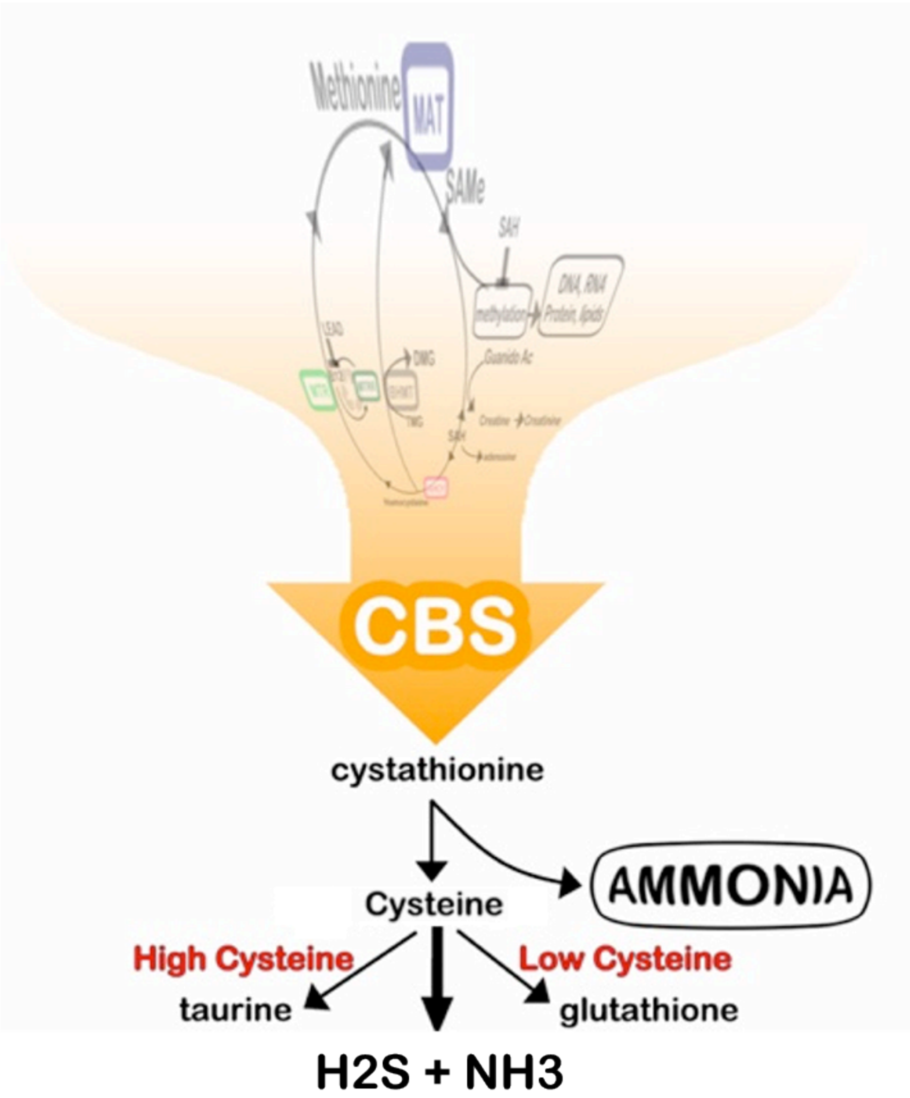
CBS

CBS


Methionine
MAT
SAMe
SAH
DNA, RNA
Protein, lipids
methylation
DMG
Guanido Ac
CBS
cystathionine
Cysteine
AMMONIA
High Cysteine
taurine
Low Cysteine
glutathione
H2S + NH3

Clin Genet 2000: 58: 455–459
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Original Article

Influence of 699C→T and 1080C→T polymorphisms of the cystathionine β-synthase gene on plasma homocysteine levels

