant mice (30, 40). Homozygous mutant mice lacking cystathionine β-synthase suffered from severe growth retardation, and the majority died within five weeks after birth.

As might be predicted, the overexpression of cystathionine β-synthase (on chromosome 21) in children with Down's syndrome results in significantly reduced plasma levels of Hcy, Met, SAH, and SAM, and a significant increase in plasma cystathionine and cyst(e)ine (62, 207). A lack of cystathionine γ-lyase leads to accumulation of cystathionine, which is released into plasma and excreted in the urine. Wang & Hegele (222) recently described two nonsense mutations and two missense mutations in the cystathionine γ-lyase gene of individuals with hereditary cystathionuria. All affected subjects were either simple homozygotes or compound heterozygotes.

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CYSTATHIONINE β-SYNTHASE AND REGULATION OF TRANSSULFURATION Human cystathionine β-synthase is a 63-kDa enzyme comprised of an N-terminal heme (protoporphyrin IX)-containing domain that exerts a regulatory influence on the protein, a catalytic domain that binds PLP, and a C-terminal domain that confers responsiveness of the protein to the allosteric activator SAM. The full-length human enzyme exists as aggregates of α4 tetramers (205). The catalytic core resembles other members of the fold II family of PLP-dependent enzymes (133, 204). It is not surprising that cystathionine β-synthase is a highly regulated enzyme, given its location at a branch point for remethylation, SAH synthesis, or transsulfuration.

The C-terminal regulatory domain inhibits activity of the full-length enzyme, but binding of SAM to this domain converts the enzyme to an activated state. Deletion of the C-terminal domain (residues 414–551) leads to formation of stable constitutively highly-activated enzyme (142), and the low activity of a number of disease-causing mutations in the catalytic core of the human enzyme can be alleviated by truncation or mutation of the C-terminal domain (176a). The activation of full-length cystathionine β-synthase by SAM involves a conformational change so that the C-terminal domain no longer plays an autoinhibitory role (98, 206). Point mutations of the C-terminal domain of cystathionine β-synthase have been identified in homocystinuric patients. These mutations result in diminished responsiveness to SAM and constitutive activation to various degrees (98). The C-terminal domain of human cystathionine β-synthase contains two hydrophobic motifs designated CBS domains, but the exact role of these domains has not been fully elucidated (142). The consequence of activation by SAM is increased removal of Hcy by transsulfuration, rather than by remethylation to Met.

The upregulation of cystathionine β-synthase during proliferation of HepG2 cells and its downregulation by contact inhibition, serum-starvation, nutrient depletion, or induction of differentiation was associated with increases or decreases, respectively, in intracellular SAM concentration (159).

The unusual heme-binding domain of human cystathionine β-synthase is constituted of a loop at the N terminus. The heme in mammalian cystathionine β-synthase may act as a redox sensor (133, 205). While reduction (e.g., by dithionite) of the heme moiety was associated with decreased enzyme activity, flux through cystathionine β-synthase was increased under oxidizing conditions (e.g., H_2O_2 or t-butylhydroperoxide) (134, 239). Deletion of the heme domain, but not the spatially adjacent vicinal thiols C272 and C275, yielded a mutant with reduced activity that was insensitive to reduction by dithionite (204). Nuclear magnetic resonance spectroscopy revealed that changes in heme oxidation state are sensed by the phosphorus nucleus of PLP bound to the catalytic domain of the enzyme (103). Regulation of cystathionine β-synthase by redox sensing may allow the cell to preferentially increase transsulfuration to generate Cys for GSH synthesis during oxidative stress.

Targeted proteolysis of the C-terminal domain of cystathionine β-synthase may also be involved in redox regulation of cystathionine β-synthase activity. TNFα, which is known to enhance production of ROS, increased cystathionine β-synthase activity in HepG2 cells; the higher enzyme activity was associated with proteolytic cleavage of the C-terminal domain to generate a truncated 45-kDa form of the enzyme with diminished sensitivity to allosteric regulation by SAM (239). Targeted proteolysis of cystathionine β-synthase was also observed in liver of mice injected with lipopolysaccharide, which is known to induce TNFα (239). The cleavage of cystathionine β-synthase was suppressed by inhibitors of superoxide production or by transfection with an expression vector for Mn-superoxide dismutase, implicating superoxide as the active agent. The activation of cystathionine β-synthase by H_2O_2 or t-butyl hydroperoxide (via heme oxidation) did not involve targeted proteolysis of the enzyme (134).

Redox regulation of cystathionine β-synthase activity is consistent with the reported reciprocal sensitivity of the transsulfuration pathway to pro- and antioxidants, which enhanced or diminished, respectively, the flux of Hcy through the transsulfuration pathway (134, 219). Transsulfuration is necessary for utilization of Met sulfur for GSH synthesis. Ames dwarf mice exhibit high levels of hepatic Met adenosyltransferase, cystathionine β-synthase, and glycine *N*-methyltransferase activities and a low SAM/SAH ratio (216). The apparently enhanced transmethylation/transsulfuration capacity and flux may play a role in the increased oxidative defense and extended life span observed in this strain of mice.

Hepatic cystathionine β-synthase gene expression is hormonally regulated at the transcriptional level. Glucagon, glucocorticoid, or cAMP elevating agents increase gene expression, whereas expression is decreased by administration of insulin (79, 96, 159). Individuals with diabetes mellitus and streptozotocin-induced diabetic rats have high hepatic cystathionine β-synthase activity and lower than normal

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levels of Hcy; insulin administration reverses these effects in a dose-dependent manner (16, 83, 95, 96).

