

Amino Acid Metabolism: Amino Acid Degradation & Synthesis

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CATABOLISM OF THE CARBON SKELETONS OF AMINO ACIDS

The pathways by which AAs are catabolized are organized according to which one (or more) of the seven intermediates is produced from a particular amino acid.

GLUCOGENIC AND KETOGENIC AMINO ACIDS

The classification is based on which of the seven intermediates are produced during their catabolism (**oxaloacetate, pyruvate, α -ketoglutarate, fumarate, succinyl coenzyme A (CoA), acetyl CoA, and acetoacetate**).

Glucogenic amino acids catabolism yields pyruvate or one of the TCA cycle intermediates that can be used as substrates for gluconeogenesis in the liver and kidney.

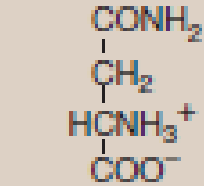
Ketogenic amino acids catabolism yields either aceto acetate (a type of ketone bodies) or one of its precursors (acetyl CoA or acetoacetyl CoA).

Other ketone bodies are 3-hydroxybutyrate and acetone

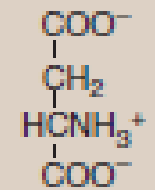
	Glucogenic	Glucogenic and Ketogenic	Ketogenic
Non essential	Alanine Arginine Asparagine Aspartate Cysteine Glutamate Glutamine Glycine Proline Serine	Tyrosine	
Essential	Histidine Methionine Threonine Valine	Isoleucine Phenyl- alanine Tryptophan	Leucine Lysine

Amino acids that form oxaloacetate

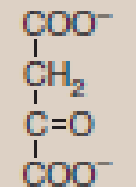
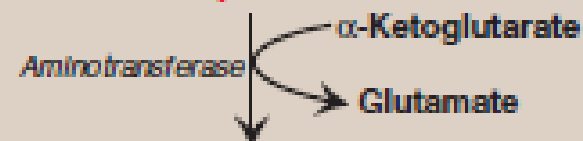
Hydrolysis



Asparagine



Aspartate



OXALOACETATE

Transamination

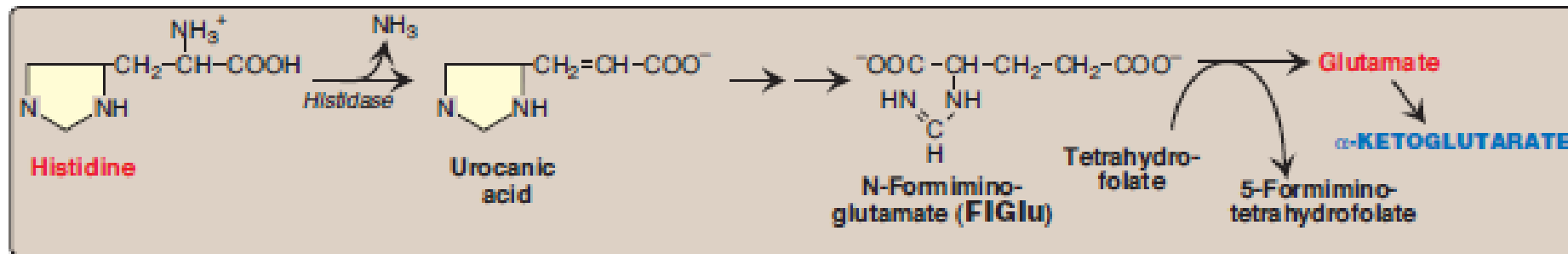
Amino acids that form α -ketoglutarate via glutamate

- 1. Glutamine** is converted to glutamate and ammonia by the enzyme glutaminase. Glutamate is converted to α -ketoglutarate by transamination, or through oxidative deamination by glutamate dehydrogenase.
- 2. Proline** is oxidized to glutamate.
- 3. Arginine** is cleaved by arginase to produce Ornithine (in the liver as part of the urea cycle). Ornithine is subsequently converted to α -ketoglutarate.

Amino acids that form α -ketoglutarate via glutamate

4. Histidine is oxidatively deaminated by histidase to urocanic acid, which then forms N-formimino glutamate (FIGlu).

FIGlu donates its formimino group to tetra hydro folate (THF), leaving glutamate

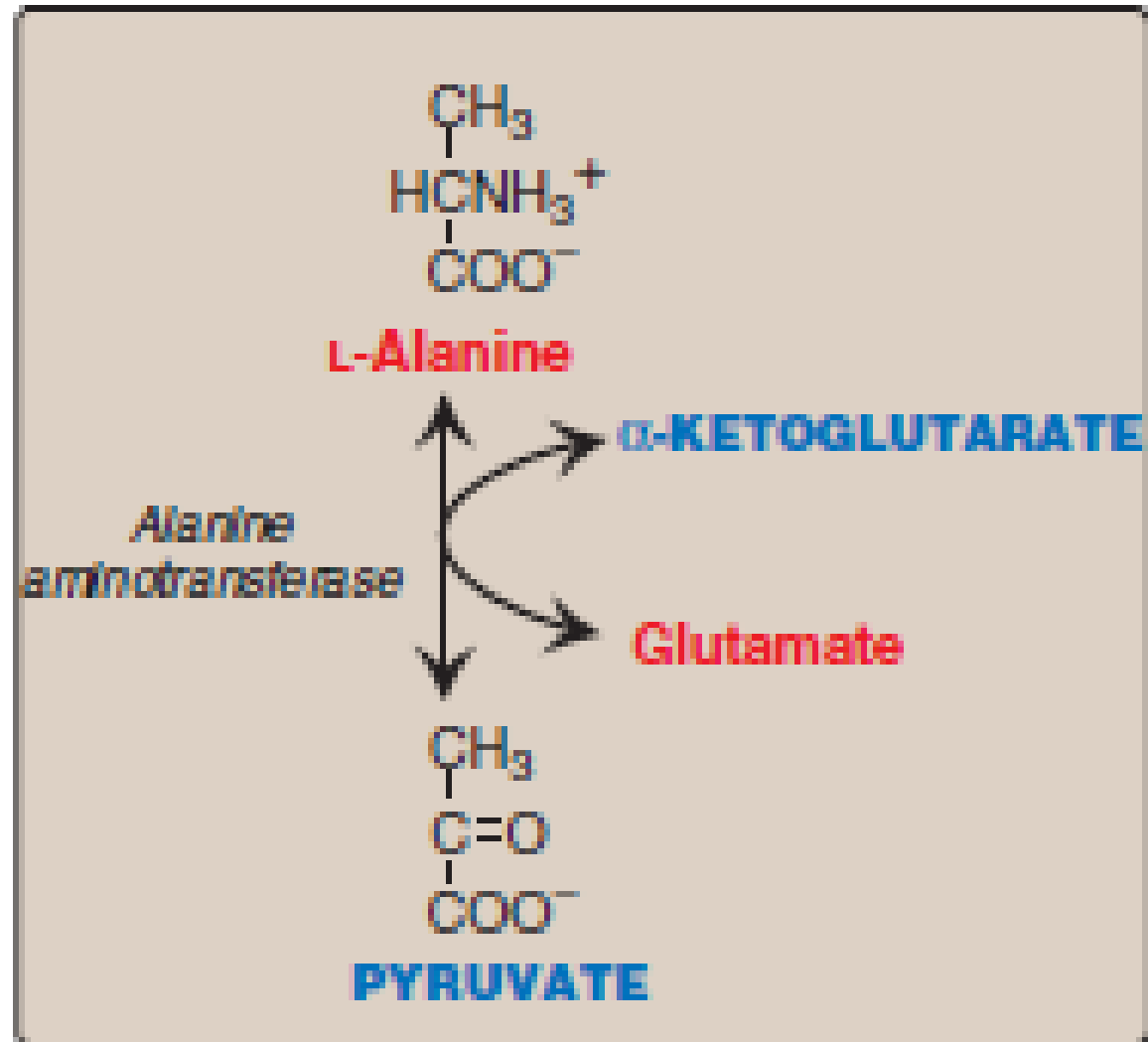


Individuals deficient in folic acid excrete high amounts of FIGlu in the urine

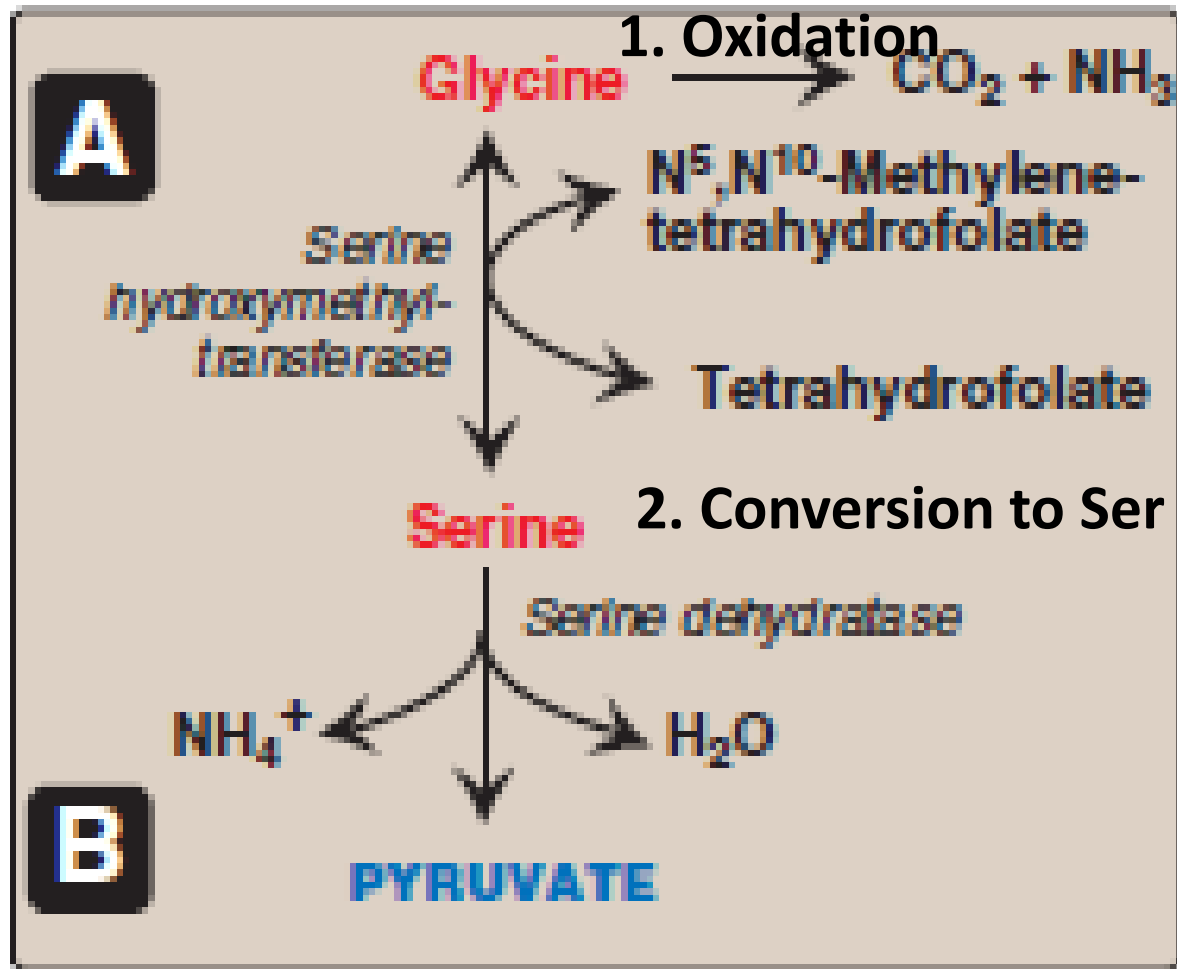
FIGlu excretion test has been used in diagnosing a deficiency of folic acid.