Aras Ö, Hanson NQ, Yang F, Tsai MY. Influence of 699C→T and 1080C→T polymorphisms of the cystathionine β-synthase gene on plasma homocysteine levels.
Clin Genet 2000: 58: 455–459. © Munksgaard, 2000

The association of moderately elevated total homocysteine (tHcy) levels with coronary artery disease is increasingly being recognized. However, the role of genetic influence on plasma tHcy levels is not completely understood. We studied 1033 individuals with respect to the effect of two silent polymorphisms, the 699C→T and the 1080C→T, of the cystathionine β-synthase (CBS) gene on plasma tHcy levels. Individuals who were heterozygous or homozygous for the T^{699} allele had lower post-methionine load (PML) tHcy levels when compared to individuals with the C/C genotype. This association was statistically significant ($p = 0.005$) for the T/T genotype compared to the C/C genotype and became even more significant ($p = 0.000002$) when individuals carrying the 68-bp insertion (844ins68) and the T^{833} allele were excluded from the analysis. With regard to the 1080C→T polymorphism, the T^{1080} allele was associated with significantly lower PML tHcy levels only when individuals carrying the 844ins68 and T^{833} allele were excluded from the study ($p = 0.01$ for 1080T/T genotype compared to 1080C/C genotype). We speculate that the 699C→T and 1080C→T polymorphisms may be in linkage disequilibrium with regulatory elements that upregulate CBS gene transcription.

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Key words: cystathionine β-synthase – genetic variants – homocysteine – post-methionine load homocysteine

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Homocysteine is a sulfur amino acid, which is formed from the essential amino acid methionine. Once formed, homocysteine can either undergo transsulfuration to form cystathionine and cysteine or be remethylated to form methionine. Cystathionine β-synthase (CBS, EC 4.2.1.22) is an important enzyme in the transsulfuration pathway of homocysteine metabolism. It has been suggested that the fasting level of total homocysteine (tHcy) in plasma may be determined by homocysteine remethylation, while increased post-methionine load (PML) tHcy may reflect abnormalities in the transsulfuration pathway (1).

Hyperhomocysteinemia is characterized by mild-to-moderately elevated levels of tHcy and can be caused by genetic factors (2), nutritional deficiencies (3), and/or renal insufficiency (4). Many studies have shown that moderately elevated levels of plasma tHcy, whether measured during fasting or 2–6 h after a dose of methionine, are important risk factors for coronary artery disease (CAD) (3, 5–11). Moderate hyperhomocysteinemia can be caused by genetic defects in either the remethylation or the transsulfuration pathway. Elevated plasma tHcy levels, particularly those measured after a methionine load, were initially thought to be caused by heterozygosity of mutations found in patients with CBS-deficient homocystinuria (12, 13). However, recent studies have shown that deleterious mutations, such as the 833T→C (I278T) and 919G→A (G307S) are present in < 1% of the general population (14, 15) and account for < 5% of the patients with hyperhomocysteinemia (15). Although a large number of mutations in the CBS gene have been identified (16), most of these mutations are rare. A more prevalent 68-bp insertion

CHARACTERIZATION OF THE C-TERMINAL REGULATORY DOMAIN IN CYSTATHIONINE BETA-SYNTHASE. SHAN, KRUGER

Our laboratory has previously developed a yeast functional assay for the human *CBS* gene. In this assay, expression of human *CBS* cDNA rescues the cysteine requirement of a yeast strain deleted for the endogenous CBS enzyme. In the course of expressing and characterizing various human mutant CBS proteins in this yeast strain, we have identified a mutation that can partially suppress a number of different disease causing *CBS* alleles. This suppressor mutation when expressed in cis can partially suppress the yeast growth defect of at least eight different *CBS* mutations. This mutation creates a stop codon at amino acid 411 of the *CBS* gene, and thus truncates about one quarter of the protein. Our hypothesis is that this truncated region of the protein acts as a negative regulatory domain, and truncation of this region allows an increase in the residual activity of the mutant proteins. To confirm this hypothesis, we have expressed and purified various forms of CBS and measured enzyme activity in vitro. **These studies have shown that truncated CBS protein is ten times more active than the full-length form.** In addition, we have discovered that this inhibition by the C terminus appears to be responsible for regulation by Sadenosylmethionine, an allosteric affector of *CBS*. These findings suggest
that the C terminus of CBS would be a good potential target for
homocysteine lowering drugs.