Regulation of Remethylation Versus Transsulfuration in Response to Diet

RESPONSE TO CHANGES IN Met INTAKE The remethylation and transsulfuration pathways can be considered to be competing for available Hcy. Studies of whole-body Met kinetics demonstrated that in young adult men fed a diet with adequate Met (~14 mmol/day), transmethylation formed about 17 mmol/day of Hcy; approximately 38% of this Hcy was remethylated to Met while 62% was catabolized by transsulfuration (194). A similar estimate for Hcy remethylation, 32%, was obtained for young women consuming a diet adequate in energy but containing negligible amino acids (39). In another study, transmethylation or Hcy formation decreased markedly in subjects fed a sulfur amino acid–free diet, from approximately 20 mmol/day in men on an adequate diet to 6 mmol/day in men on a sulfur amino acid–free diet; the percentage of Hcy remethylated to Met increased from 36% in men on the adequate diet to 67% in men on the sulfur amino acid–free diet (193). As a result of decreased transmethylation or Hcy formation and the greater percentage remethylation of Hcy, transsulfuration or oxidation of Met was reduced from 12 mmol/day in men fed the Met-adequate diet to 2 mmol/day in subjects fed the sulfur amino acid–free diet. In a study with elderly subjects, women had slightly higher rates of transmethylation and remethylation, but similar rates of transsulfuration, compared to men (73).

The flux of Met through transsulfuration versus remethylation is regulated by the concentration of Hcy via the kinetic parameters of the enzymes in these pathways. The K_ms of transsulfuration enzymes for their substrates tend to be higher than those of the enzymes involved in the re- and transmethylation cycles. The K_m of cystathionine β-synthase is at least one order of magnitude greater than the K_m of the two Hcy methyltransferases. Thus, remethylation with Hcy conservation would be favored at low concentrations of the metabolite. Conversely, cystathionine β-synthase can utilize Hcy at higher concentrations that exceed the capacity of the Hcy methyltransferases. Activities of enzymes involved in the transmethylation, remethylation, and transsulfuration pathways are altered in response to protein or sulfur amino acid intake, but it is not clear to what extent the changes in activities are due to changes in enzyme concentration versus activation state. Liver of rats fed diets high in Met or protein had elevated Met adenosyltransferase, glycine *N*-methyltransferase, betaine-Hcy methyltransferase, cystathionine β-synthase, and cystathionine γ-lyase activities and reduced Met synthase activity (59, 67, 108, 109, 196). The abundance of betaine-Hcy methyltransferase and glycine *N*-methyltransferase was increased by excess dietary Met as determined by immunodetectable protein (148, 165). Clearly, increases in amounts of at least some of the enzymes in the Met metabolic pathways can be induced by increases in Met intake.

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RESPONSE TO SAM AS AN EFFECTOR The metabolism of Hcy by remethylation versus transsulfuration seems to be coordinated in response to cellular SAM concentrations or the need to generate Met methyl groups (176). In the liver, higher intracellular concentrations of SAM, usually as the result of excess Met intake, facilitate transsulfuration while limiting Hcy remethylation. Lower concentrations of SAM enhance Met conservation.

SAM is both an allosteric inhibitor of $N^{5,10}$-methylene-THF reductase (118) and an allosteric activator of cystathionine β-synthase. Hence, when the cellular SAM concentration is low, the synthesis of N^5-methyl-THF proceeds uninhibited, whereas cystathionine synthesis is suppressed. This results in the conservation of Hcy for Met synthesis. Conversely, when the SAM concentration is high, inhibition of N^5-methyl-THF synthesis is accompanied by the diversion of Hcy through the transsulfuration pathway because of stimulated cystathionine synthesis. In addition, the decrease in N^5-methyl-THF in response to high SAM concentration relieves inhibition of glycine *N*-methyltransferase, thus promoting removal of Met by transmethylation plus transsulfuration. Low levels of SAM have the reverse effect: relief of $N^{5,10}$-methylene-THF reductase inhibition, which leads to an increase in N^5-methyl-THF and greater inhibition of glycine *N*-methyltransferase, favoring remethylation of Hcy. The outcome of this coordinate control is both the regulation of the cellular SAM concentration and the maintenance of a concentration of Hcy that is compatible with the need for methyl groups synthesized de novo.

Redox regulation of cystathionine β-synthase may provide a means to promote transsulfuration at the expense of remethylation, independently of methylation status, when the body has an increased need for Cys for GSH synthesis. Hormonal regulation of hepatic cystathionine β-synthase expression may serve to conserve Met for protein synthesis in the fed state and to promote catabolism of the Met/Hcy carbon chain to α-ketobutyrate, a gluconeogenic substrate, in the starved state.