Amino acids that form pyruvate

Alanine



Amino acids that form pyruvate



Serine

Glycine can be converted to glyoxylate which is then oxidized to oxalate, or transaminated to **Gly**.

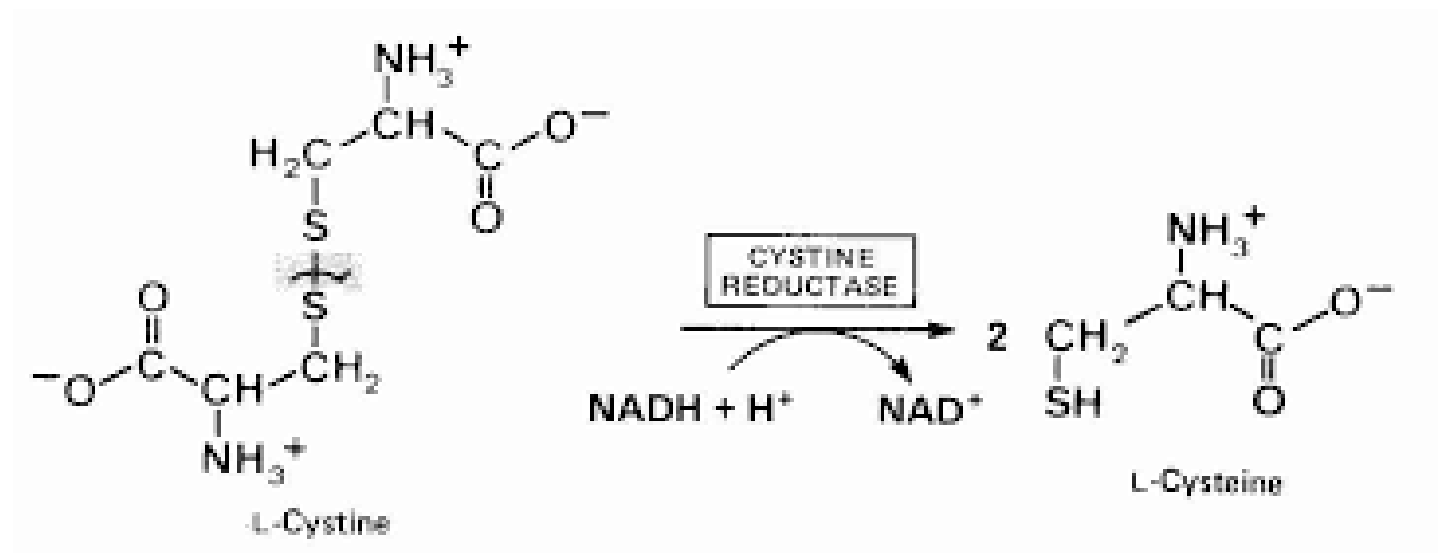
Deficiency of the transaminase causes overproduction of oxalate and kidney damage (primary oxaluria Type 1)

Amino acids that form pyruvate

Cystine is reduced to cysteine

NADH + H⁺ act as a reductant.

Cysteine desulfuration yields pyruvate.



Threonine is converted to pyruvate or to α -ketobutyrate, which forms succinyl CoA.

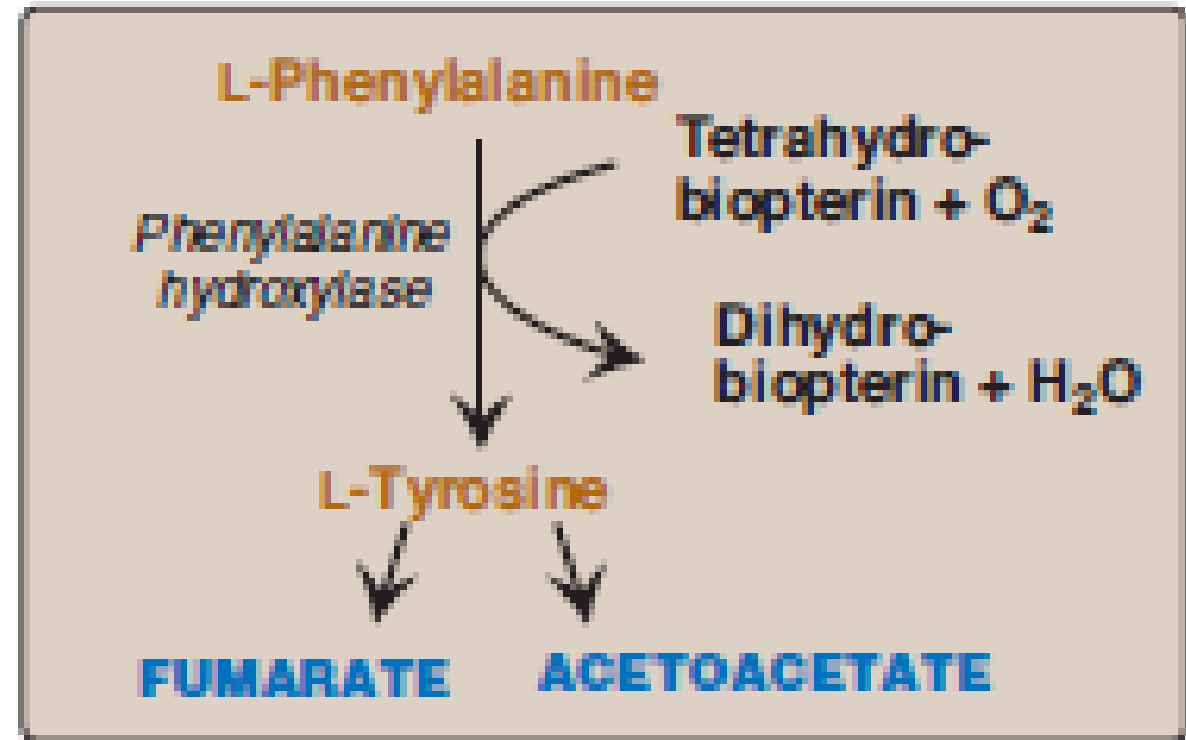
Amino acids that form fumarate

Phenylalanine and tyrosine:

Hydroxylation of phenylalanine produces tyrosine

Phenylalanine and tyrosine are both glucogenic and ketogenic.

Inherited deficiencies in the enzymes that metabolize Phe and Tyr lead to **phenylketonuria, alkaptonuria and albinism**



Amino acids that form succinyl CoA

(a TCA cycle intermediate and glucogenic compound)

Valine and isoleucine are branched-chain amino acids

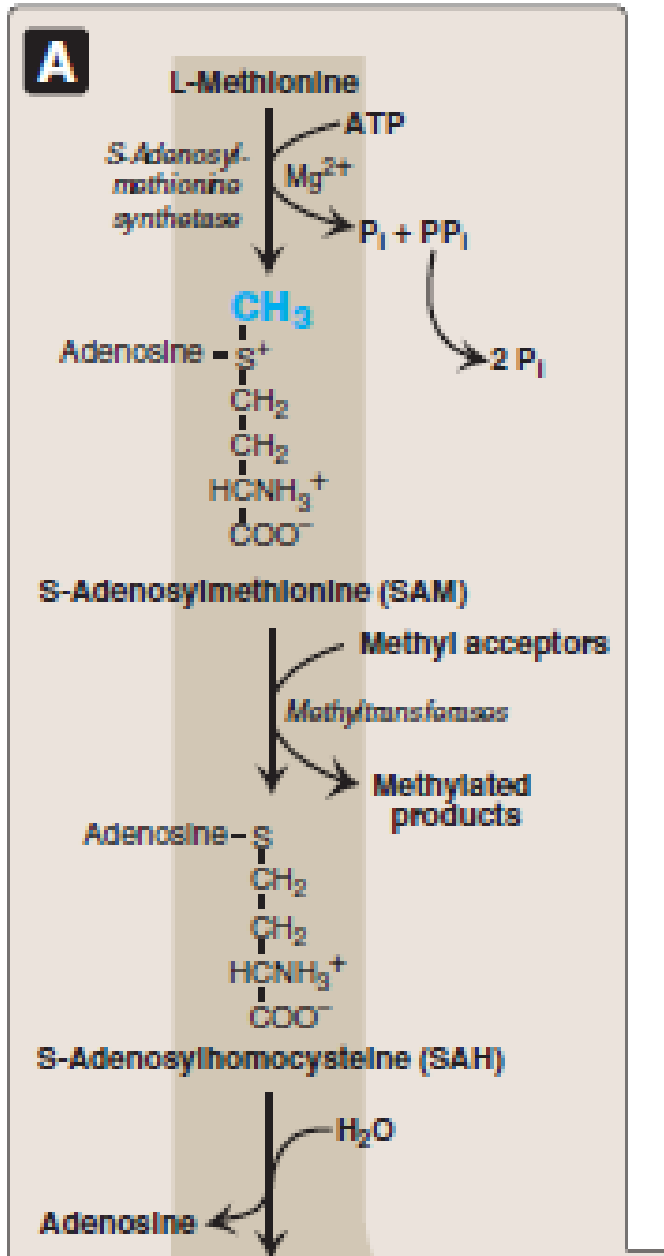
They generate propionyl CoA that is converted to succinyl CoA by biotin- and vitamin B12–requiring reactions

Threonine is dehydrated to α -ketobutyrate, which is converted to propionyl CoA and then to succinyl CoA.

Thr can also be converted to pyruvate.

Methionine is converted to S-adenosyl methionine (SAM), the major methyl-group donor in one-carbon metabolism.

Methionine Metabolism



1. Synthesis of SAM (a high-energy compound that has no phosphate) requires energy (ATP)

2. Methyl group activation to be ready for transfer to acceptor molecules, such as norepinephrine in the synthesis of epinephrine. Methyl group is transferred to O, N, or C atoms. Methyl transfer is irreversible because of free energy loss.