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Production of the Neuromodulator H_2S by Cystathionine β-Synthase via the Condensation of Cysteine and Homocysteine*

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Hydrogen sulfide (H_2S) has been observed in relatively high concentrations in the mammalian brain and has been shown to act as a neuromodulator. However, there is confusion in the literature regarding the actual source of H_2S production. Reactions catalyzed by the cystathionine β-synthase enzyme (CBS) are one possible source for the production of H_2S. Here we show that the CBS enzyme can efficiently produce H_2S via a β-replacement reaction in which cysteine is condensed with homocysteine to form cystathionine and H_2S. The production of H_2S by this reaction is at least 50 times more efficient than that produced by hydrolysis of cysteine alone via β-elimination.

CBS

Science News April 23, 2005

Inducing a “topor like” state with hydrogen sulfide gas. The gas competes with oxygen in mitochondria, slowing the metabolic activity.

Topor is an extreme state of metabolic slowdown in which the heart rate drops, breathing slows and body temperature plunges.

Nutr Rev. 2004 Sep;62(9):348-53

New roles for cysteine and transsulfuration enzymes: production of H2S, a neuromodulator and smooth muscle relaxant.

Dominy JE, **Stipanuk MH**.

Division of Nutritional Sciences, Cornell University, Ithaca, NY 14853, USA.

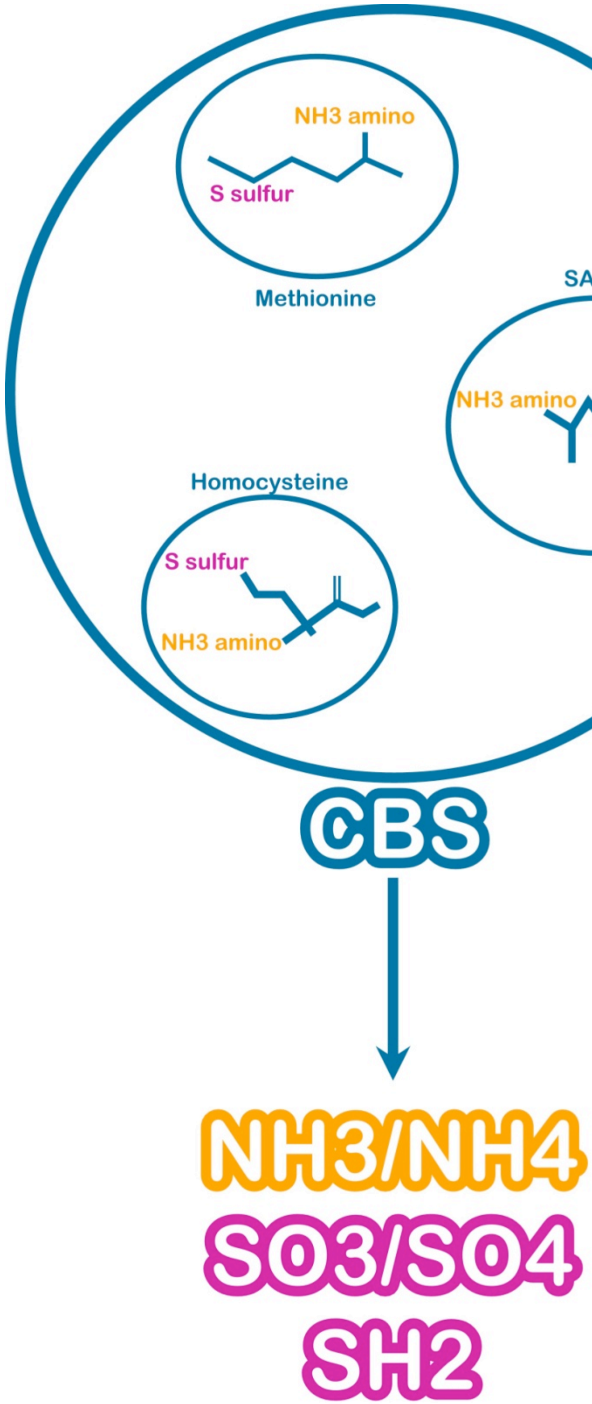
The enzymes of the transsulfuration pathway also have the capacity to catalyze the desulfhydration of cysteine. Recent studies demonstrate a role of the transsulfuration enzymes, cystathionine gamma-lyase and cystathionine beta-synthase, in catalyzing the desulfhydration of cysteine in brain and smooth muscle. The H2S produced from cysteine functions as a neuromodulator and smooth muscle relaxant. **In glutamatergic neurons, the production of H2S by cystathionine beta-synthase enhances N-methyl-D-aspartate (NMDA) receptor-mediated currents.** In smooth muscle cells, H2S produced by cystathionine gamma-lyase enhances the outward flux of potassium by opening potassium channels, leading to hyperpolarization of membrane potential and smooth muscle relaxation.