Met-SPARING EFFECT OF Cys Cys is said to have a Met-sparing effect by reducing Met catabolism via the transsulfuration pathway, and this appears to occur with intakes of typical food proteins in which the Met:Cys ratio ranges from ~1:1 to 2:1 (43). Maximal sparing of Met is about 64% as judged by observations on subjects consuming excess Cys and minimal Met (44). The action of supplemental Cys when it is added to a sulfur amino acid–free diet or to a low-Met diet may be explained at least partially by promotion of the incorporation of Met into protein such that less Met is catabolized (186, 193). The action of cyst(e)ine when it is used to replace part of the dietary Met, keeping the total molar amount of sulfur amino acids the same, may be explained by a reduction in the hepatic concentrations of Met and SAM and, hence, less activation of hepatic cystathionine β-synthase. When the Met:Cys ratio of the diet was increased from 1:0 to 1:1 to 1:3, the ratio of metabolism of Hcy by remethylation versus transsulfuration increased from 0.75 to 1.3 to 1.9 (42). This sparing effect of Cys is largely due to the "first-pass" metabolism of Met in the splanchnic region and was not observed in

studies where Met was administered intravenously (44). Less catabolism of Hcy by transsulfuration would result in an increase in the recycling of Hcy to Met using methyl groups generated by the folate coenzyme system.

RESPONSE TO SUPPLEMENTAL BETAINE Betaine is used extensively in the treatment of patients who have elevated Hcy levels due to impaired folate-dependent remethylation via Met synthase (141), but not those who have high Hcy levels due to impaired transsulfuration (170, 221, 226). Presumably, increased remethylation induced by betaine increases SAM concentration, which in turn stimulates cystathionine β-synthase. This hypothesis is supported by the observation of increased SAM, SAH, and Met levels in liver of rats and mice given supplemental betaine (108), and with kinetic studies showing that normal adult subjects given a control diet with a betaine supplement had increased rates of both Met transmethylation and transsulfuration (195). Caution with use of betaine therapy is suggested by a recent report of a child with B_6-nonresponsive cystathionine β-synthase deficiency whose Met levels reached 3 mmol/L during betaine supplementation and who subsequently developed massive cerebral edema (226). It is also likely that a high dietary intake of betaine when coupled with a marginal intake of methionine could interfere with the normal coordinated regulation of remethylation versus transsulfuration.

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METABOLIC BASIS OF HOMOCYSTEINEMIA AND HOMOCYSTINURIA

An increase in plasma Hcy could be due to an increased production rate (i.e., transmethylation), a decreased rate of removal by transsulfuration, a decreased rate of remethylation to Met, or a decrease in the uptake and metabolism/excretion of Hcy by the kidney. Examples of the latter three have been well established (104, 174, 218).

Impaired removal of Hcy by transsulfuration is associated with decreased activity of cystathionine β-synthase. The most common cause of severe homocysteinemia and homocystinuria is inborn errors in cystathionine β-synthase (60, 132, 153). Heterozygosity for a gene coding for nonfunctional cystathionine β-synthase causes a milder form of homocysteinemia. Vitamin B_6 deficiency can also impair Hcy removal by transsulfuration because both cystathionine β-synthase and cystathionine γ-lyase are PLP-dependent enzymes (36, 84, 215).

Decreased remethylation due to inborn errors of $N^{5,10}$-methylene-THF reductase activity is the second leading known cause of severe homocysteinemia and homocystinuria (154, 183). A milder form of $N^{5,10}$-methylene-THF reductase deficiency that results in ~50% residual enzyme activity in homozygotes is caused by a point mutation (677C $\rightarrow$ T) in the $N^{5,10}$-methylene-THF reductase gene (54, 97, 167). A second locus of impaired remethylation is Met synthase. Remethylation by Met synthase is blocked in patients with inborn errors affecting Met synthase itself or various steps in the synthesis of methylcobalamin, an essential cofactor for Met

synthase (140). Deficiencies of folate or vitamin B_{12}, particularly in individuals with underlying genetic predispositions, result in homocysteinemia (84, 112, 171, 175, 214, 215), and elevated plasma Hcy is recognized as a functional indicator of folate or vitamin B_{12} deficiency state.

Urinary excretion of extracellular Hcy is limited, even in individuals with defective Hcy metabolism, due to the extensive binding of plasma Hcy to proteins, which limits filtration, and due to the normally active renal reabsorption of free Hcy. Of the plasma Hcy filtered by the kidney, only about 1%–2% is excreted in the urine (161, 199). Normal urinary Hcy excretion ranges from 3.5 to 9.8 μmol/day (161). Renal cortical tubules take up homocystine from the filtrate by a high-affinity system shared with cystine and dibasic amino acids, which is probably the $b^{0,+}$ transporter (70). It seems likely that reabsorption from the renal filtrate leads to further catabolism of Hcy by the kidney. High levels of Hcy in urine are indicative of very high plasma Hcy concentrations due to an inborn error of metabolism.

Plasma Hcy is significantly increased in patients with moderate renal failure and rises steeply in patients with terminal uremia (26). The main cause of the rise in plasma Hcy in patients with renal failure is thought to be the diminished renal clearance of the plasma. If the plasma is not filtered, the parenchymal cells of the kidney do not take up and metabolize the plasma Hcy. Patients with renal disease may also exhibit a diminished renal capacity for Hcy metabolism by transsulfuration or remethylation (90, 217).