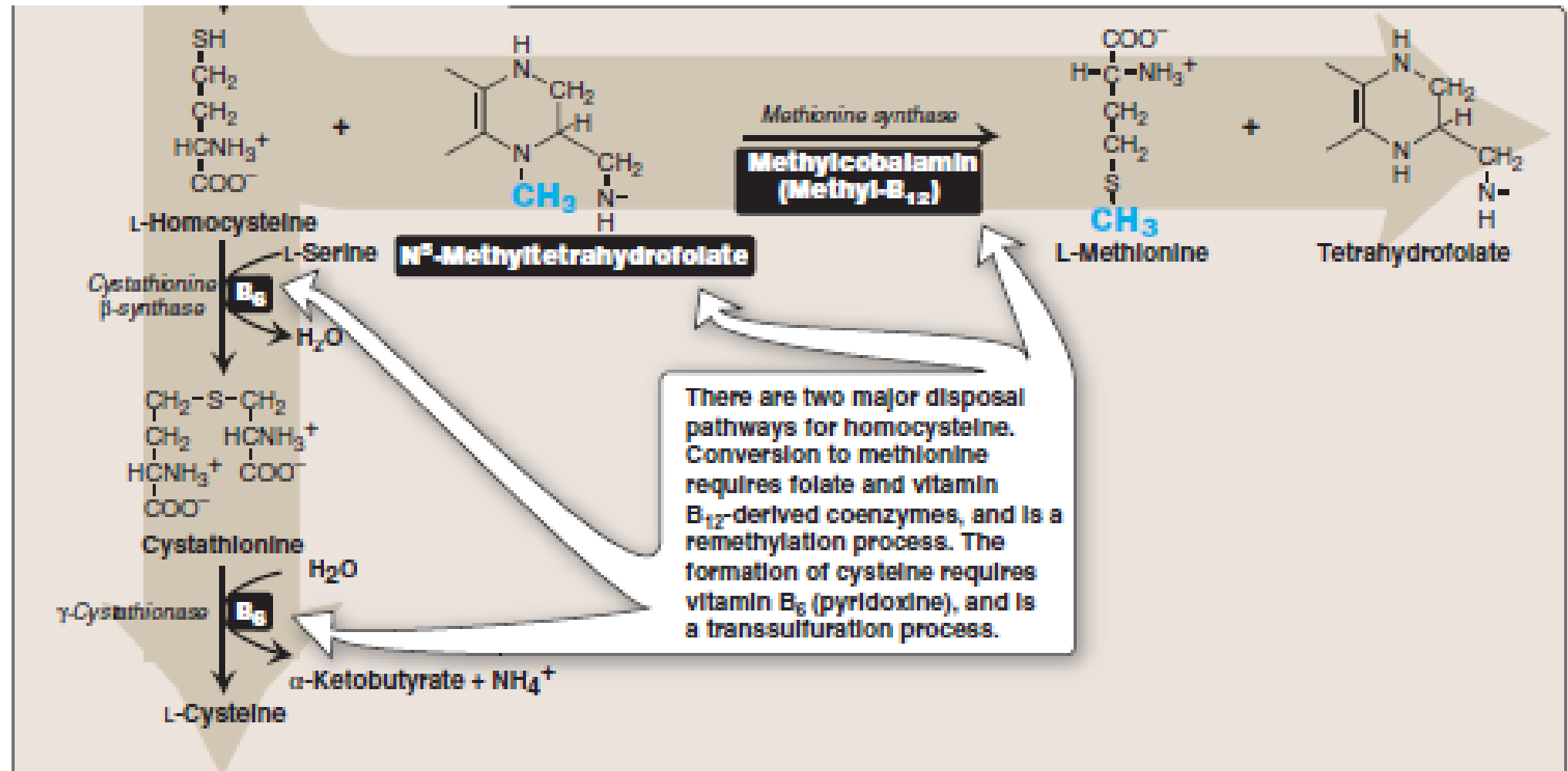
3. Hydrolysis of SAH to homocysteine and adenosine.

Homocysteine fates:

A. Remethylation if Met is deficient

B. Transsulfuration pathway if Met is available to be converted to Cys

Synthesis of cysteine and methionine



The resulting α -ketobutyrate is oxidatively decarboxylated to form propionyl CoA that is then converted to succinyl CoA.

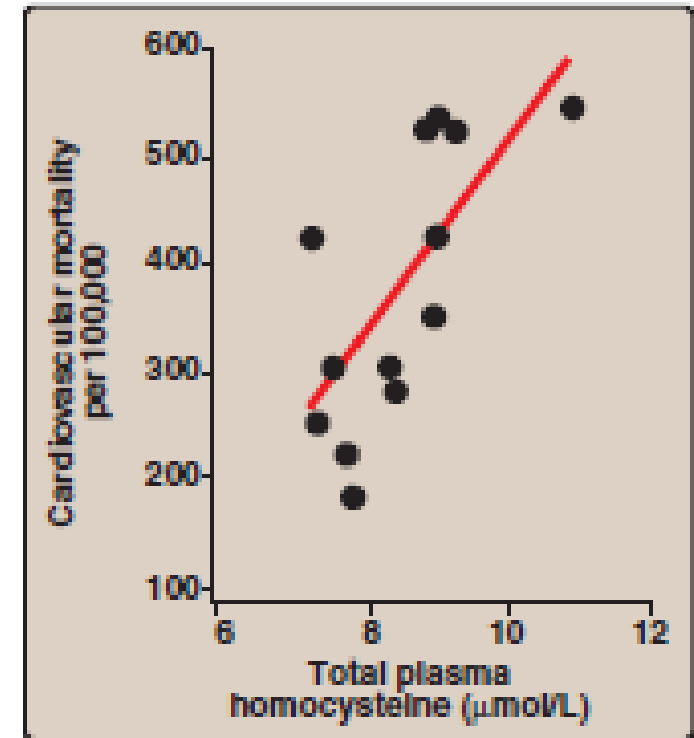
Clinical hint: Homocysteine and vascular disease

High homocysteine promote oxidative damage, inflammation, and endothelial dysfunction, and increases risk for occlusive vascular disease

Homocysteine levels are inversely related to levels of folate, B12, and B6.

Deficiencies in cystathionine β -synthase increase plasma homocysteine as in homocystinuria and results in premature vascular disease and death due to thrombotic complications before 30 years of age.

Elevated homocysteine or decreased folic acid levels during pregnancy increases the incidence of neural tube defects (improper closure, as in spina bifida) in the fetus.



Amino acids that form acetyl CoA or acetoacetyl CoA

Leu, Ile, Lys, and Trp form acetyl CoA or acetoacetyl CoA directly, without pyruvate as an intermediate through the pyruvate dehydrogenase reaction.

Phe and Tyr produce acetoacetate during their catabolism

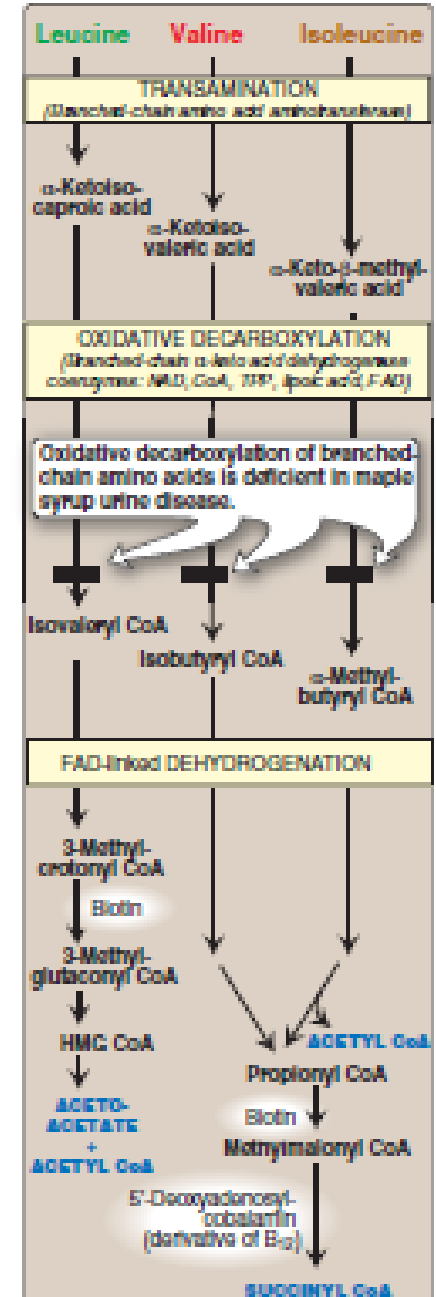
The initial steps in Leu, Ile and Val catabolism are similar

Leucine is exclusively ketogenic (acetoacetate and acetyl CoA)

Isoleucine is both ketogenic and glucogenic (acetyl CoA and succinyl CoA)

Lysine is an exclusively ketogenic (acetoacetyl CoA). Neither of the Leu's amino groups undergoes transamination as the first step in catabolism.

Tryptophan is both glucogenic and ketogenic (alanine and acetoacetyl CoA)



Catabolism of the branched-chain amino acids

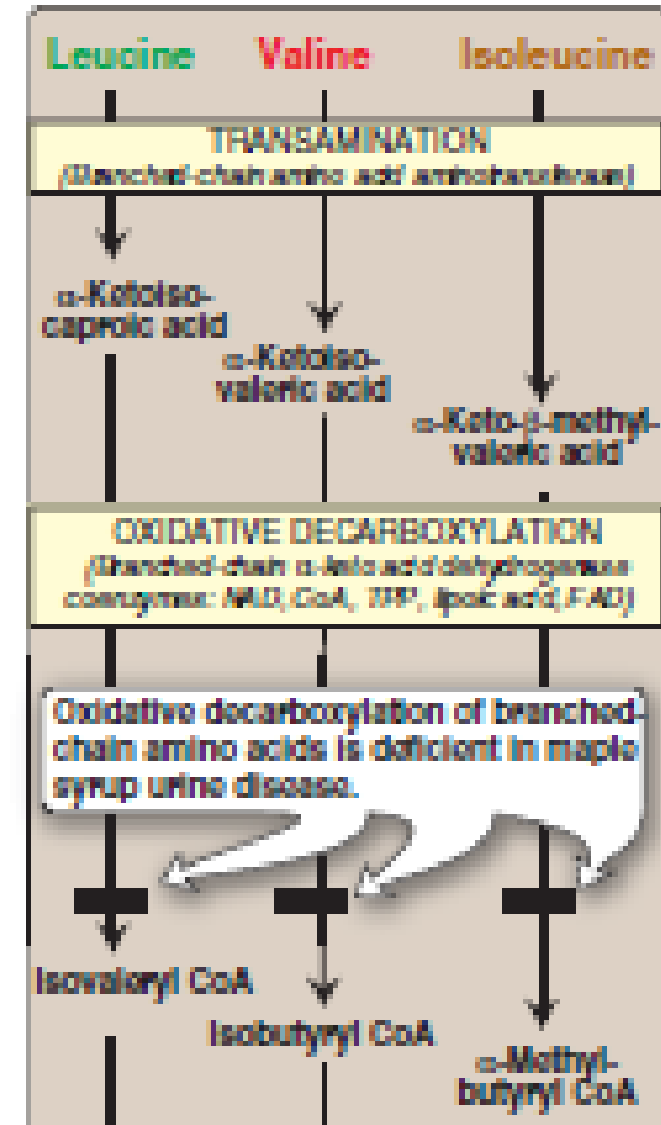
Ile, Leu, Val

Ile, Leu, Val are essential amino acids.