The essentiality of sulfur is closely related to nitrogen metabolism: a clue to hyperhomocysteinaemia

N and S metabolisms are closely interwoven throughout both the plant and animal kingdoms. The essentiality of S relates to its participation in the structure of S-containing amino acids (SAA), to its inclusion in many sulfonated molecules, and to a myriad of metabolic and catalytic reactions of vital importance. Methionine (Met) is the indispensable SAA supplied by food proteins and its plasma homeostasis is achieved via a number of highly efficient regulatory mechanisms. In all conditions characterized by a negative body protein balance such as in dietary restriction or cytokine-induced hypercatabolic losses, N and S endogenous pools manifest parallel tissue depletion rates. **Adaptive conservation of N and S body stores is reached by a functional restraint of the trans-sulfuration cascade, through the depression of cystathionine -synthase activity. As a result, upstream accumulation of homocysteine favors its re-methylation conversion to Met which helps maintain metabolic pathways of survival value.**

Yves Ingenbleek1; Vernon R. Young
Nutrition Research Reviews, December 2004, vol. 17, no. 2, pp. 135-151(17)

CBS


NH3 amino
S sulfur
Methionine
SAMe
NH3 amino
S sulfur
Homocysteine
S sulfur
NH3 amino
CBS
NH3/NH4
SO3/SO4
SH2

Enzymes and Metabolites of Cysteine Metabolism in Nonhepatic Tissues of Rats Show Little Response to Changes in Dietary Protein or Sulfur Amino Acid Levels[1]