Certain drugs can interfere with normal Hcy metabolism. Many of these drug effects are due to secondary functional vitamin deficiencies. For example, theophylline is a vitamin B_6 antagonist and valproate has antifolate activity. Ubbink et al. (214) assessed the response of asthma patients deficient in vitamin B_6 as a consequence of being treated with theophylline to a Met load. In response to the Met load, the vitamin B_6–deficient subjects had an increase in plasma Hcy and cystathionine, whereas control subjects had no increase in Hcy and a smaller increase in cystathionine. For both groups, increases were eliminated after vitamin supplementation. Exposure of pregnant rats to valproate, a drug widely used to treat epilepsy, reduced maternal hepatic Met synthase activity and plasma Met level. It also reduced the fetal SAM/SAH transmethylation ratio and resulted in DNA hypomethylation in fetuses. Co-administration of folinic acid prevented valproate-induced alterations in Met synthesis and corrected fetal DNA hypomethylation (2). Children who had been receiving either carbamazepine or valproate for epilepsy for the past year had elevated plasma Hcy and lower plasma folate levels compared to a control group of healthy children (105).

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METABOLISM OF CYSTEINE

Partitioning of Cys Among Various Pathways

Cys, whether formed from Met and serine via transsulfuration or supplied preformed in the diet, serves as a precursor for synthesis of proteins and several other

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essential molecules. These metabolites include GSH, coenzyme A, taurine, and inorganic sulfur. In addition to the specific metabolic functions of GSH, GSH serves as a reservoir of Cys and as a means for transporting Cys to extrahepatic tissues. At intakes near the requirement, a large proportion of available Cys is used for synthesis of proteins and GSH. Synthesis of GSH is catalyzed by glutamate-cysteine ligase (EC 6.3.2.2) and GSH synthetase (EC 6.3.2.3). Glutamate-cysteine ligase catalyzes the rate-limiting step for GSH synthesis, and it is highly regulated by feedback inhibition by GSH, association with its modifier subunit, and transcriptional regulation in response to oxidative or chemical stress. The activity of glutamate-cysteine ligase and the capacity for GSH synthesis is reduced in liver of rats fed high-protein or high-sulfur amino acid diets, although net synthesis remains high due to the increased Cys/substrate concentration (8, 9, 123, 191). This downregulation in response to increased Cys availability facilitates Cys catabolism to taurine and sulfate rather than conservation as GSH.

A large proportion of the sulfur amino acid intake is converted to GSH by the liver and released into the circulation (74). γ-Glutamyl transpeptidase (EC 2.3.2.2), an enzyme located on the outer surface of the plasma membrane of cells in a number of tissues, hydrolyzes GSH (or its disulfide) to yield CysGly (or its disulfide), which can be further degraded by dipeptidases to release Cys (or cystine) into the plasma. The normal turnover of GSH in humans is estimated to account for the flux of about 40 mmol Cys per day, a flux similar to that for turnover of Cys in the body protein pool (72, 122).

Cys is also a precursor for the synthesis of coenzyme A and for the production of taurine and inorganic sulfur (sulfide, sulfate). These three fates of Cys involve loss of the Cys moiety as such. Cys is substrate for coenzyme A synthesis in that it is used to form the cysteamine (decarboxylated Cys) moiety of the coenyzme A molecule and, hence, contributes the reactive sulfhydryl group. Very little is known about the rate of coenzyme A turnover or the fate of the cysteamine moiety. However, the recent identification of the pantothenate kinase gene PANK2 as the gene responsible for Hallervorden-Spatz syndrome, which is characterized by the accumulation of Cys in the basal ganglia, suggests that coenzyme A turnover may consume a substantial amount of Cys (78, 237).

Both taurine and inorganic sulfur are products of Cys catabolism. There are several pathways for Cys catabolism. Cys may be oxidized to cysteinesulfinate, which is then further metabolized to taurine + CO_2 or to pyruvate + inorganic sulfur. In addition, Cys catabolism may occur by desulfuration of Cys to yield pyruvate and reduced sulfur (often in the form of a persulfide such as thiocysteine, mercaptopyruvate, or thiosulfate). In all Cys catabolic pathways except that for taurine formation, the carbon chain of Cys is released as pyruvate, the sulfur is released as inorganic sulfur, and the amino group is released as ammonia or transferred to a keto acid acceptor. When taurine is the end product, only the carboxyl carbon of Cys is released and the other two carbons as well as the nitrogen and sulfur atoms remain in the end product. Thus, the distribution of Cys among its catabolic pathways potentially affects the utilization of amino acid carbon chains

for energy, the net production of acid or fixed anions (sulfate), and the synthesis of essential metabolites (inorganic sulfur and taurine). Although taurine and sulfate are end products of cellular Cys catabolism, both of these compounds participate in conjugation reactions and have a variety of essential physiological functions prior to their ultimate excretion.

Oxidation of Cys to Cysteinesulfinate

In the cysteinesulfinate-dependent pathways of Cys catabolism, the sulfur is partially oxidized prior to its cleavage from the carbon chain or its decarboxylation to form hypotaurine. This initial oxidation of the Cys thiol is carried out by Cys dioxygenase (EC 1.13.11.20). Cys dioxygenase is a 23-kDa iron-containing enzyme that has a high specificity for Cys as substrate and a K_m for Cys of ~0.45 mmol/L (5, 190, 228). Cys dioxygenase is expressed in high levels in liver, where it is uniformly distributed in hepatocytes (10, 86, 191). Expression of Cys dioxygenase is very limited in nonhepatic tissues; modest levels of expression are found in the kidney, lung, and brain (86, 191, 212). Strong expression of CDO mRNA has also been reported in adipose tissue of rats (92). Hepatic Cys concentration is maintained at ~0.01 to 0.1 mmol/L (123, 191), which is substantially below the K_m of Cys dioxygenase for Cys, so the enzyme is able to respond to changes in tissue substrate concentration.

