

Metabolism of Sulphur Containing Amino Acids

Sulphur containing amino acids are three:

- L- Methionine: essential amino acid,
- L- Cysteine
- L- Cystine, } both are non-essential amino acids

METHIONINE (MET) (M)

It is **sulfur-containing, essential, glucogenic** amino acid. Degradation of methionine results in the synthesis of cysteine.

Metabolism of sulfur-containing amino acids may be studied under the following major headings:

- A. Activation of methionine and transmethylation
- B. Conversion of methionine to cysteine
- C. Degradation of cysteine.

1. Activation of methionine : methionine is activated to '**active methionine**' or S-adenosyl methionine (SAM) by the enzyme, **methionine adenosyl transferase**.

2. Methyl transfer. In methionine, the thio-ether linkage (C–S–C) is very stable. In SAM, due to the presence of a high energy bond, the methyl group is labile, and may be transferred easily to other acceptors .

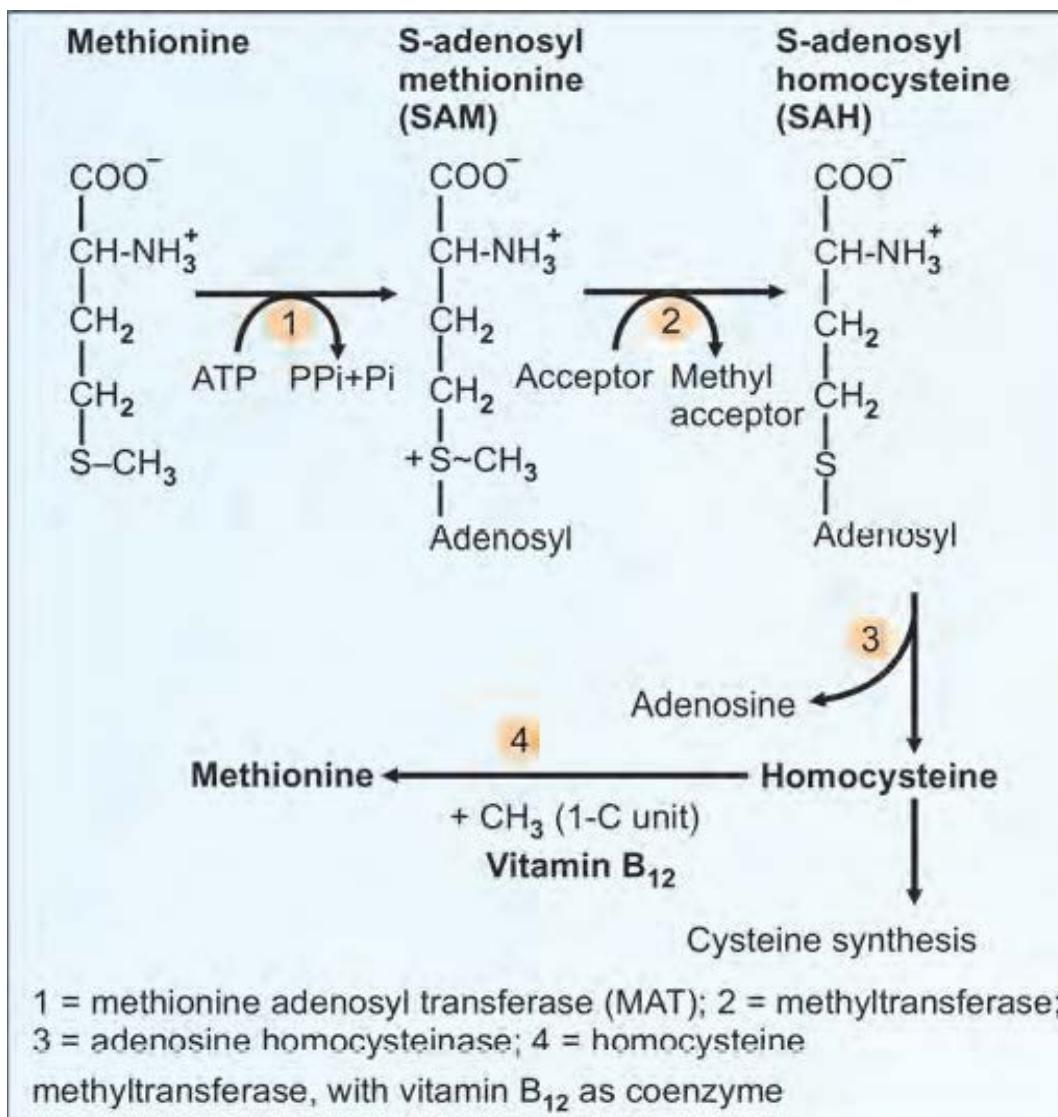
3. Homocysteine. From the S-adenosyl homocysteine (SAH), the adenosyl group is removed to form homocysteine, which is the higher homologue of cysteine .

