Amino acids degradation and synthesis

Shyamal D. Desai Ph.D.
Department of Biochemistry & Molecular Biology
MEB. Room # 7107
Phone- 504-568-4388
sdesai@lsuhsc.edu

Nitrogen metabolism

N2

Atmospheric nitrogen N2 is most abundant but is too inert for use in most biochemical processes.

Dietary proteins

Atmospheric nitrogen is acted upon by bacteria (nitrogen fixation) and plants to nitrogen containing compounds. We assimilate these compounds as proteins (amino acids) in our diets.

Amino acids

Conversion of nitrogen into specialized products

Other nitrogen containing compounds

Lecture III

Body proteins

α-amino groups

NH4+

Disposal of Nitrogen

Lecture I

Urea

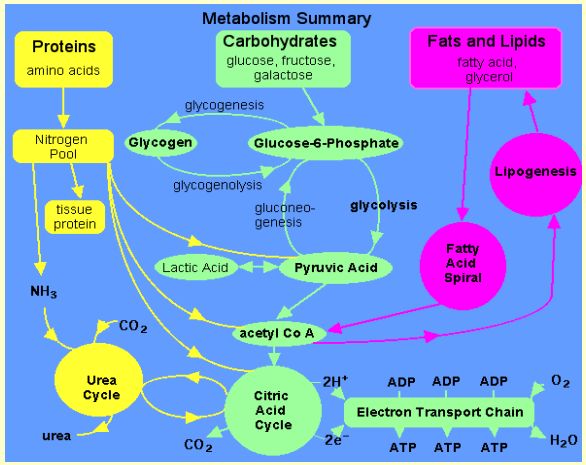
excreted

Carbon skeletons

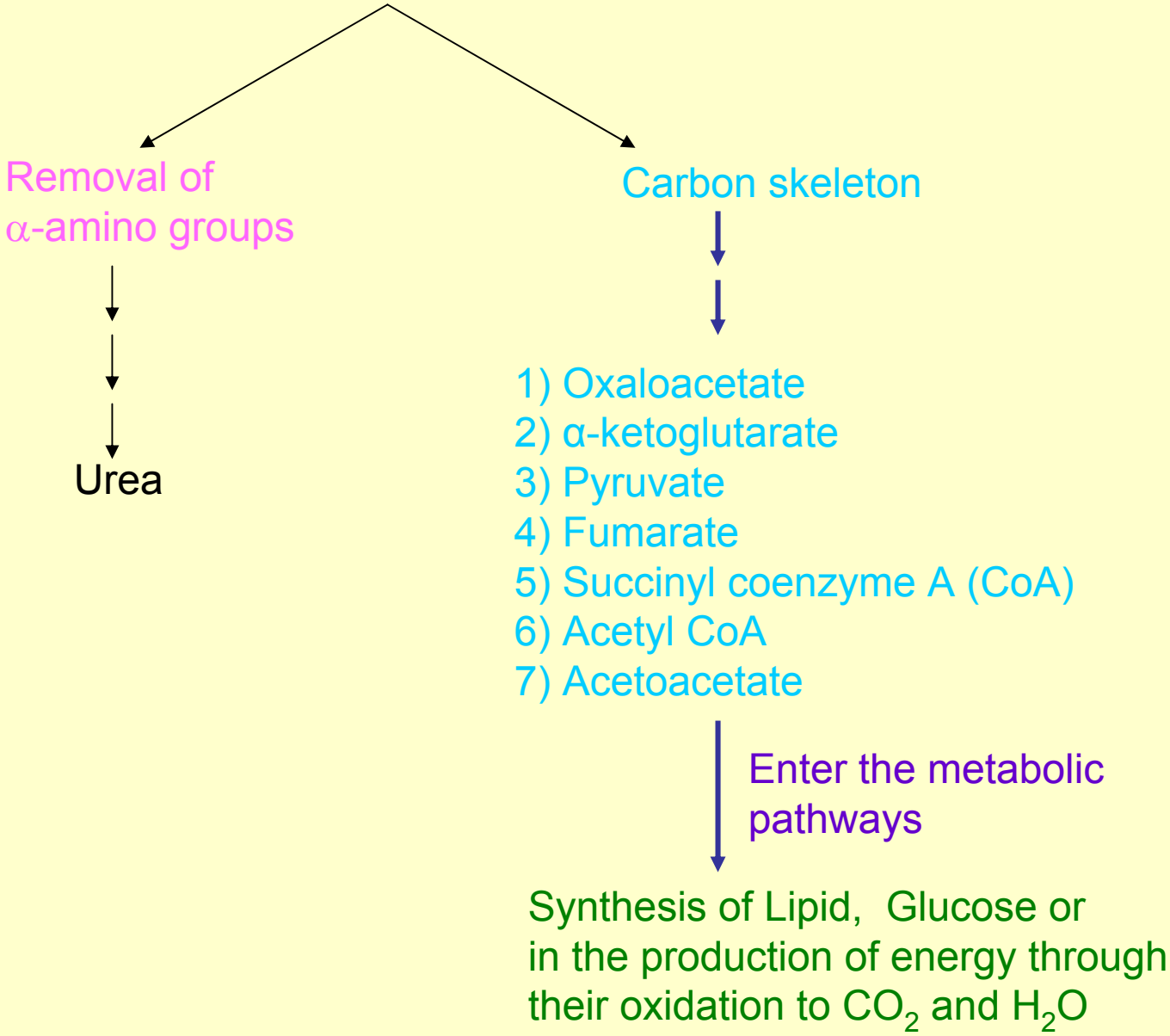
Amino acids synthesis & degradation

Lecture II

Enters various metabolic pathways



Amino acids catabolism



Essential *versus* Nonessential Amino Acids

Cannot be synthesized de novo, *hence, must be* supplied in the diet.

Synthesized by body

Essential	Nonessential
Arginine[a]	Alanine
Histidine	Aspartate
Isoleucine	Cysteine
Leucine	Glutamate
Lysine	Glycine
Methionine[b]	Proline
Phenylalanine[c]	Serine
Threonine	Tyrosine
Tryptophan	
Valine	