In addition, upregulation of hepatic Cys dioxygenase concentration occurs in animals fed diets with increased levels of dietary protein or sulfur amino acids, and Cys dioxygenase reaches a new steady state within a few hours of a change in diet (4, 6, 8, 9, 113, 120, 123). In animals fed diets that provide protein or sulfur amino acids at levels near or above the requirement, Cys catabolism occurs predominantly by cysteinesulfinate-dependent pathways (11, 183). Although dietary Met is as effective as dietary Cys in the upregulation of Cys dioxygenase, the effectiveness of Met depends upon a functioning transsulfuration pathway (35, 120). This regulation is clearly posttranscriptional because the hepatic Cys dioxygenase mRNA level is not affected by diet (8, 9, 12, 123, 191). Regulation of Cys dioxygenase has recently been shown to occur at the level of polyubiquitination of Cys dioxygenase (12, 189). Cys dioxygenase is rapidly degraded in liver of rats fed low-protein diets, keeping Cys dioxygenase activity very low. However, when rats are fed high levels of protein or sulfur amino acids, hepatic Cys levels increase and prevent the polyubiquitination of Cys dioxygenase and, hence, its degradation by the 26S proteasome (189). Whereas most reducing agents, GSH, or Cys analogs with oxidized or blocked sulfhydryl groups were ineffective at reducing Cys dioxygenase polyubiquitination and degradation, L-cysteamine (2-mercaptoethylamine) was almost as effective as L-cysteine. L-Cysteamine is not an effective substrate or inhibitor of Cys dioxygenase and it cannot be converted to Cys, leading to the hypothesis that Cys, or cysteamine, may act allosterically to block ubiquitination of Cys dioxygenase. Regardless of the precise signaling mechanism, the regulation of Cys dioxygenase degradation allows a

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robust regulation of hepatic Cys dioxygenase in response to changes in dietary sulfur amino acid influx (123, 189).

Cys dioxygenase in nonhepatic tissues is not regulated in response to dietary sulfur amino acid intake, perhaps because the liver effectively controls body Cys levels (191). In contrast to the liver, Cys dioxygenase in kidney and lung has been reported to be highly localized in renal tubular or bronchial epithelial cells (178). Little is known about Cys metabolism in the kidney, although this organ is unique in that it has unusually high Cys levels that approach 1 mmol/kg (66, 191) and has 10 to 30 times as much glutamate-cysteine ligase activity as does the liver (191). The kidney has a high rate of GSH turnover, and it may partition Cys to GSH rather than to catabolism (see Figure 2).

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Cysteinesulfinate Metabolism

Cysteinesulfinate, formed by action of Cys dioxygenase on Cys, may be decarboxylated to hypotaurine by cysteinesulfinate decarboxylase (EC 4.1.1.29). The hypotaurine is subsequently oxidized to taurine. Alternatively, cysteinesulfinate may be transaminated (with α-ketoglutarate) in a unidirectional reaction to form the enzyme-bound keto acid β-sulfinylpyruvate, which gives rise to pyruvate and sulfite, which is readily oxidized to sulfate. Thus, oxidation of Cys by Cys dioxygenase leads to both taurine and sulfate formation, with sulfate being the dominant product excreted in the urine and the dominant product formed by isolated tissues (13, 203, 208, 234). Rats fed low- or high-protein diets excreted 94%–99% of total sulfur as sulfate, and sulfate accounted for 93%–96% of total Cys catabolites formed by isolated hepatocytes from rats that had been fed either low- or high-protein diets (13). In contrast, rats fed excess Met excreted 49% of total sulfur as sulfate, and sulfate accounted for 68% of the total Cys catabolites formed by hepatocytes from rats fed excess Met (13). The mechanism underlying the much higher taurine formation and excretion in rats fed excess Met than in rats fed excess protein is not understood, but a switch to taurine formation would have a favorable effect on acid-base balance in these animals who received excess sulfur amino acid without an overall increase in amino acids.

When cysteinesulfinate itself was used as substrate, the intact rat as well as isolated hepatocytes, renal cortical tubules, and enterocytes all exhibited a high capacity for cysteinesulfinate metabolism to CO_2 or SO_4, with rates of cysteinesulfinate oxidation far exceeding those for Cys catabolism to CO_2 or SO_4. However, only hepatocytes had a high capacity for taurine synthesis from cysteinesulfinate, which suggests that partitioning of cysteinesulfinate between decarboxylation and transamination also plays a role in determining the capacity of a given tissue for taurine formation (32, 45, 188, 192).