Metabolism primarily by the peripheral tissues (particularly muscle), rather than by the liver.

1. **Transamination** by a vitamin B6–requiring enzyme, branched-chain amino acid aminotransferase.
2. **Oxidative decarboxylation** by a single multienzyme complex, branched-chain α -keto acid dehydrogenase complex.

Coenzymes: thiamine pyro - phosphate, lipoic acid, FAD, NAD⁺, and CoA



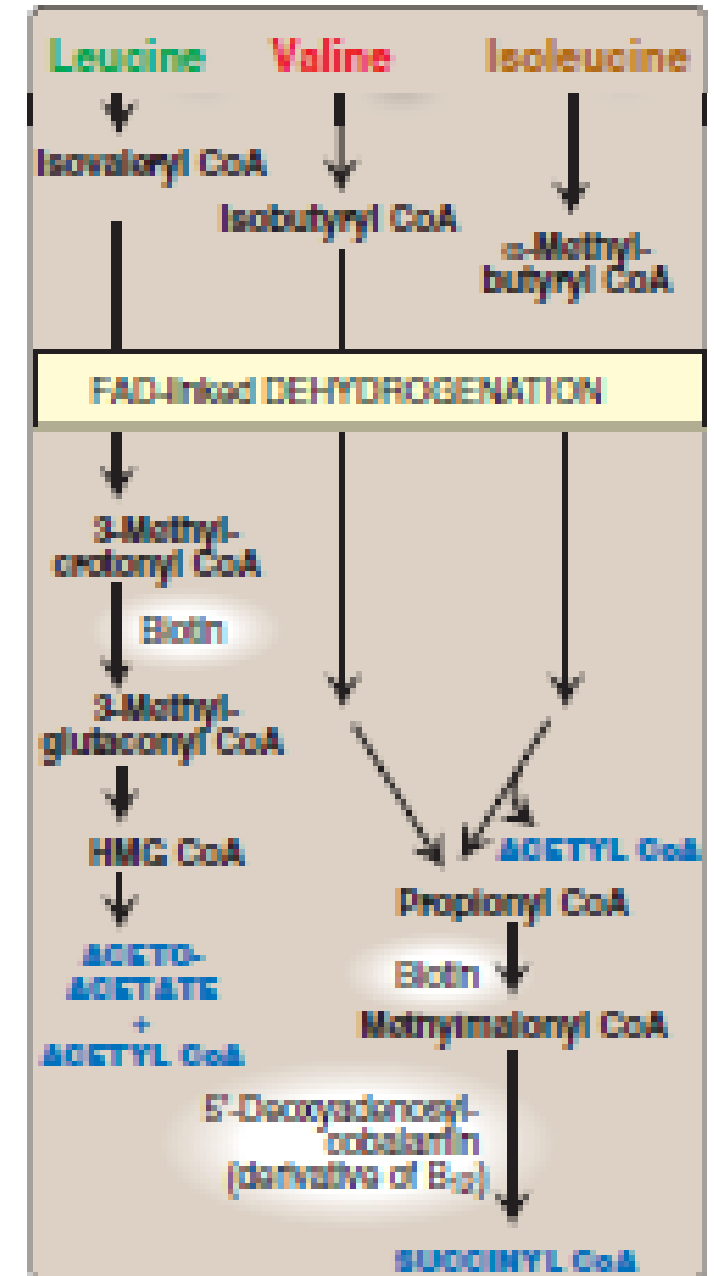
Catabolism of the branched-chain amino acids Ile, Leu, Val

3. Dehydrogenation: Oxidation of the products yields α - β -unsaturated acyl CoA derivatives.

4. End products:

Ile yields acetyl CoA and succinyl CoA (both ketogenic and glucogenic)

Val yields succinyl CoA (glucogenic). Leu yields acetoacetate and acetyl CoA (ketogenic)



Amino acid metabolism and single amino acid groups

Some synthetic pathways require the addition of single carbon groups

Single carbon groups exist in a variety of oxidation states, including formyl, methenyl, methylene, and methyl.

Single carbon groups can be transferred from carrier compounds such as THF and SAM to molecules that are being synthesized

Role of folic acid in amino acid metabolism

Folic acid: a carrier of one-carbon units

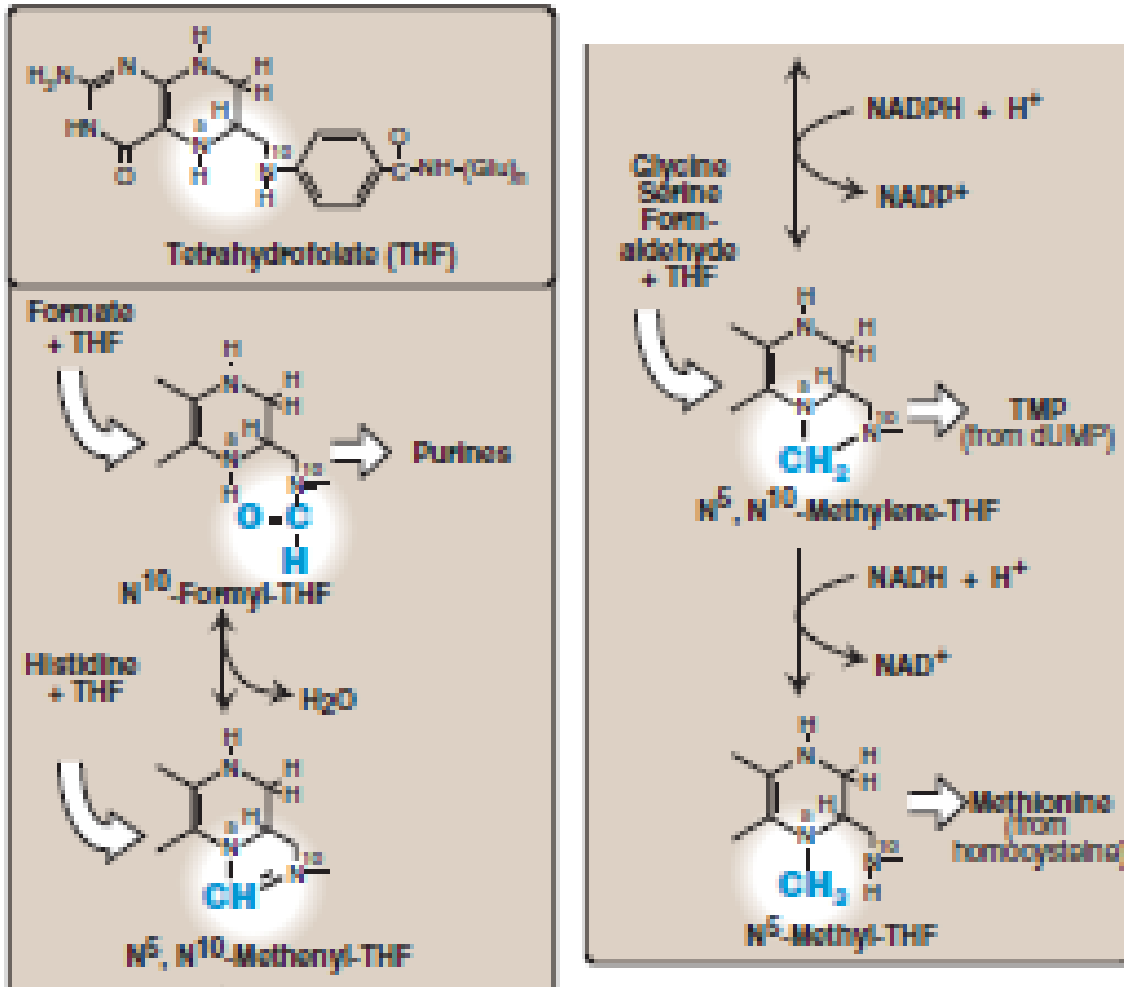
Tetrahydrofolic acid (THF) is the active form

THF is produced from folate by dihydrofolate reductase in a two-step reaction requiring two NADPH.

The carbon unit carried by THF is bound to nitrogen N5 or N10, or to both N5 and N10.

One-carbon compounds bound to THF can be recognized and manipulated by biosynthetic enzymes.

Folate deficiency presents as a megaloblastic anemia due to decreased availability of the purines and of the TMP needed for DNA synthesis



Biosynthesis of Nonessential Amino Acids

Essential: Phe, Val, Thr, Trp, Met, Leu, Ile, Lys & His

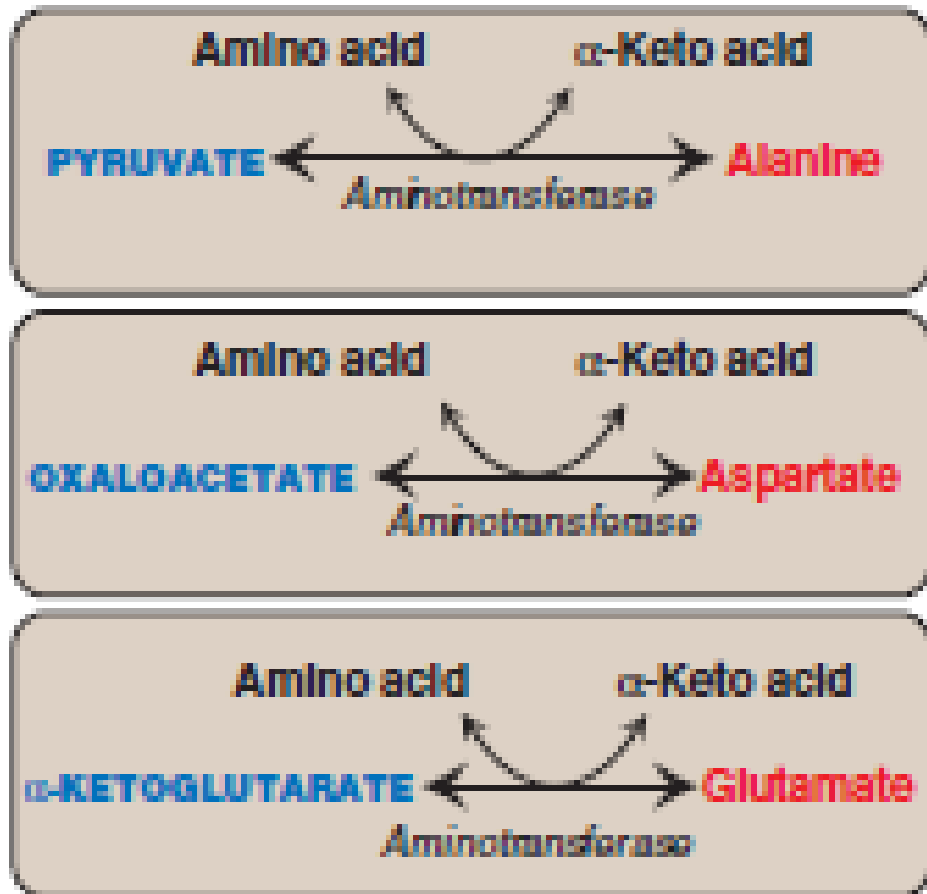
Nonessential: Ala, Arg, Asp, Asn, Cys, Glu, Gln, Gly, Pro, Ser & Tyr

Nonessential amino acids are synthesized from:

1. Metabolic intermediates
2. Or from the essential amino acids.

Example: Tyr and Cys are synthesized from Phe and Met, respectively.