[a] Arginine is synthesized by mammalian tissues, but the rate is not sufficient to meet the need during growth.
[b] Methionine is required in large amounts to produce cysteine if the latter is not supplied adequately by the diet.
[c] Phenylalanine is needed in larger amounts to form tyrosine if the latter is not supplied adequately by the diet.

Glucogenic and Ketogenic Amino acids

Amino acids are classified as glucogenic, ketogenic, or both based on which of the seven intermediates are produced during their catabolism.

Glucogenic

↓

Amino acids that can be converted into glucose through gluconeogenesis

Ketogenic

↓

Amino acids that can be converted into ketone bodies through ketogenesis

Amino acids whose catabolism yields pyruvate or one of the intermediates of the citric acid cycle are termed glucogenic or glycogenic

Amino acids whose catabolism yields either acetoacetate or one of its precursor, (acetyl CoA or acetoacetyl CoA) are termed ketogenic.

Some amino acids are both glucogenic or ketogenic

Ketone bodies

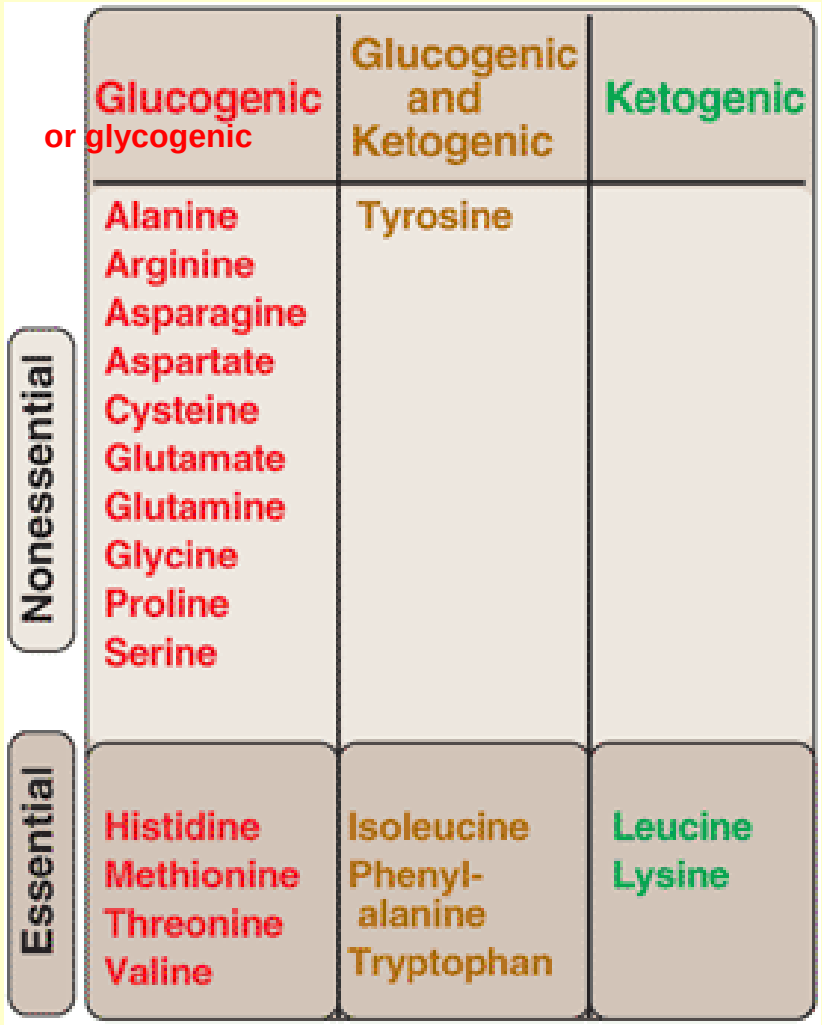
Ketone bodies are three water-soluble compounds that are produced as by-products when fatty acids are broken down for energy in the liver and kidney.