Martha H. Stipanuk,[2] Monica Londono, Jeong-In Lee, Mindy Hu and Anthony F. Yu

Division of Nutritional Sciences, Cornell University, Ithaca, NY 14853

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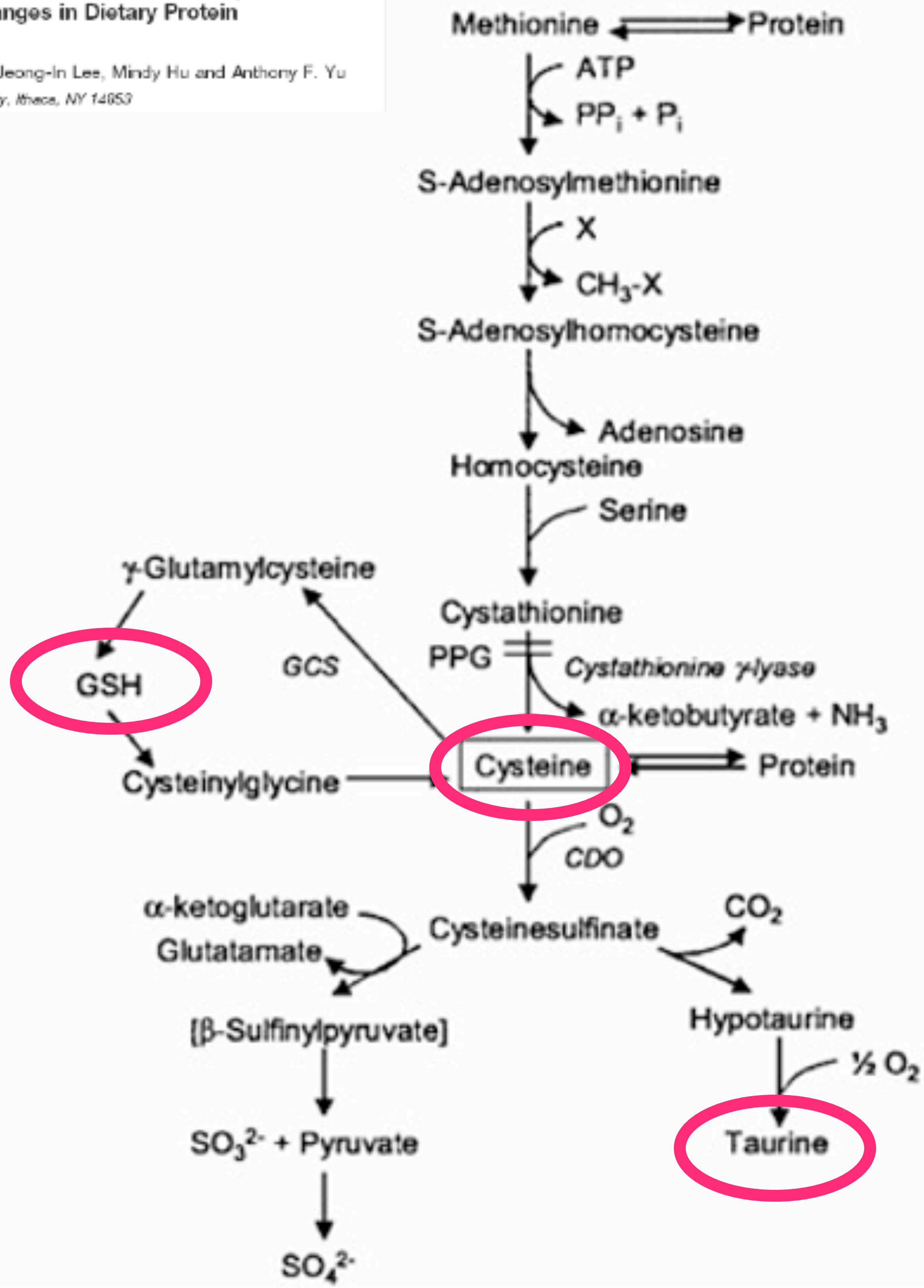
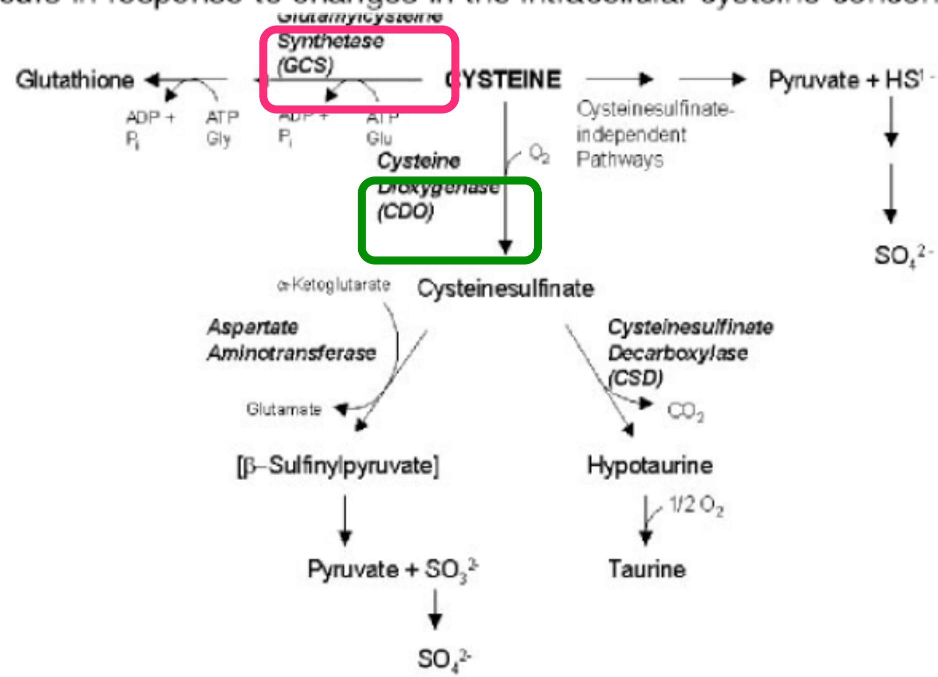