Synthesis from α -keto acids

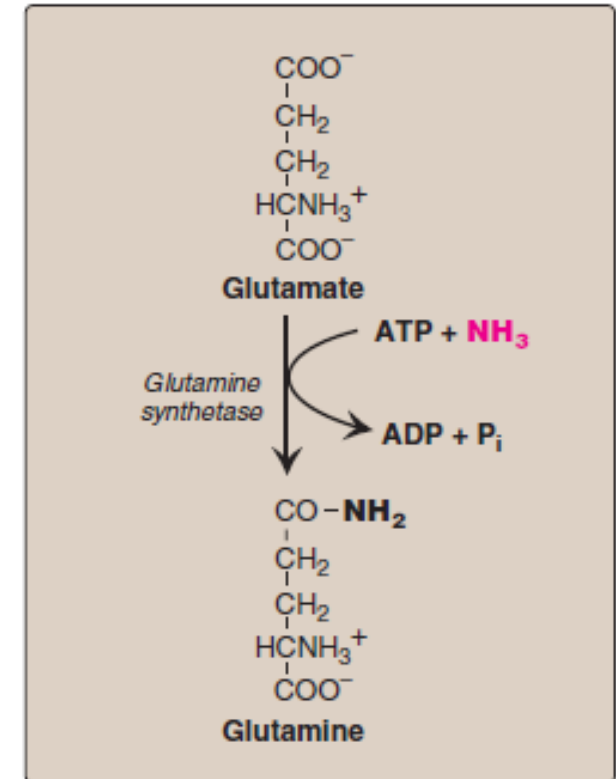
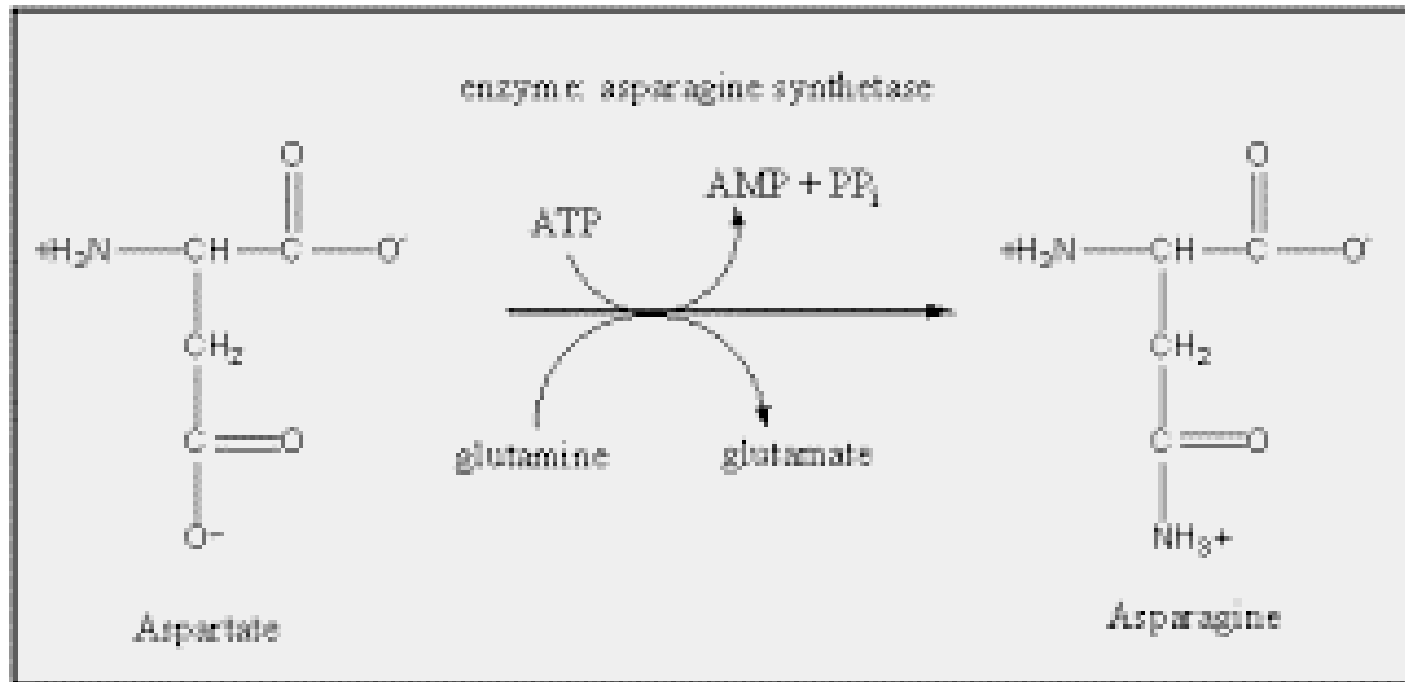


Ala, Asp, and Glu are synthesized by transfer of an amino group to the α -keto acids pyruvate, oxaloacetate, and α -ketoglutarate, respectively.

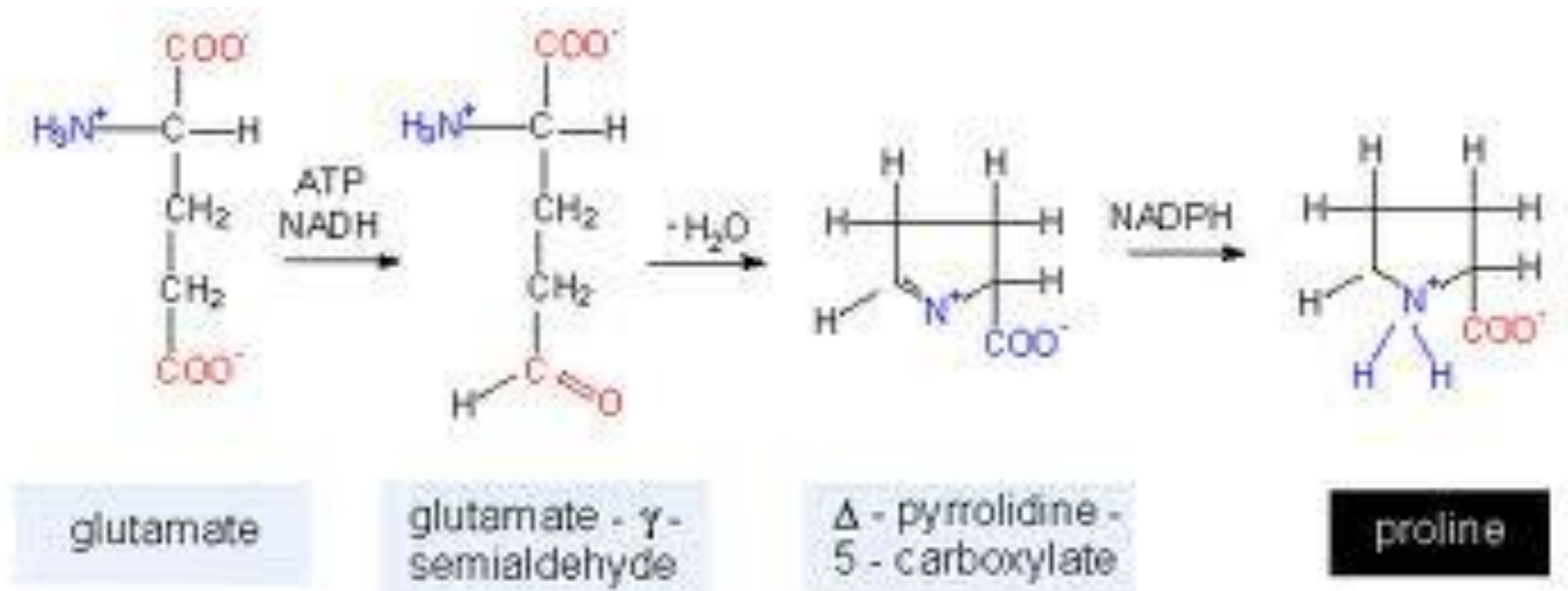
Glu can also be synthesized by the reverse of oxidative deamination, catalyzed by glutamate dehydrogenase

Synthesis by amidation

1. **Gln** is formed from Glu by glutamine synthetase
2. **Asn** is formed from Asp by asparagine synthetase, using glutamine as the amide donor.



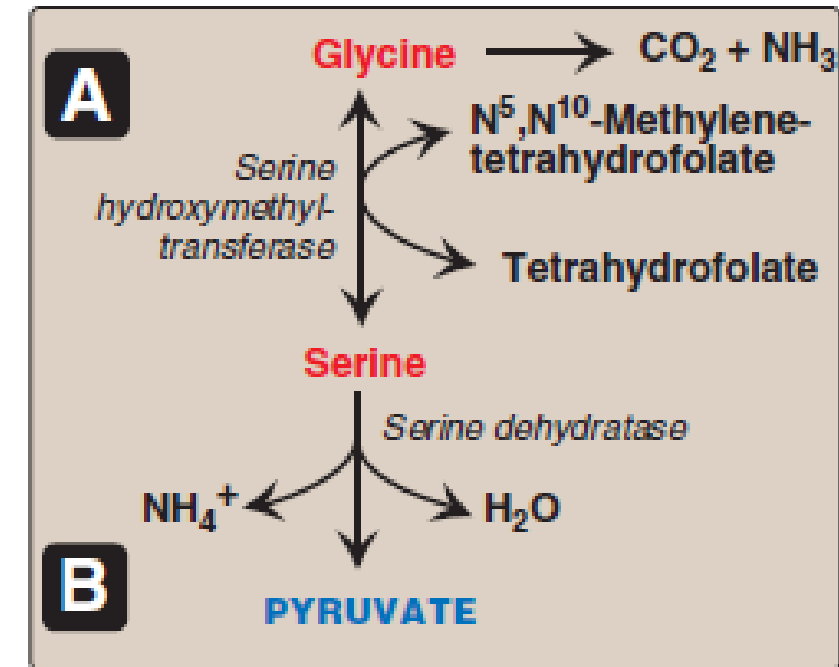
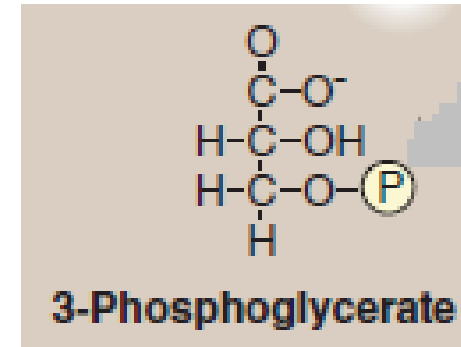
Proline



Glutamate is converted to proline by cyclization and reduction

Serine, glycine, and cysteine

1. **Ser** arises from 3-phosphoglycerate that is oxidized to 3-phosphopyruvate, and then transaminated to 3-phosphoserine. Serine is formed by hydrolysis of the phosphate ester.
 - Ser can also be formed from glycine through transfer of a hydroxymethyl group by serine hydroxymethyl transferase
 - N^5,N^{10} -methylene- THF is the one carbon donor
2. **Gly** is synthesized from serine by removal of a hydroxymethyl group, also by serine hydroxymethyl transferase
 - THF is the one carbon acceptor.