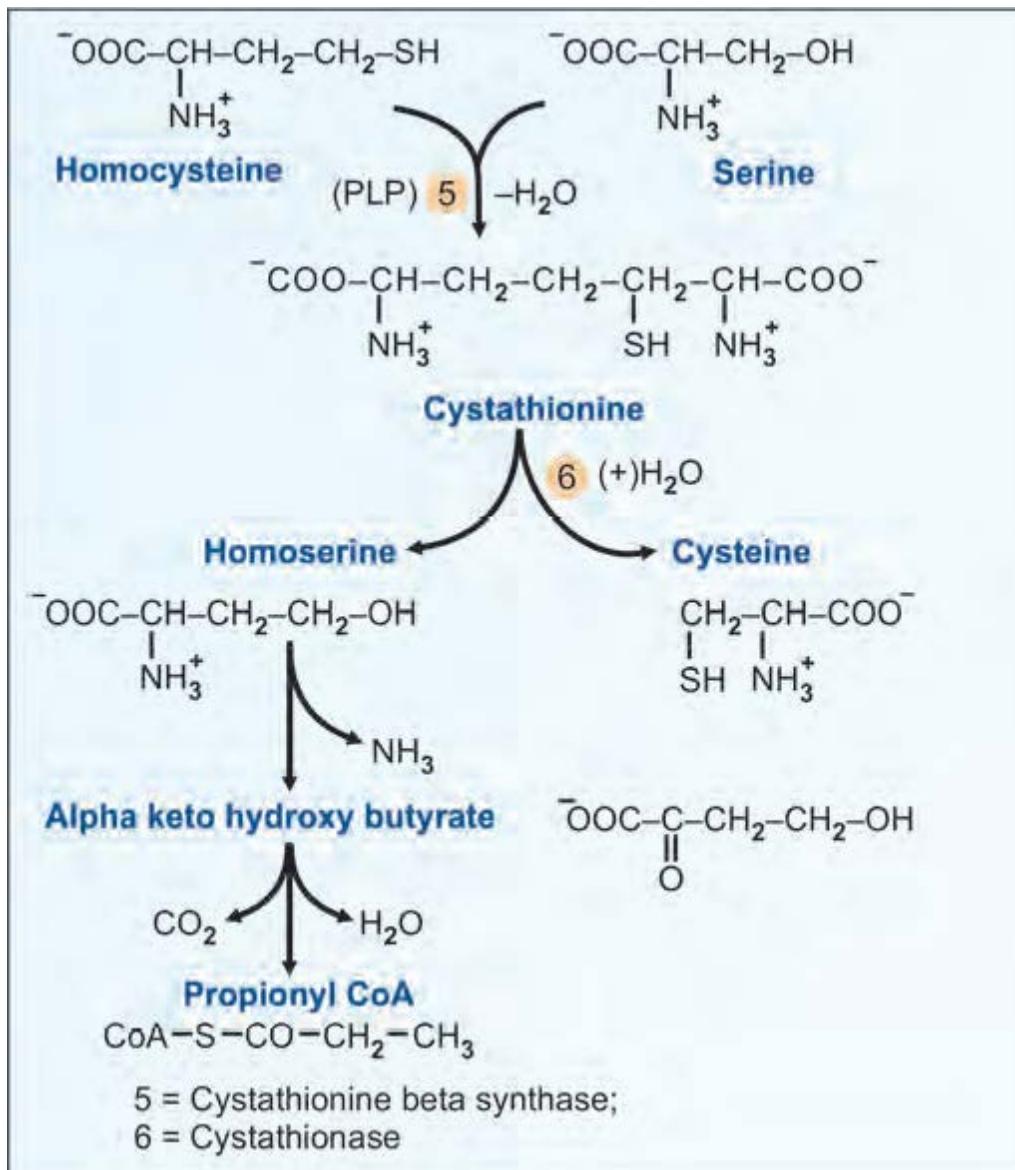
4. Methionine synthesis. Homocysteine can be converted to methionine by addition of a methyl group. This methyl group is donated from **one-carbon pool** with the help of vitamin B12 .