Mammalian Cysteine Metabolism: New Insights into Regulation of Cysteine Metabolism[1,2]

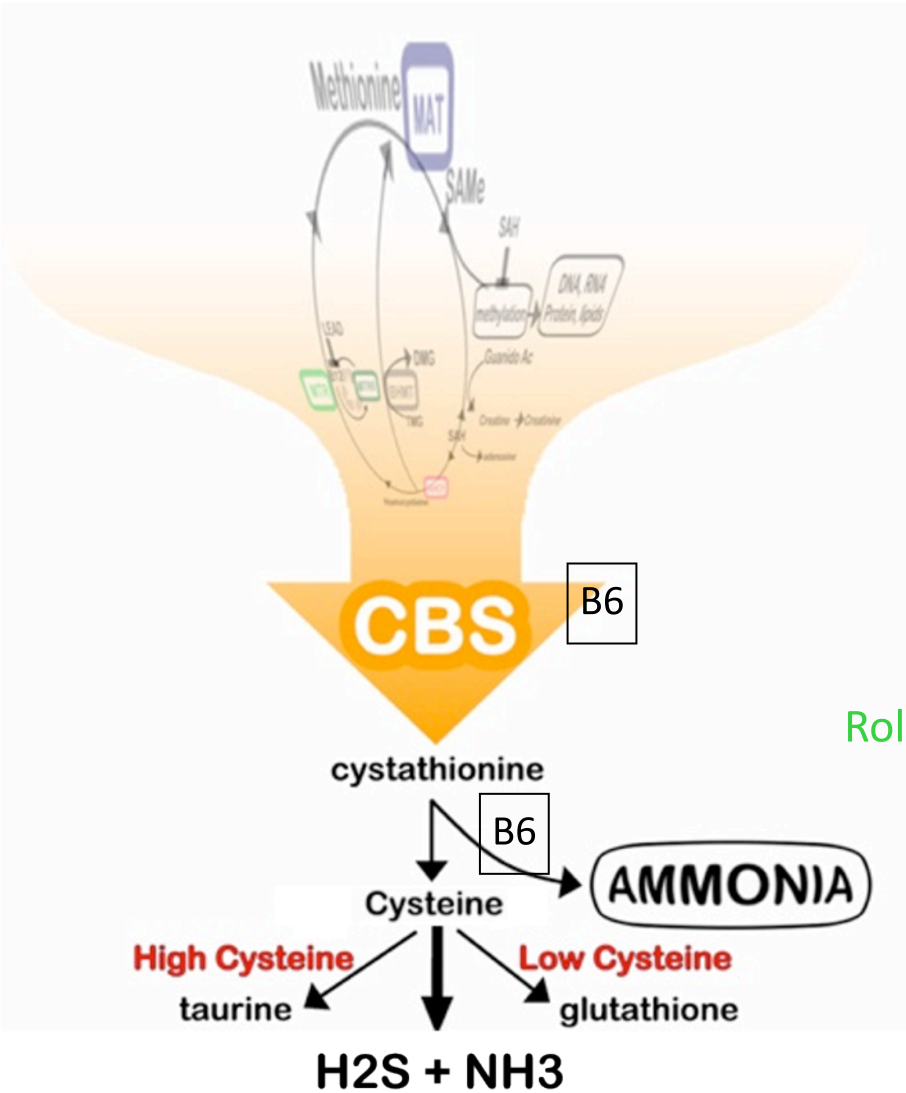
Martha H. Stipanuk,[3] John E. Dominy, Jr., Jeong-In Lee, and Relicardo M. Coloso
Division of Nutritional Sciences, Cornell University, Ithaca, NY