Taurine synthesis requires the presence of both Cys dioxygenase and cysteinesulfinate decarboxylase. Cysteinesulfinate decarboxylase, a PLP-dependent enzyme, converts cysteinesulfinate to hypotaurine (2-aminoethanesulfinate). The K_m of cysteinesulfinate decarboxylase for cysteinesulfinate is ~0.04–0.17 mM

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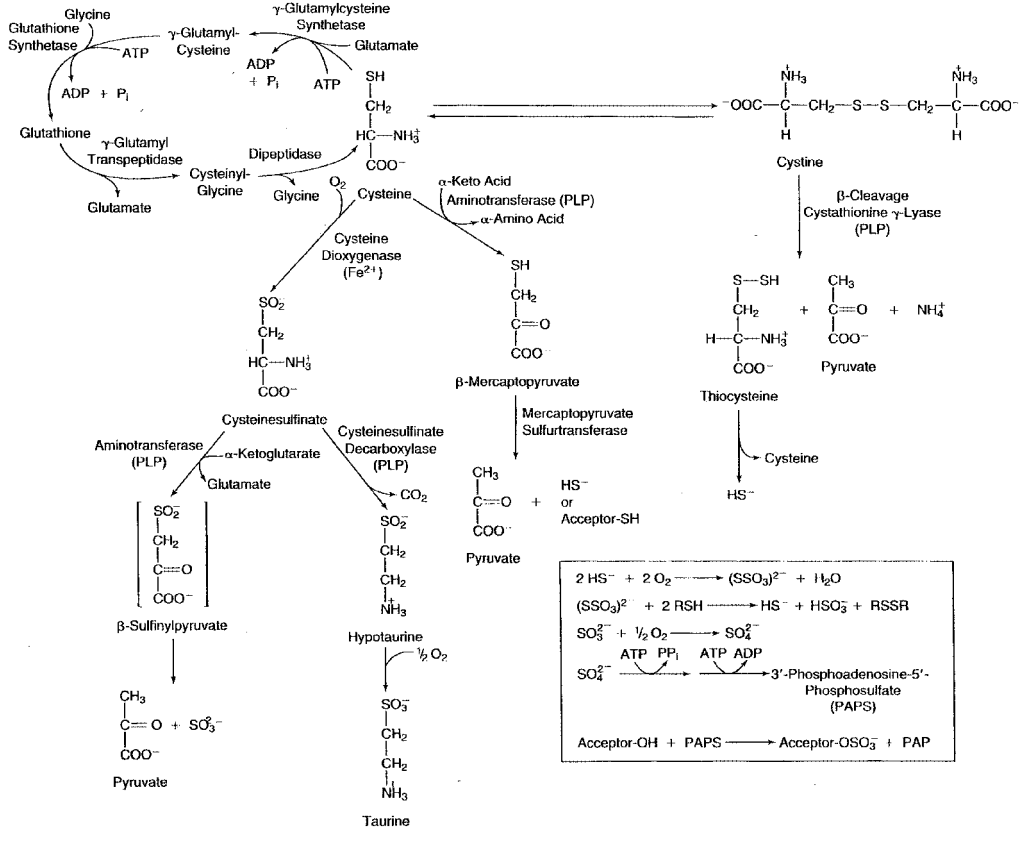

Figure 2 Pathways of cysteine and inorganic sulfur metabolism, including glutathione synthesis and degradation. The desulfhydration of cysteine catalyzed by cystathionine β-synthase is not shown but may involve the formation of a thioether from two cysteine molecules with the release of H_2S. From Reference 192a, p. 268.

(82, 140) versus ~3–25 mM for aspartate aminotransferase (160, 227). Cysteinesulfinate decarboxylase is present in high levels in rat liver where it is markedly enriched in perivenous versus periportal hepatocytes (10). Arterial-venous difference measurements indicated that taurine synthesis occurs predominantly in the liver of rats (74). Taurine synthesis from Cys has been demonstrated in isolated rat hepatocytes (6, 11, 13) and cultured rat astroglial cells (18), but not in rat enterocytes (33) or rat renal cortical tubules (188).

Cysteinesulfinate decarboxylase mRNA levels in kidney are similar to those in liver, but the amounts of enzyme protein and activity are much lower in kidney (92, 191). Cysteinesulfinate decarboxylase mRNA and enzyme protein/activity are found in lower levels in brain and lung of rats (162, 191), and high levels of mRNA and activity have been reported for rat adipose tissues (92). Hypotaurine is further oxidized to taurine and does not typically accumulate in tissues; the mechanism of hypotaurine oxidation is not well understood. Hypotaurine did accumulate and was observed in the urine of rats following a two-thirds hepatectomy (19).

Cysteinesulfinate transamination is catalyzed by aspartate aminotransferase (EC 2.6.1.1) (224, 227). The sulfite resulting from transaminative metabolism of cysteinesulfinate is readily oxidized by sulfite oxidase (EC 1.8.3.1) to sulfate. Sulfate can either be excreted in the urine or activated to 3′-phosphoadenosine-5′-phosphosulfate, which, in turn, serves as a sulfate donor for sulfate ester formation. Several patients with inborn errors of the sulfite oxidase gene or errors affecting molybdenum cofactor synthesis have been described; these patients have elevated urinary levels of thiosulfate and *S*-sulfocysteine ($CySSO_3^-$), which is formed nonenzymatically by reaction of Cys and sulfite (33, 100, 110, 168, 209). About half of the total Cys catabolism by enterocytes and renal cortical tubules appeared to be cysteinesulfinate-dependent, presumably catalyzed by Cys dioxygenase plus aspartate aminotransferase but not cysteinesulfinate decarboxylase (33, 188).

A low capacity to oxidize Cys to sulfate has been observed in some individuals with liver diseases or rheumatoid arthritis (17, 38), and inconsistently in individuals with some chronic neurological diseases (85, 152). These individuals had elevated plasma ratios of Cys to sulfate due to lower sulfate and higher Cys concentrations, excreted a smaller percentage of a dose of acetaminophen as the sulfate versus the glucuronide conjugate, or had a lower sulfate concentration of synovial fluid, all of which are consistent with impaired Cys oxidation at the level of Cys dioxygenase.