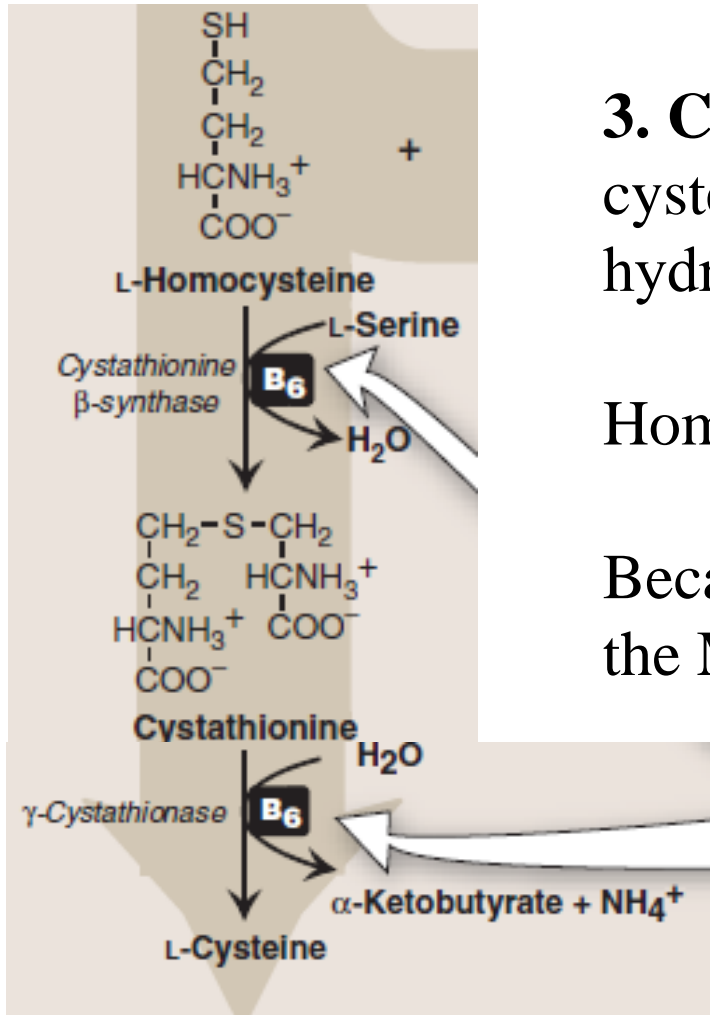


Serine, glycine, and cysteine

3. Cys is synthesized by two consecutive reactions in which homocysteine combines with serine, forming cystathionine that is hydrolyzed to α -ketobutyrate and Cys

Homocysteine is derived from Met

Because Met is an essential amino acid, Cys can be synthesized if the Met dietary intake is adequate.



Tyrosine

Tyr (non essential AA) is formed from Phe (essential AA) by phenylalanine hydroxylase.

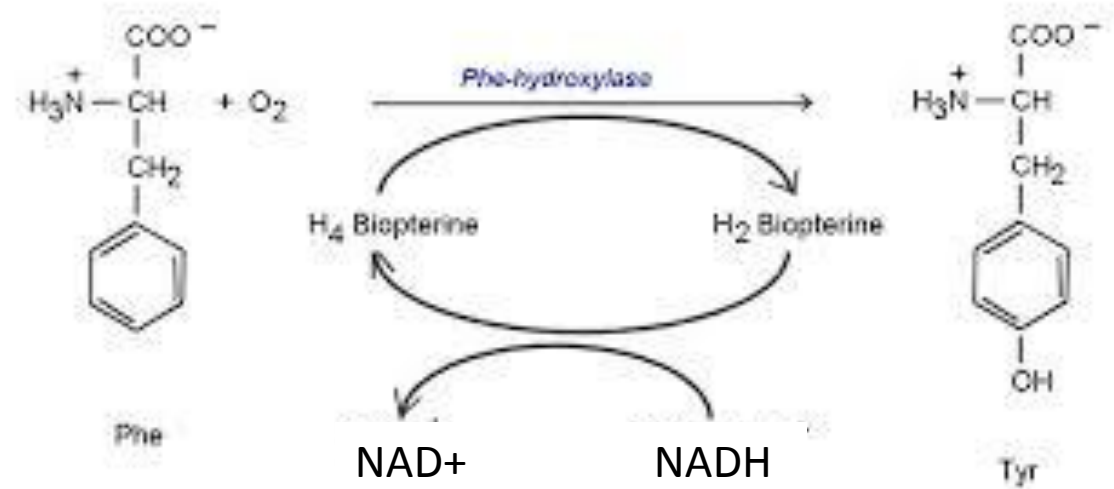
The reaction requires molecular oxygen and the coenzyme tetra hydrobiopterin (BH4)

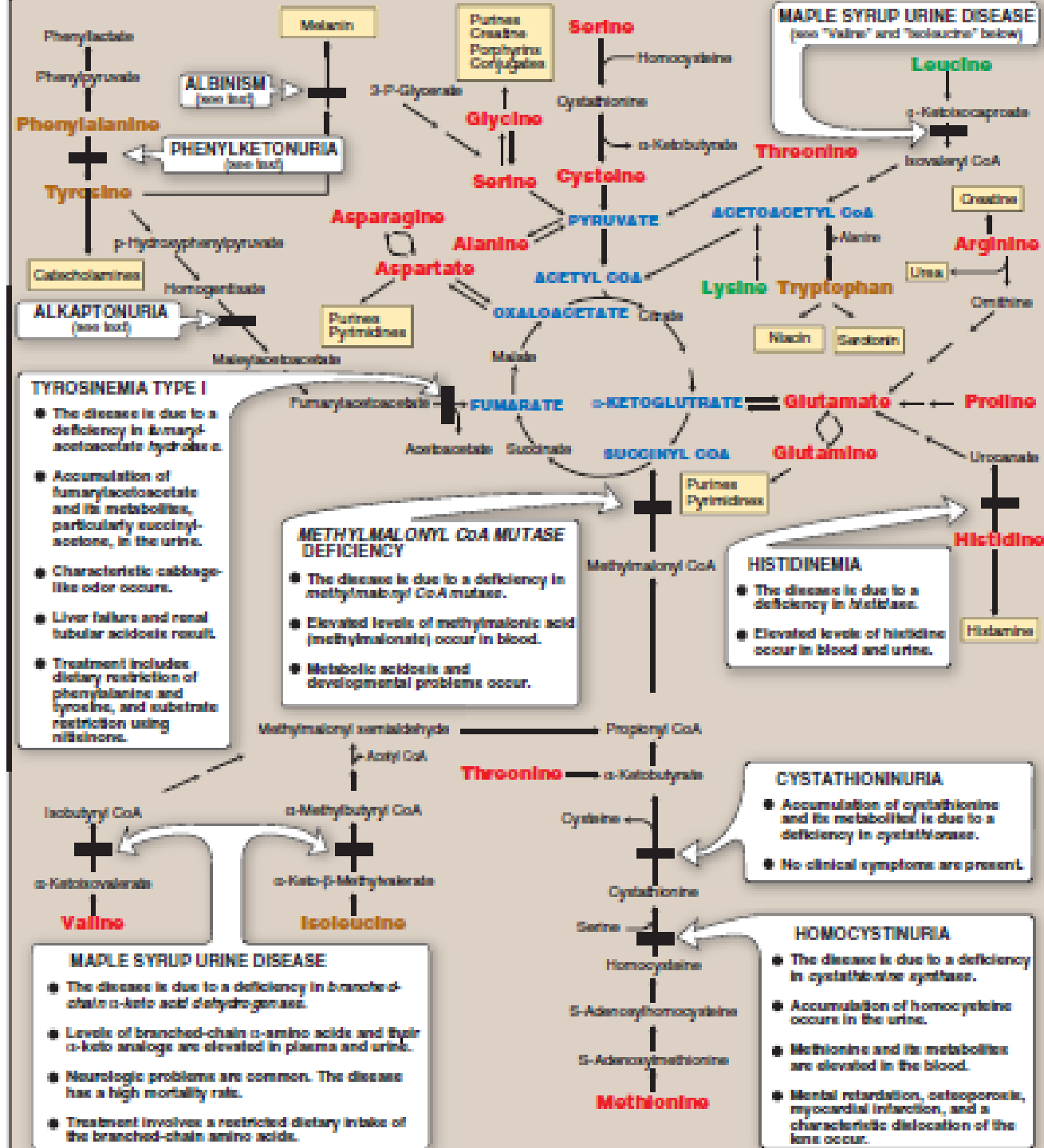
BH4 can be synthesized from GTP

One atom of molecular oxygen becomes the hydroxyl group of Tyr, and the other atom is reduced to water.

BH4 is oxidized to dihydrobiopterin (BH2).