The three ketone bodies are acetone, acetoacetic acid and beta-hydroxybutyric acid.

Ketone bodies are transported from the liver to other tissues, where acetoacetate and beta-hydroxybutyrate can be reconverted to acetyl-CoA to produce energy, via the Krebs cycle.

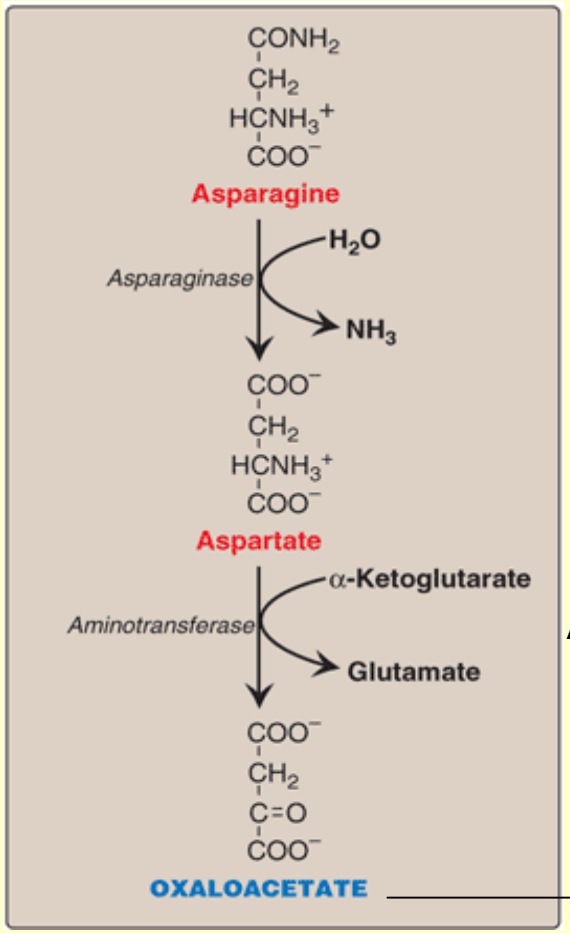
Excess ketone bodies accumulate, this abnormal (but not necessarily harmful) state is called Ketosis

Glucogenic and Ketogenic Amino acids



Catabolism of the carbon skeletons of amino acids

Amino acids that enter metabolism as oxaloacetate (Aspargine and Aspartate)