5. Homocysteine degradation: Homocysteine condenses with serine to form **cystathionine**. This is catalyzed by pyridoxal phosphate (PLP) dependent cystathionine-beta **synthase**. Absence of this enzyme leads to **homocystinuria**.

6. Cysteine synthesis: In the next step cystathionine is hydrolyzed by **cystathionase** to form cysteine and homoserine. Net result is that the **SH group from methionine is transferred to serine to form cysteine**. This is called **trans-sulfuration** reaction.

7. Final oxidation: Homoserine is deaminated and then decarboxylated to propionyl CoA. It finally enters into the TCA cycle as succinyl CoA.





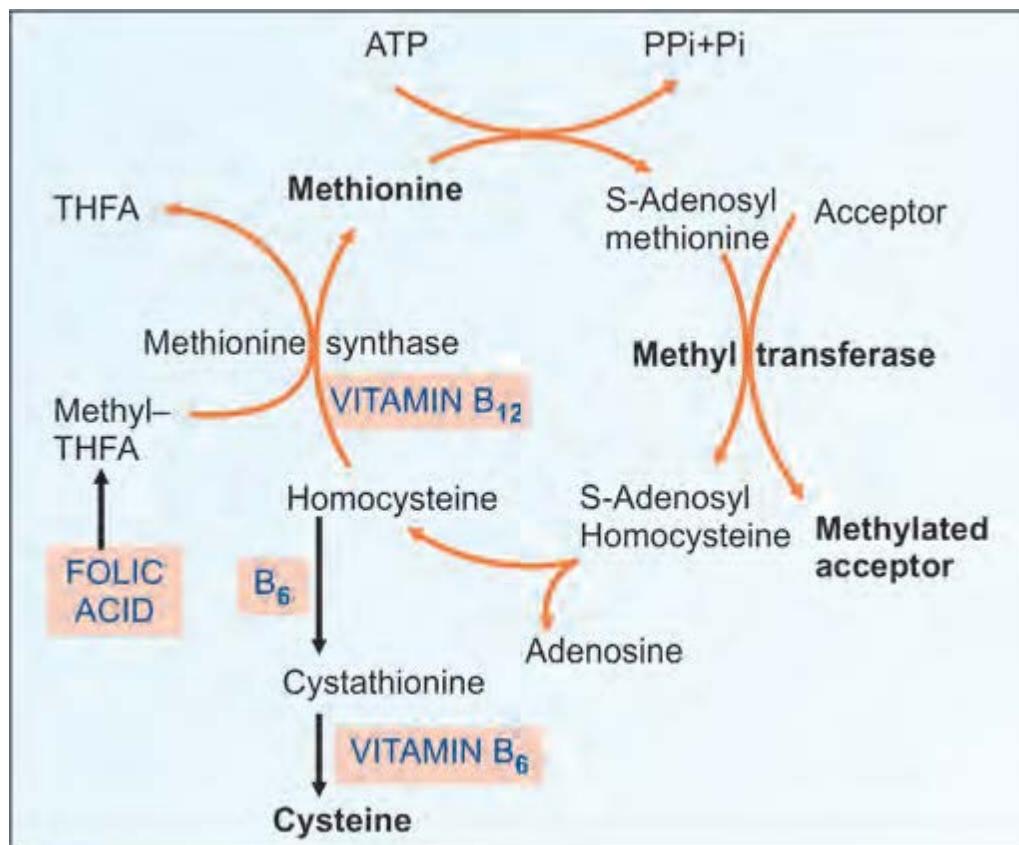
Methionine in Transmethylation Reactions

Some important products of methylation reactions are:

1. Creatine
2. Epinephrine
3. Choline
4. Melatonin

These reactions are called **methyl transfer reactions**, and these are carried out with the help of **S-adenosyl methionine (SAM)**. Methyl groups are originally derived

from the one carbon pool. The methyl tetrahydrofolic acid (methyl-THFA) can transfer the methyl group to homocysteine .**Vitamin B12** is the co-enzyme for the reaction. This would account for the deficiency of folic acid associated with B12 deficiency (folate trap). SAM is the methyl donor for all the transmethylation reaction.