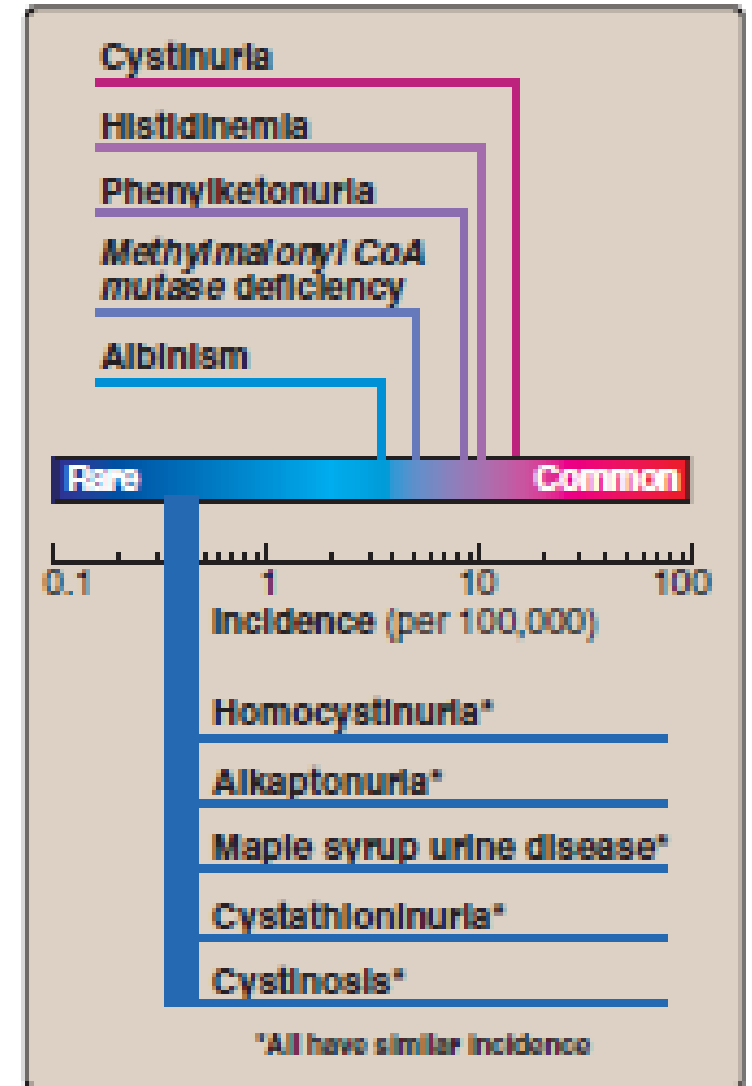
BH4 is regenerated from BH2 by NADH-requiring dihydro pteridine reductase.



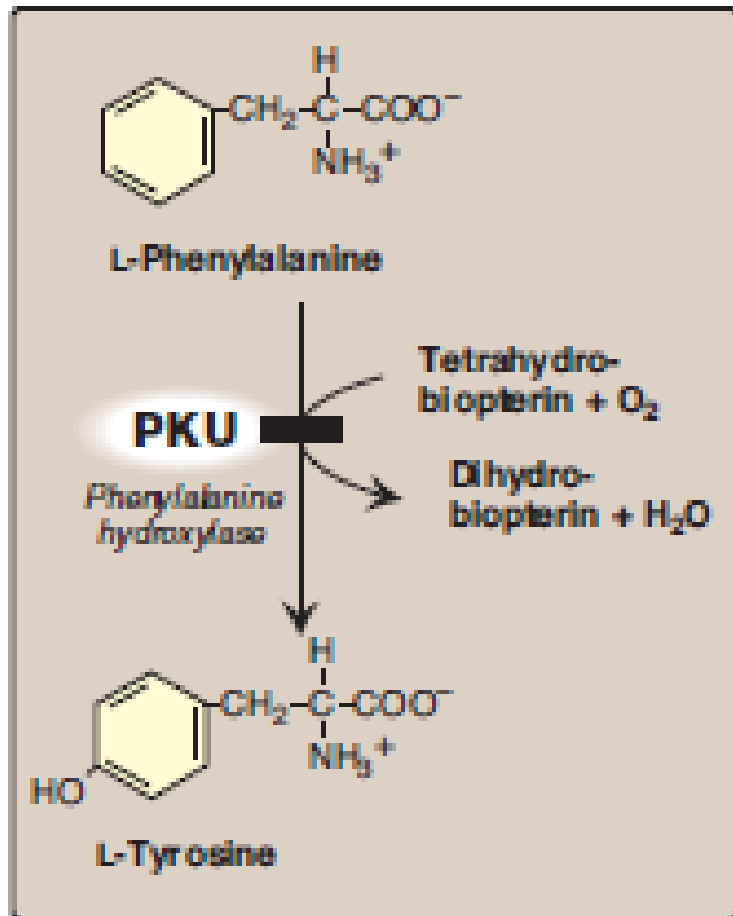


Metabolic defects in amino acid metabolism

The inherited defects of AA metabolism if stay untreated result in mental retardation or other developmental abnormalities because of the harmful accumulation of metabolites.



Metabolic disorders: Phenylketonuria (PKU)



The most common inborn error of amino acid metabolism (prevalence 1:15,000).

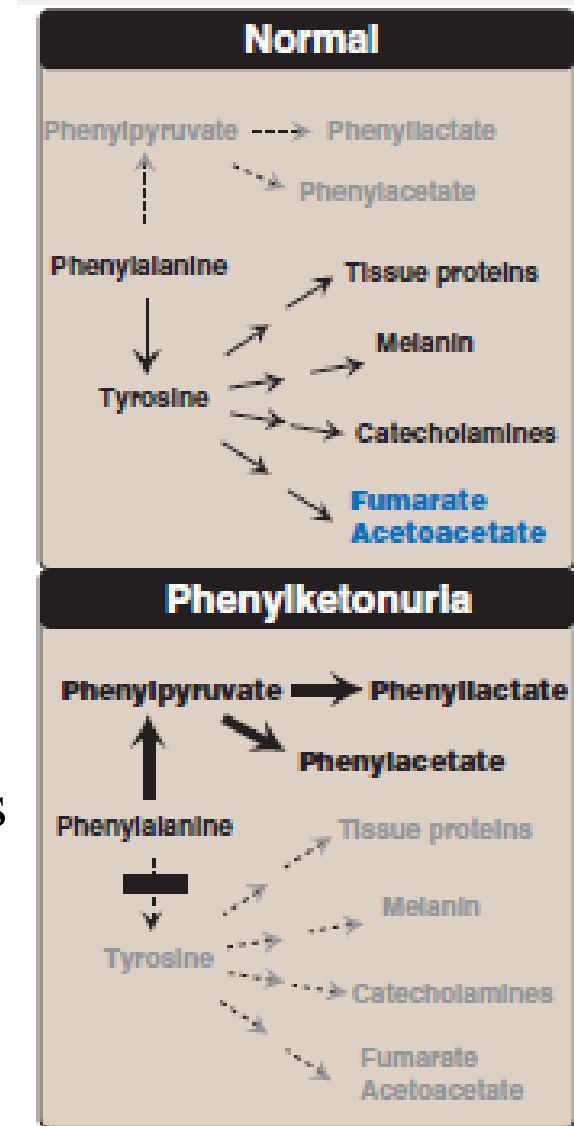
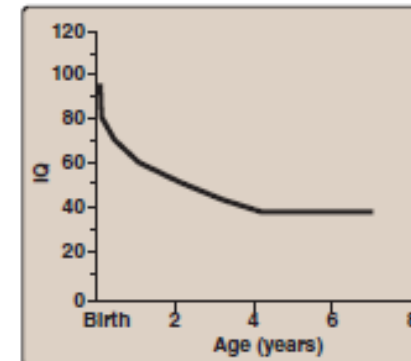
Due to phenylalanine hydroxylase deficiency

Biochemical changes: accumulation of phenylalanine (and a deficiency of tyrosine).

Characteristics of classic PKU:

- **Elevated phenylalanine** in tissues, plasma, and urine.
- **The characteristic musty “mousey” urine odor** due to phenyllactate, phenylacetate, and phenylpyruvate
- **CNS symptoms:** Mental retardation ($\text{IQ} < 50$), failure to walk or talk, seizures, hyperactivity, tremor, microcephaly, and failure to grow
- **Hypopigmentation:** fair hair, light skin color, and blue eyes because the hydroxylation of Tyr by tyrosinase (the first step in melanin formation) is competitively inhibited by the high levels of Phe.

Neonatal screening programs



Neonatal screening and diagnosis of PKU:

PKU is treatable by dietary restriction.

Lack of neonatal symptoms, so laboratory testing for elevated blood levels of Phe is mandatory

The infant with PKU frequently has normal blood levels of Phe at birth because the mother clears the extra Phe through placenta

Exposure protein feeding for 24–48 hours elevates Phe, thus, screening should be done after this to avoid false negatives.

Prenatal diagnosis of PKU:

Caused by any of 100 or more different mutations in the gene that codes for phenylalanine hydroxylase (PAH).

PKU is often doubly heterozygous (the PAH gene has a different mutation in each allele)

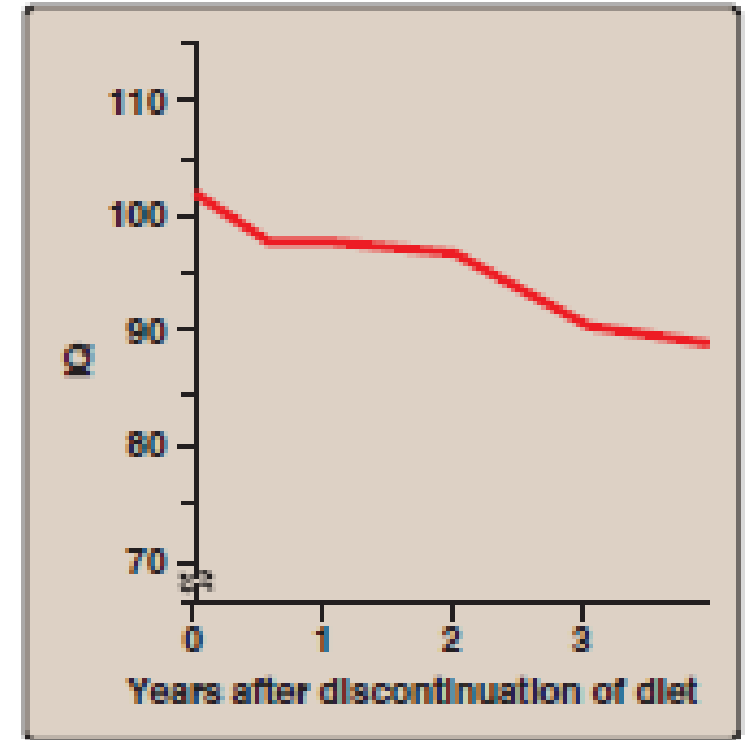
Treatment of PKU:

Dietary restriction: synthetic amino acid preparations low in Phe, supplemented with natural foods low in Phe content (fruits, vegetables, and certain cereals)

-Earlier treatment (prevents neurologic damage days of life) prevents neurologic complications (mental retardation)

Tyr cannot be synthesized from Phe and becomes an essential amino acid.