Asparagine is hydrolyzed by Asparaginase, liberating ammonia and Aspartate

Aspartate loses its amino group by transamination to form oxaloacetate

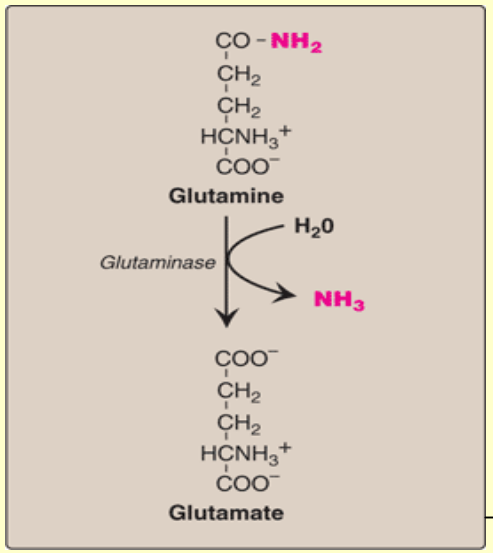
condenses with acetyl CoA to form citrate in the first reaction of the Krebs cycle. → **Glucogenic**

Amino acids that form α-ketoglutarate

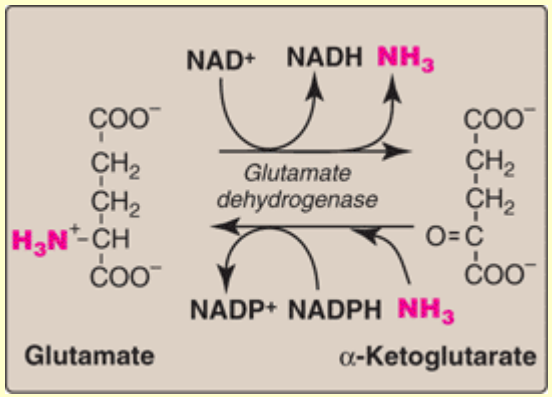
Glucogenic

(Glutamine, Proline, Arginine, Histidine)

1) Glutamine:



Oxidative deamination



oxidative deamination by glutamine dehydrogenase → α-ketoglutarate

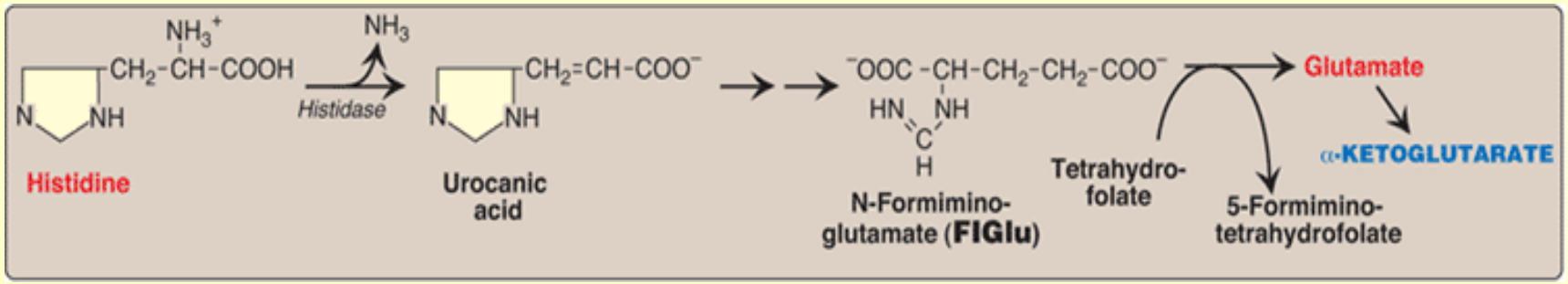
2) Proline:

It is oxidized to glutamate. Glutamate is then oxidatively deaminated to form **α-ketoglutarate**

3) Arginine:

This aa is cleaved by arginase to produce ornithine. Ornithine is subsequently converted to **α-ketoglutarate**

4) Histidine:

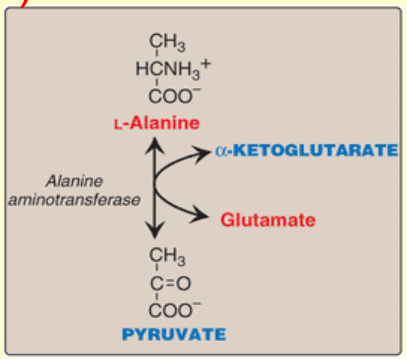


Amino acids that enter metabolism as pyruvate

Glucogenic

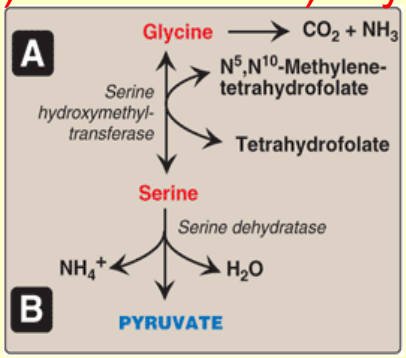
Alanine, Serine, Glycine, Cystine Threonine

1) Alanine



Alanine loses its amino group by transamination to form **pyruvate**

2) Serine and 3) Glycine



Inter conversion of serine and glycine

Serine can be converted to glycine and N5, N10-methylenetetrahydorfolate or to pyruvate by serine dehydratase.