Summary of methionine to cysteine conversion. Note the role played by vitamins

CYSTEINE (CYS) (C)

It is non-essential and **glucogenic**. Cysteine is present in large quantity in keratin of hair and nails.

Formation of Cysteine is by using the carbon skeleton contributed by serine and sulfur originating from methionine.

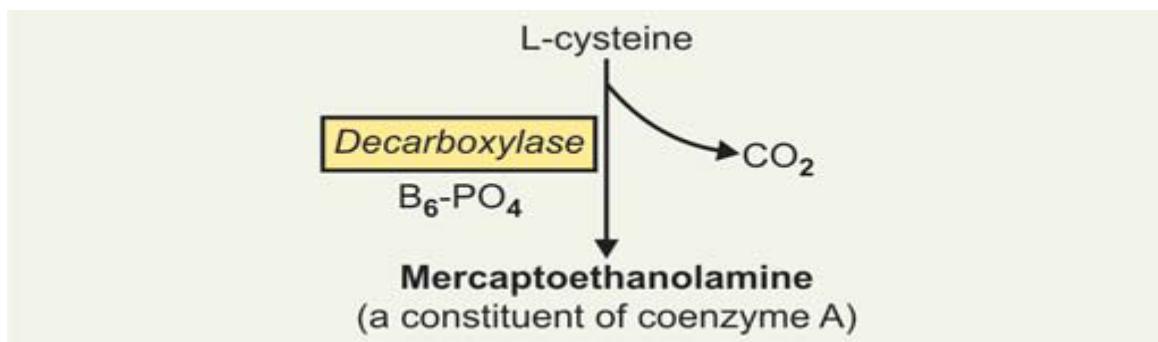
Methionine → SAM → SAH → Homocysteine → Cystathionine → Cysteine

A- Metabolic Fate of cysteine:

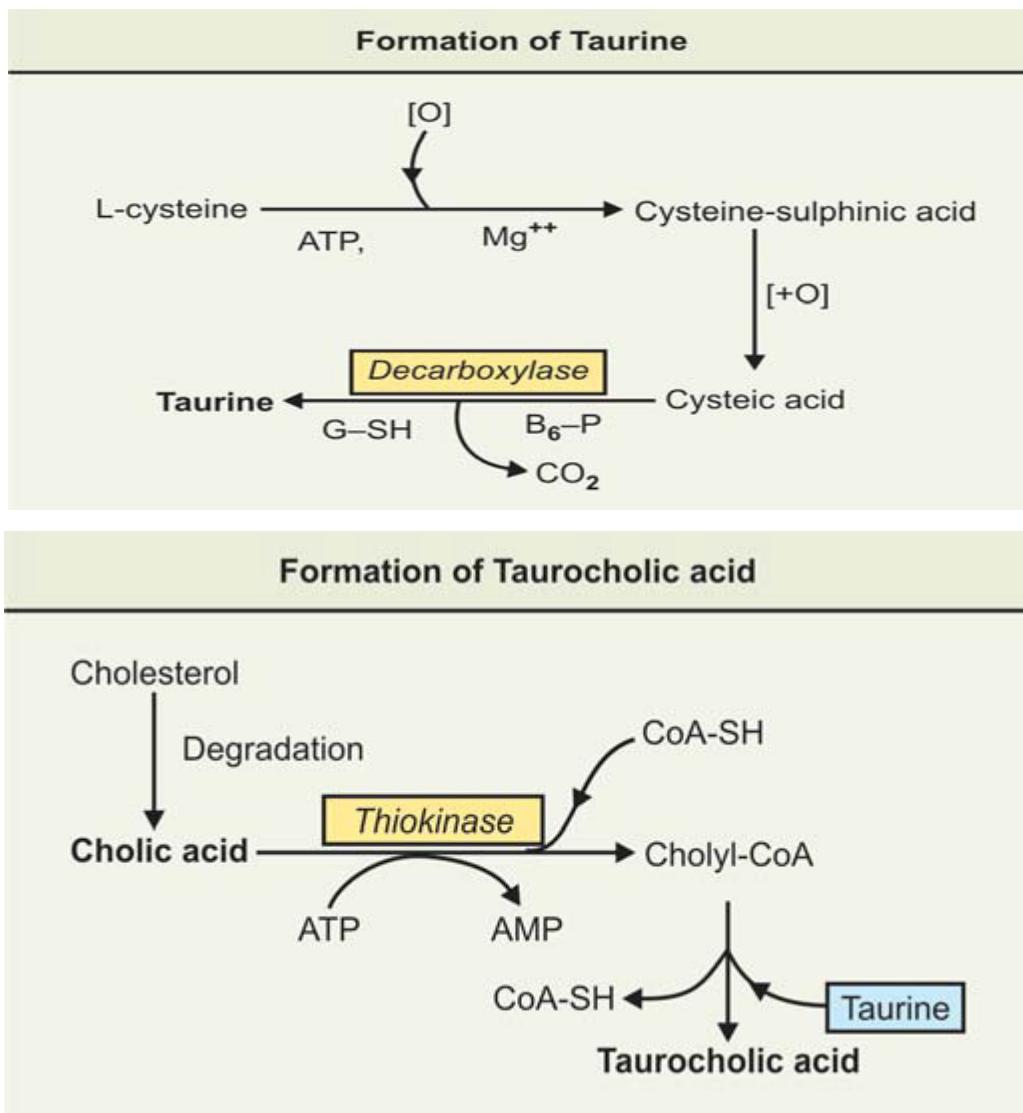
Cysteine is catabolized to form pyruvic acid, which can be converted to glucose. Thus cysteine is a glucogenic amino acid.