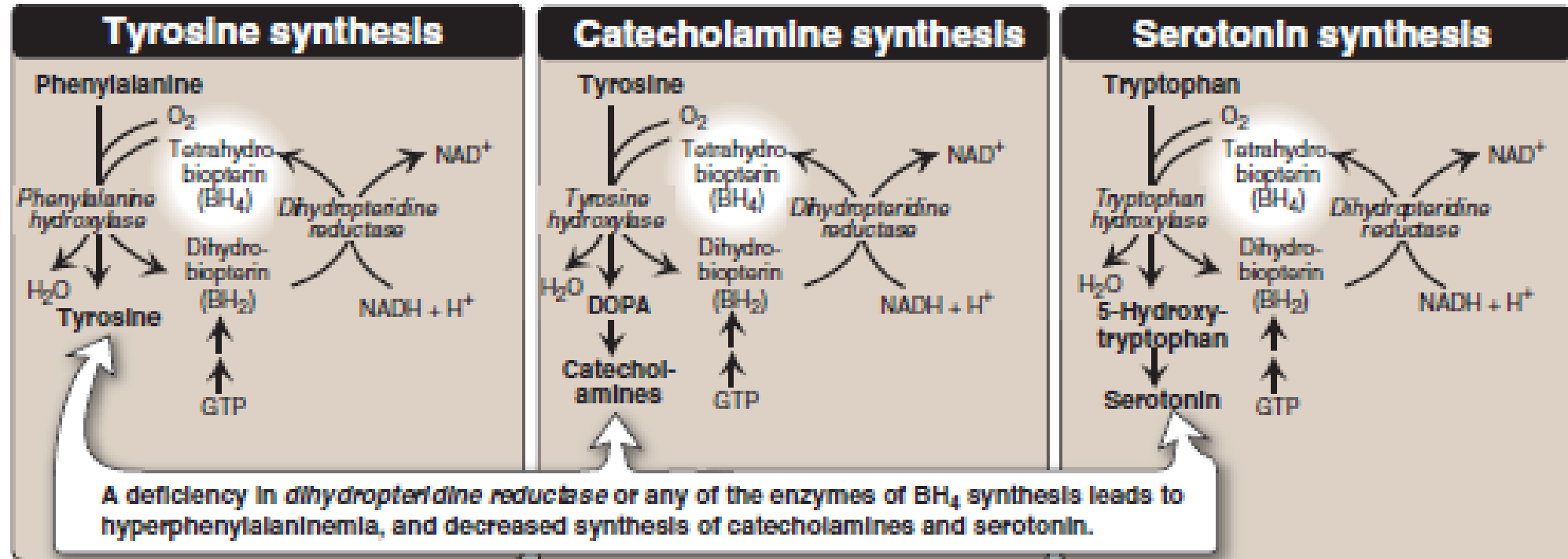
Aspartame should be avoided since it contains Phe.



Maternal PKU:

- High blood Phe levels in the mother cause microcephaly, mental retardation, and congenital heart abnormalities in the fetus
- Phenylalanine is a teratogen.
- Dietary control of blood phenylalanine must begin prior to conception, and must be maintained throughout the pregnancy.

Metabolic disorders: Hyperphenylalaninemia



Dihydropteridine reductase deficiency:

Restricting dietary Phe does not reverse the CNS effects due to deficiencies in neurotransmitters.

Replacement therapy with BH₄ or L-DOPA and 5-hydroxytryptophan (products of the affected tyrosine hydroxylase—and tryptophan hydroxylase—catalyzed reactions) improves the clinical outcome

Maple syrup urine disease (MSUD)

Rare (1:185,000)

Autosomal recessive (AR) disorder, most cases are heterozygotes

Partial or complete deficiency in branched-chain α -keto acid dehydrogenase complex that decarboxylates Leu, Ile, and Val



Branched-chain amino acids are an important energy source in times of metabolic need

Accumulation in the blood causes a toxic effect that interferes with brain functions.

Signs and symptoms: feeding problems, vomiting, dehydration, severe metabolic acidosis, and a characteristic maple syrup odor to the urine.

If untreated, MSUD leads to mental retardation, physical disabilities, and even death.

Maple syrup urine disease (MSUD)

Classification: classic type and several variant forms

Classic MSUD: symptoms within the first several days of life.

If not diagnosed and treated, classic MSUD is lethal in the first weeks of life.

Intermediate forms have a higher level of enzyme activity (3–15% of normal) resulting in milder symptoms and delayed onset.

Screening and diagnosis: prenatal diagnosis and neonatal screening are available.

Treatment: a synthetic formula that contains limited amounts of Leu, Ile, and Val to provide the branched-chain amino acids necessary for normal growth and development without producing toxic levels.

Early diagnosis and lifelong dietary treatment is essential for child normal development.

Albinism

A group of conditions in which a defect in Tyr metabolism results in a deficiency in the production of melanin.

Partial or full absence of pigment from the skin, hair, and eyes.

Inheritance modes:

AR (primary mode), AD, or X-linked.

Complete albinism (tyrosinase-negative oculocutaneous albinism) results from a deficiency of copper-requiring tyrosinase



Complete albinism:

The most severe form.

Total absence of pigment from the hair, eyes, and skin, vision defects and photophobia (sunlight hurts their eyes).

Higher risk for skin cancer.

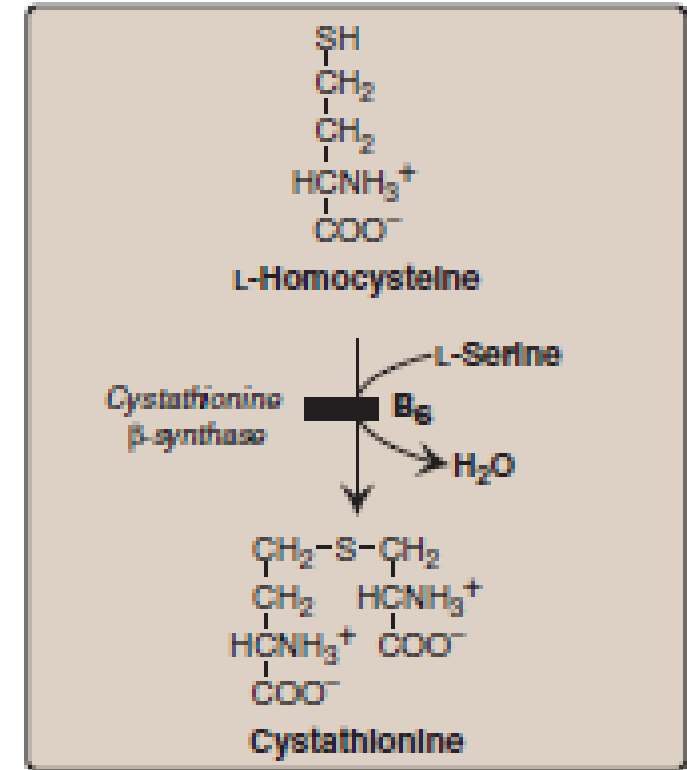
Homocystinuria

Defects in the metabolism of homocysteine.

Mode of inheritance: AR

High plasma and urinary levels of homocysteine and Met and low levels of Cys.

The most common cause is a defect in cystathionine β -synthase that converts homocysteine to cystathionine



Symptoms: homozygous individuals exhibit ectopia lentis, skeletal abnormalities, a tendency to form thrombi, osteoporosis, and neurological deficits.

Treatment: oral administration of pyridoxine (vitamin B6) may help

If responsive to vit B6, symptoms are milder and disease onset is delayed

Restriction of methionine intake and supplementation with vitamins B6, B12, and folate.

Alkaptonuria (Alcaptonuria)

A rare metabolic condition

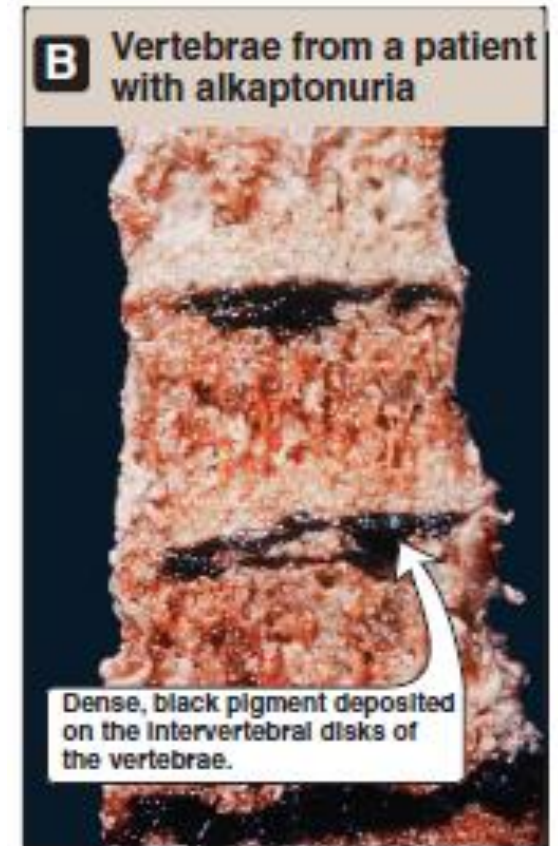
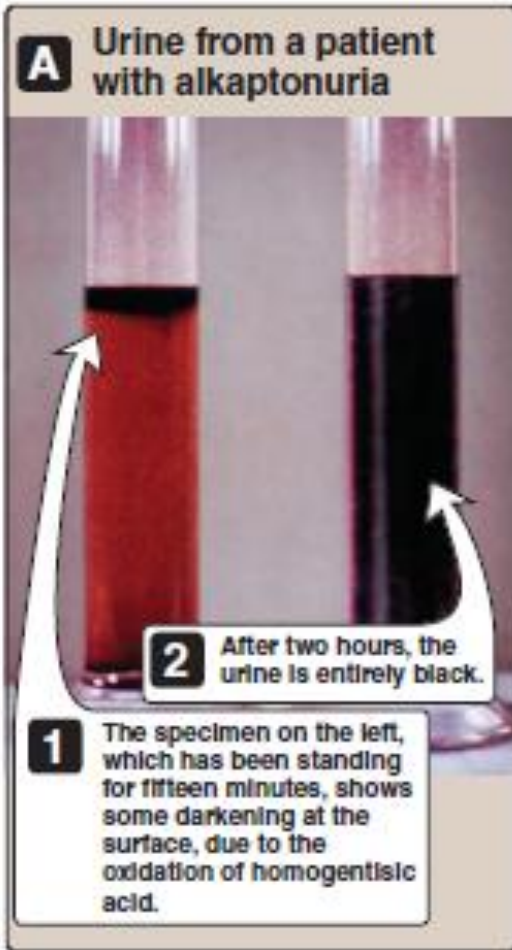
A deficiency in homogentisic acid oxidase, resulting in the accumulation of homogentisic acid (a reaction that occurs in the degradative pathway of Tyr)

Characteristic symptoms: Not life threatening

Homogentisic aciduria

Large joint arthritis

Black ochronotic pigmentation of cartilage and collagenous tissue



Alkaptonuria (Alcaptonuria)

Patients are usually asymptomatic until age 40.

Dark staining of the diapers can indicate the disease in infants

Treatment: diets low in protein—especially in phenylalanine and tyrosine—reduce homogentisic acid levels, and the pigment deposited in body tissues.