In rats fed high-protein or very high sulfur amino acid–containing diets, the amount of hepatic cysteinesulfinate decarboxylase decreases by up to 80% (6, 8, 9, 37, 191). Nevertheless, taurine levels in tissues and urine of rats and taurine production from Cys by hepatocytes isolated from rats fed these diets were elevated. Although the elevation of taurine level may be partly attributed to the greater available substrate in animals fed high-protein or high-sulfur amino acid diets, studies with hepatocytes clearly show that the higher level of Cys dioxygenase activity plays a dominant role in increasing the rate of both taurine and sulfate formation

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(4, 6, 13). Clearly, cysteinesulfinate decarboxylase is not the limiting factor in taurine production or Cys catabolism in the rat liver. Some species, notably the cat, have little capacity for taurine formation, and this limited capacity is associated with low activities of both Cys dioxygenase and cysteinesulfinate decarboxylase (161b).

The human liver has been reported to have a low activity of cysteinesulfinate decarboxylase relative to the rat (75). Nevertheless, the adult human seems to have a significant ability to synthesize taurine. In vivo assessment of the ability of adults to synthesize taurine, based upon incorporation of ^{18}O (from inhaled $^{18}O_2$) into taurine, resulted in conservative estimates of synthesis in the range of 200–400 μmol per day (94). These estimates are equivalent to 1%–3% of the total sulfur amino acid intake and compare favorably with the mean taurine excretion of $\sim$250 μmol/day observed in strict vegans consuming an essentially taurine-free diet (121, 157). Thus, the percentage of the sulfur amino acid intake or total urinary sulfur excretion that is represented by urinary taurine in humans fed taurine-free diets is similar to that observed in rats fed taurine-free diets (2%–6%) (13). This similar pattern of metabolism between rats and humans seems to dispute the often-made statement that the rat has a high capacity for taurine synthesis whereas humans have a low capacity. It seems possible that a relatively high hepatic Cys dioxygenase activity in man may permit high rates of Cys catabolism to cysteinesulfinate and that relatively high concentrations of cysteinesulfinate may allow adequate rates of taurine synthesis despite relatively low cysteinesulfinate decarboxylase activity.

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Catabolism of Cys by Desulfuration Reactions

Cys DESULFURATION AND SULFIDE OXIDATION Catabolism of Cys also occurs by several somewhat nonspecific reactions that cleave the sulfur from Cys prior to its oxidation (185). These pathways include (*a*) the β-cleavage of cystine by cystathionine γ-lyase to yield pyruvate, ammonia, and thiocysteine, followed by further reaction of thiocysteine to release sulfide; (*b*) the transamination of Cys or cystine by aminotransferases to yield 3-mercaptopyruvate, which is further metabolized by mercaptopyruvate sulfurtransferase (EC 2.8.1.2) to release or transfer the sulfur; and (*c*) the substitution of the thiol group of Cys with a variety of thiol compounds to form the corresponding thioether in a reaction catalyzed by cystathionine β-synthase (183, 185). H_2S is a potential product of each of these desulfuration pathways. The reduced sulfur may be used in synthesis of molecules requiring a source of reduced sulfur, or it may be oxidized to thiosulfate (inner sulfur atom), sulfite, and finally sulfate. Although most of the inorganic sulfur is eventually oxidized to sulfate, mammals do not have the ability to reduce inorganic sulfate or sulfite to thiosulfate or sulfide and are thus dependent upon the cysteinesulfinate-independent or desulfhydration pathways of Cys metabolism as a source of reduced forms of inorganic sulfur.

Koj et al. (115) and Szczepkowski et al. (201) elucidated the reactions involved in sulfide oxidation.

$$2HS^- + 2O_2 \rightarrow (SSO_3)^{-2} + H_2O$$

$$(SSO_3)^{-2} + 2GSH \rightarrow HS^- + HSO_3^- + GSSG$$

$$SO_3^{-2} + {}^1/_2O_2 \rightarrow SO_4^{-2}$$

These reactions are consistent with the GSH dependence of sulfate production by hepatocytes incubated with 10 mM Cys reported by Huang et al. (91). GSH depletion or GSH depletion plus inhibition of glutamate-cysteine ligase markedly reduced sulfate production from L-cysteine and resulted in accumulation of thiosulfate. When thiosulfate was used as a substrate, GSH depletion similarly blocked its conversion to sulfate.

Studies of Cys desulfhydration in rat tissues (185) suggested that cystathionine γ-lyase and cystathionine β-synthase were responsible for sulfide production from Cys. Propargylglycine, an irreversible inhibitor of cystathionine γ-lyase, inhibited desulfhydration, and SAM, an activator of cystathionine β-synthase, enhanced desulfhydration. Cys transamination did not appear to make a significant contribution under more physiological assay conditions. In other studies, about half of the Cys catabolism by rat enterocytes or renal cortical tubules occurred via cysteinesulfinate-independent pathways as evidenced by thiosulfate formation and inhibition by propargylglycine (33, 188). Although it has been difficult to assess the physiological significance of Cys transamination, individuals with a rare inborn error of β-mercaptopyruvate sulfurtransferase excrete the mixed disulfide of Cys and β-mercaptolactate, which suggests that transamination of Cys to mercaptopyruvate occurs to some extent in humans (34). These patients excrete normal levels of urinary sulfate, indicating that overall Cys catabolism is not impaired.