4) Cystine

Cystine —(reduced by NADH + H+)→ Cysteine —(desulfuration)→ pyruvate

5) Threonine

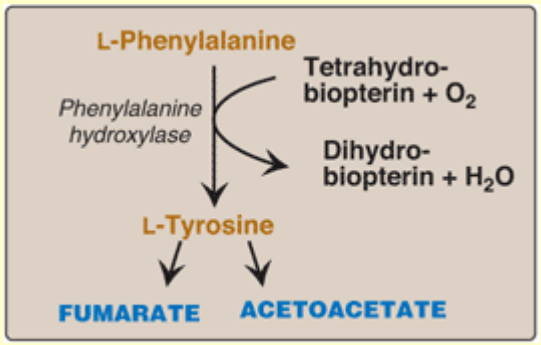
Threonine → pyruvate

Threonine → α-ketobutyrate → Succinyl CoA

Amino Acids that enter metabolism as fumarate

Phenylalanine and Tyrosine

1) Phenylalanine and 2) Tyrosine



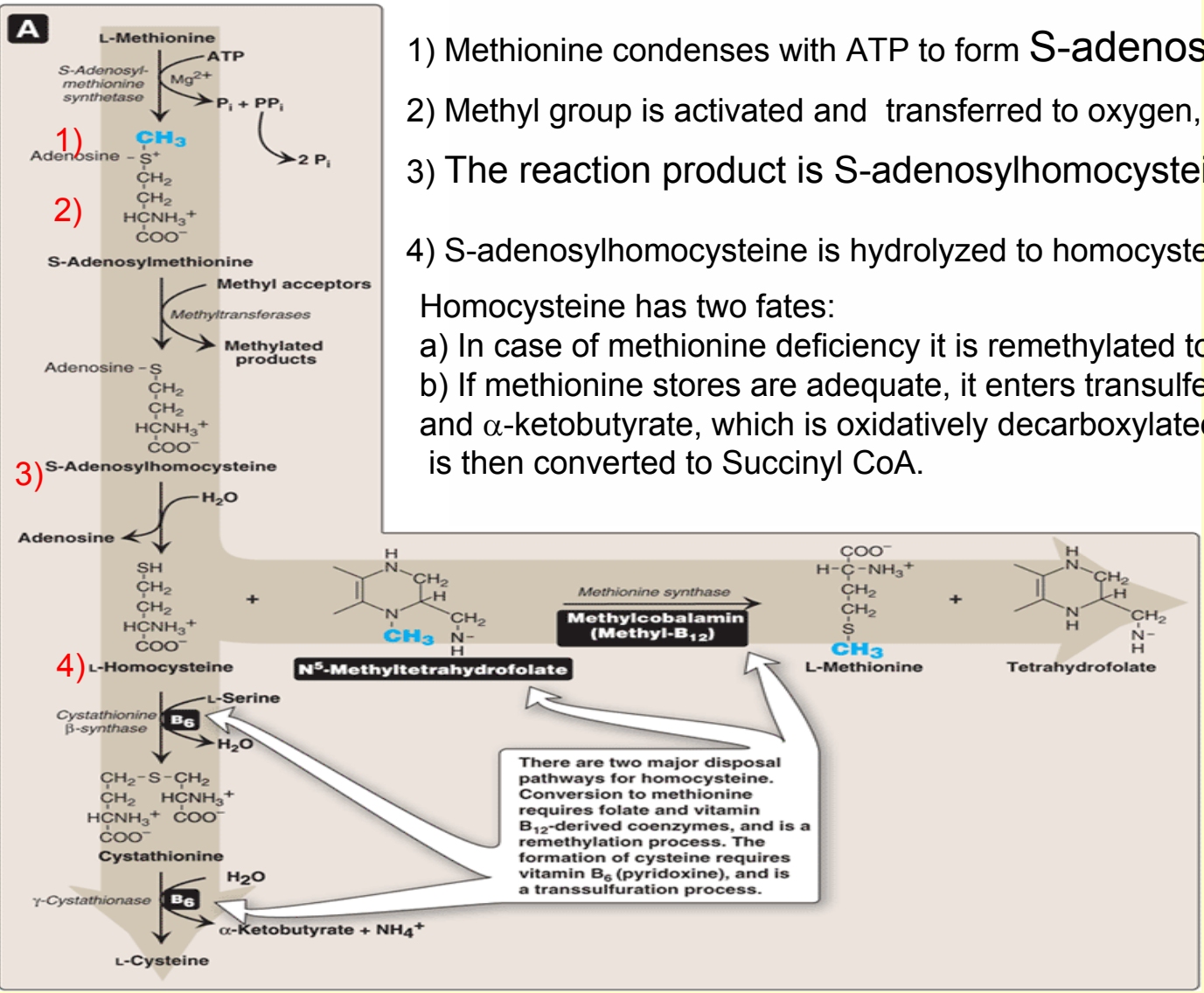
Phenylalanine —(**hydroxylated**)→ **Tyrosine** → **Fumarate** + **Acetoacetate**