B- Metabolic role of cysteine:

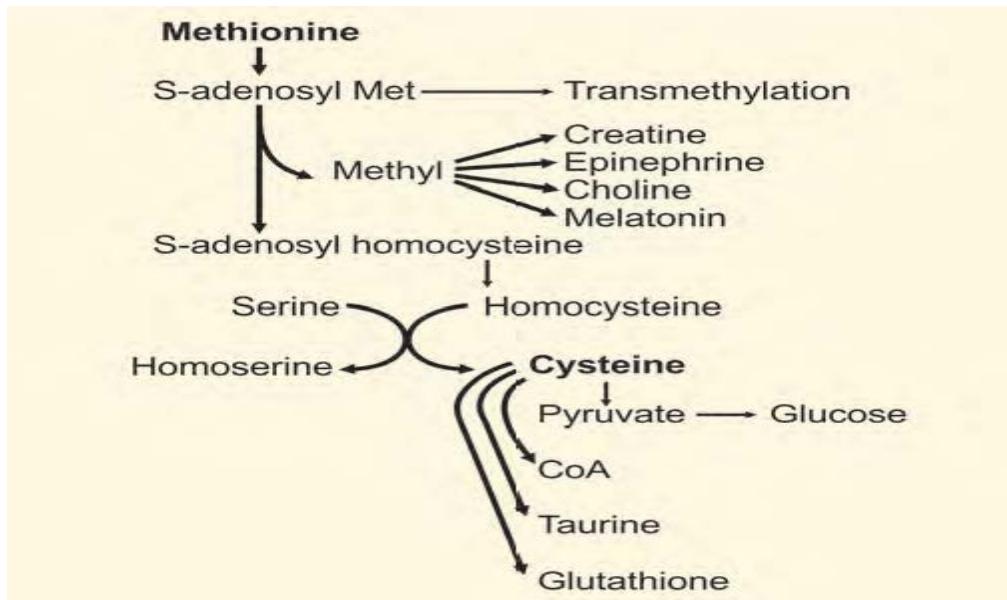
- Glucogenic: cysteine is catabolized to pyruvic acid which is glucogenic.
- Formation of glutathione: cysteine is required for synthesis of glutathione.
- G-SH is the reduced form, active group is SH group. G-S-S-G is the oxidized form.
- Formation of mercaptoethanolamine: which is an important constituent of coenzyme A.?



- Formation of taurine: cysteine is utilized in the formation of taurine, which combines with cholic acid (obtained from degradation of cholesterol in liver) to form bile acid "taurocholic acid".