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



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

CBS



Role of B6 in this pathway

Plasma Glutathione and Cystathionine Concentrations Are Elevated but Cysteine Flux Is Unchanged by Dietary Vitamin B-6 Restriction in Young Men and Women[1,2]

Steven R. Davis,* Eoin P. Quinlivan,* Peter W. Stacpoole,†** and Jesse F. Gregory III*[3]

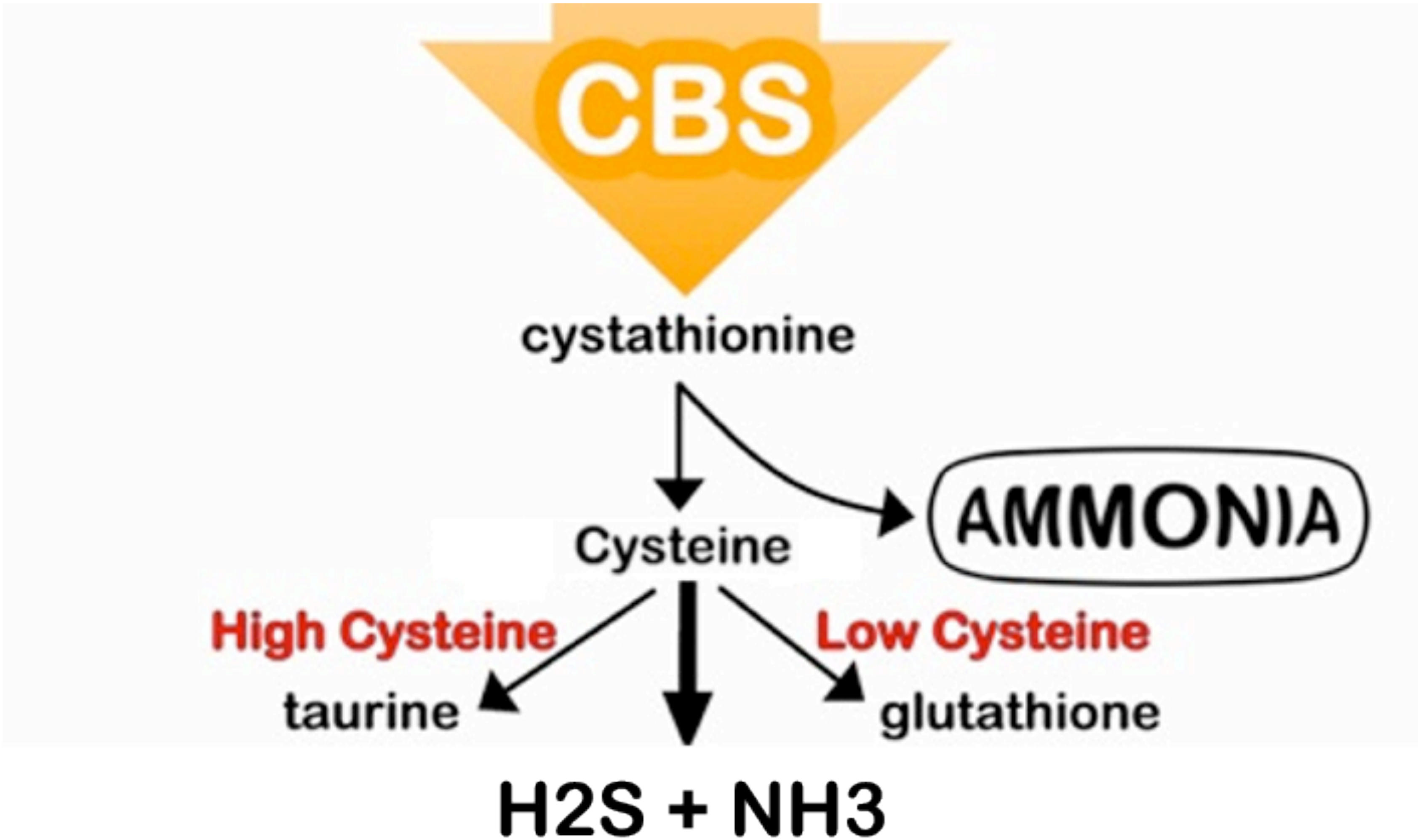
Dietary vitamin B-6 restriction caused the concentration of glutathione in plasma to increase by 40% (Table 1).