The capacity of Cys desulfhydration pathways is low and minimally responsive to increased intakes of Met or Cys (37, 182), but these pathways may provide a constitutive pathway for production of reduced sulfur. On the other hand, the cysteinesulfinate-dependent catabolic pathways provide a robust and responsive system for removal of excess Cys without production of toxic H_2S. Thus, hepatic Cys dioxygenase activity is low and the desulfuration or cysteinesulfinic acid–independent pathways appear to be the dominant pathways of Cys catabolism in rats fed diets that are low in protein and sulfur amino acids. In contrast, the desulfhydration pathways appear to be of negligible quantitative significance in rats fed normal or high levels of protein because these rats have high levels of hepatic Cys dioxygenase and a much greater overall capacity for Cys catabolism (8, 13, 45).

Physiological Significance of H_2S Production

A series of recent studies provide evidence that regulated production of H_2S has important physiological functions and further document the role of cystathionine β-synthase and cystathionine γ-lyase in H_2S production from Cys. Kimura and

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coworkers (1, 56) demonstrated that the brain produces endogenous H_2S from Cys by cystathionine β-synthase-dependent desulfuration. Endogenous H_2S was below detectable levels in the brains of cystathionine β-synthase knockout mice (57). Eto et al. (55) also found that levels of H_2S were severely decreased in the brain of Alzheimer's disease patients compared with the brains of age-matched normal individuals. Brain of Alzheimer's patients also had reduced cystathionine β-synthase activity, elevated Hcy, and a reduced level of SAM, an activator of cystathionine β-synthase. Patients with Alzheimer's disease also have elevated plasma Hcy levels (31). These observations on patients with Alzheimer's disease are consistent with a role of cystathionine β-synthase in H_2S production.

Production of H_2S appears to be regulated by a Ca^{2+}- and calmodulin-mediated pathway that is activated in response to neuronal excitation (56, 57). Cystathionine β-synthase contains a calmodulin-binding sequence in its C-terminal domain, and it appears that this sequence suppresses desulfhydration activity in the absence of Ca^{2+}/calmodulin. Physiological concentrations of H_2S specifically potentiate the activity of the N-methyl-D-aspartate receptor, and induce long-term potentiation in the hippocampus (1, 109a).

H_2S may also play a role as a smooth muscle relaxant. Hosoki et al. (89) reported that cystathionine γ-lyase mRNA is expressed in the ileum, portal vein, and thoracic aorta, tissues that produce H_2S. Inhibitor studies suggested that the production of H_2S in portal vein and thoracic aorta was catalyzed by cystathionine γ-lyase, whereas that in ileum was catalyzed by both cystathionine γ-lyase and cystathionine β-synthase. Relaxation of rat aortic tissues, rabbit ileum, and rabbit vas deferens in response to H_2S occurred in a dose-related manner (207a, 235a). Additionally, sodium hydrosulfide produced significant dose-dependent decreases in uterine spontaneous contractility (179). Of the amino acids tested, only L-Cys produced a significant reduction in spontaneous contractility at a dose of 1 mM.

The mechanism by which H_2S brings about smooth muscle relaxation is not fully understood. Zhao et al. (236) demonstrated that H_2S decreased blood pressure of rats and relaxed aortic tissues by directly opening K_{ATP} channels in vascular smooth muscle cells. Cystathionine γ-lyase was expressed in vascular smooth muscle cells but not in endothelial cells. The vasorelaxant property of H_2S on rat aortic tissues was attenuated by Ca^{2+}-dependent K channel blockers or by omission of Ca^{2+} (235a). The action of H_2S did not require nitric oxide (NO), but low concentrations of H_2S acted synergistically to enhance NO-induced smooth muscle relaxation (89). Sodium nitroprusside, an NO donor, increased cystathionine γ-lyase expression and stimulated cystathionine γ-lyase desulfhydration activity in rat aortic and rat lung tissues (236). Thus, the synergistic effects of H_2S and NO may be partially explained by NO-induction of H_2S production.

SUMMARY

Research in the area of sulfur-containing amino acid metabolism during the past decade or two has resulted in several large contributions within this field. Although our understanding of the basic pathways of methionine metabolism have

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not changed substantially, our understanding of the complexity and integration of the regulation of these pathways has grown greatly. The contributions to a greater understanding of the role of glycine *N*-methyltransferase and cystathionine β-synthase in regulation of the flux through the transmethylation and transsulfuration pathways are notable examples. The focus on adverse effects of plasma Hcy has been a great stimulus to research in this area. Our understanding of Cys metabolic pathways has lagged behind our understanding of those for Met metabolism, but we now have a firm understanding of the nature of the cysteinesulfinate-dependent and cysteinesulfinate-independent pathways and their specific roles. Notable advances in our understanding of Cys metabolism include (*a*) the robust cysteine-responsive downregulation of the polyubiquitination/degradation of hepatic Cys dioxygenase, the first step in cysteinesulfinate-dependent pathways of Cys metabolism, which catalyzes; and (*b*) the role of cystathionine β-synthase and cystathione γ-lyase in generating H_2S to act as a neuromodulator and smooth muscle relaxant. The role of Cys as the substrate for H_2S production via cysteinesulfinate-independent pathways may be one reason the body needs a nondesulfhydration (i.e., the cysteinesulfinate-dependent) pathway for rapid removal of excess Cys.

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