- Cysteine is particularly prominent amino acid in the proteins of nails, hairs, hoofs and keratin of the skin (sclera-proteins).
- Cysteine is also a constituent of many other proteins, including certain protein hormones like insulin, vasopressin etc., where it is of great importance in maintaining secondary and tertiary structures of the proteins



Clinical Aspect

Inherited Disorders of S- Containing Amino Acids

1- Cystinuria: An inherited disorder of cystine metabolism. Excretion of cystine in urine increases 20-30 times of normal. Also there occurs increased excretion of dibasic amino acids: Lysine, arginine and ornithine (*specific dibasic aminoaciduria*).It is an inherited disorder and occurs at frequency of (1:7000) individuals

Defect:

It is considered to be due to a renal transport defect in the reabsorption of the above four amino acids do not occur. a single reabsorptive site is involved.

Complications:

Cystine is relatively insoluble amino acid, which may precipitate in renal tubules, ureters and bladder to form cystine calculi. Cystine stones account for 1-2% of all urinary tract calculi. It forms a major complication of the disease.

A "mixed disulfide" consisting of L- cysteine and L- homocysteine has been found in urine. This is more soluble and thus reduces the tendency to formation of cystine crystals / and calculi.

Diagnosis:

- **Urine examination:** detection of hexagonal, flat crystals in urinary deposit in a patient who is not taking sulpha drugs is pathognomonic.
- **Cyanide-nitroprusside test (Lewis):** It is a simple and valuable test. Urine sample is made alkaline with ammonium hydroxide and then sodium cyanide is added and mixed. Sodium cyanide reduces cystine, if any present, to cysteine. Cysteine forms magenta-red color, when sodium nitroprusside is added. The intensity of the colour is proportional to free –SH content.

2. Cystinosis

A second hereditary abnormality of cystine metabolism is “**cystinosis**” or also called **cystine-storage disease**.

A rare familial disease characterised by widespread deposition of cystine, sometimes as distinct crystals in various tissues. Patients with cystinosis accumulate cystine in liver, spleen, bone marrow, peripheral leucocytes, lymph nodes, kidney and cornea. Cystine accumulates with lysosomes of cells of reticuloendothelial (RE) system.

Defect: The cause of the condition may be an impaired conversion of cystine to cysteine in the involved tissues due to deficiency of the enzyme cystine reductase.

Clinical features

The condition may appear in children as well as in adults. **Three types** are known to occur:

(a) In children (nephropathic): The disease runs an acute course and leads to renal insufficiency. There may be associated aminoaciduria, glucosuria, polyuria, chronic acidosis leading to uraemia, and death.

(b) Juvenile type: Renal features as stated above seen in second decade.

(c) Adult type: Runs a benign clinical course. Cystine gets deposited in cornea but not in kidney.

Diagnosis

- Cystine crystals can be detected easily in cornea by slit lamp microscopy.

- Cystine crystal can be demonstrated in unstained preparation of peripheral blood or in biopsies of rectal mucosa.
- Confirmed by chemical determination of cystine content of peripheral leucocytes or cultured fibroblasts.

3. Homocystinuria Type-1 (classical type)

An inborn error of metabolism, which involves the catabolism of methionine or more specifically its metabolic intermediates, homocysteine/and homocystine.

Enzyme deficiency: Genetic deficiency of the enzyme **cystathionine synthetase**.

The enzyme defect leads to accumulation of homocystine. Plasma level of homocystine increases and excreted in urine (“overflow” aminoaciduria), 50 to 100 mg or more excreted in urine per day. In some cases, Sadenosyl methionine is also excreted.

Incidence: 1 in 60,000 live births.

Clinical features

- **Mental retardation:** In children and surviving adults.
- Some affected individuals, are extraordinarily tall, with long extremities, frequently with flat feet with toes out.
- Liver is enlarged (**hepatomegaly**).
- **Skeletal deformities:** Involving spine, (vertebrae), and thorax, resulting to kyphosis, scoliosis, arachnodactyly.

Ectopia lentis: Curious dislocation of lens of the eye. Not seen at birth, may show at the age of 2 to 3 years.

- **Life-threatening arterial/venous thrombosis.:** Most of the patients show abnormal EEG(Electroencephalography).

Urine: Sodium cyanide-nitroprusside test is positive and helps in diagnosis.

In addition to classical type, two more types have been described:
Homocystinuria Type-2, Homocystinuria Type-3