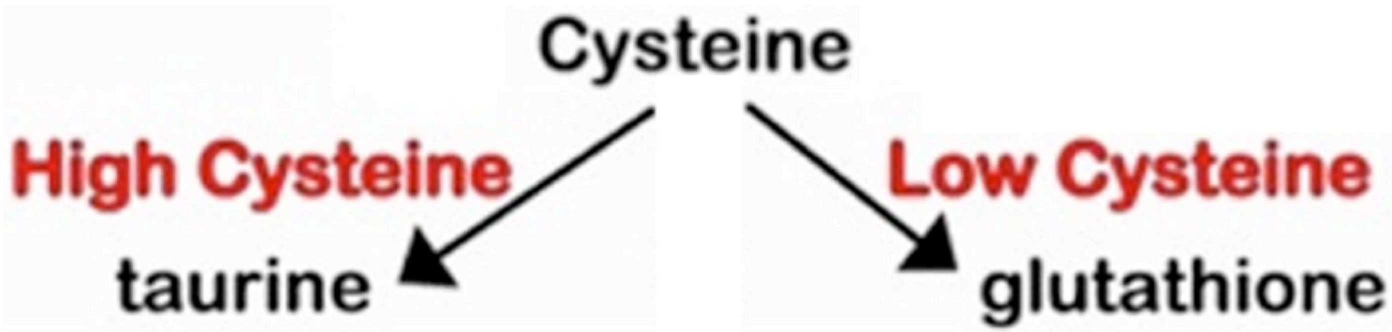
TABLE

Concentrations of amino acids ar... in plasma in humans at baseline and after 4 w... vitamin B-6 restriction (<0.5

	Cystathionine	Cysteine	Glutathione	Cysteinylglycine
		μmol/L		
Baseline	0.261 ± 0.028	257 ± 9	6.9 ± 0.3	31.9 ± 1.3
Restricted	0.585 ± 0.062‡	243 ± 6	9.5 ± 0.7‡‡	33.8 ± 1.5

1 Values are means ± SE, $n = 9$. S... ate different from baseline: ‡$P < 0.001$; ‡‡$P = 0.008$.


CBS
cystathionine
Cysteine
AMMONIA
High Cysteine
Low Cysteine
taurine
glutathione
H2S + NH3


Cysteine
High Cysteine
taurine
Low Cysteine
glutathione