Hence these two aa are both glucogenic and ketogenic

Amino acids that enter metabolism as succinyl CoA (Methionine Valine, Isoleucine, Threonine)

Methionine

- Converted into S-adenosylmethionine (SAM), (a major universal methyl donor in one-carbon metabolism)
- It is also a source of homocysteine---a metabolite associated with artherosclerotic vascular disease



1) Methionine condenses with ATP to form S-adenosylmethionine

2) Methyl group is activated and transferred to oxygen, nitrogen or carbon atoms.

3) The reaction product is S-adenosylhomocysteine

4) S-adenosylhomocysteine is hydrolyzed to homocysteine.

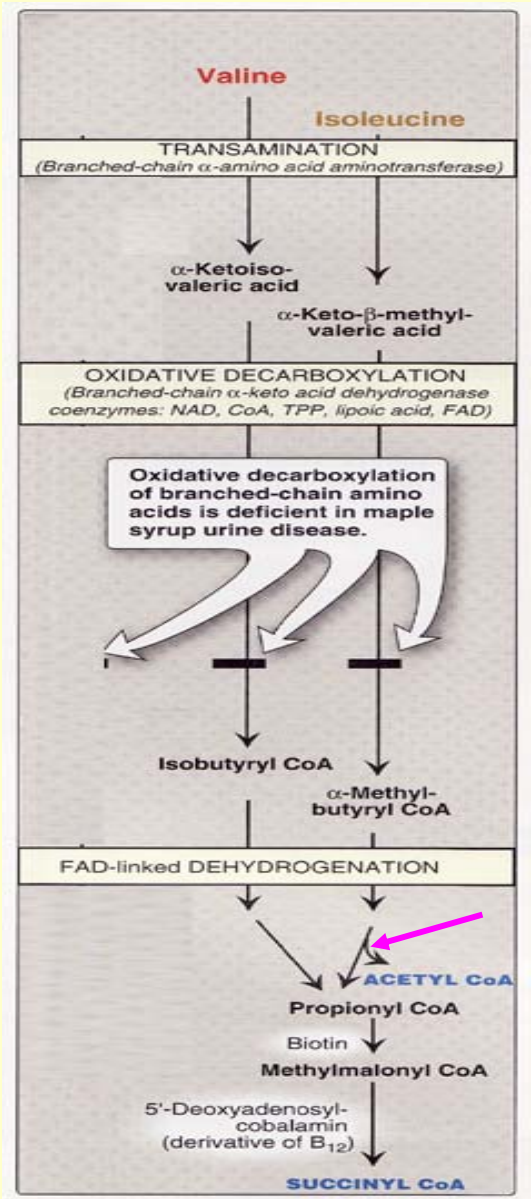
Homocysteine has two fates:

a) In case of methionine deficiency it is remethylated to methionine

b) If methionine stores are adequate, it enters transulferation pathway to form cysteine and α-ketobutyrate, which is oxidatively decarboxylated to form propionyl CoA which is then converted to Succinyl CoA.

Amino acids that form succinyl CoA

Valine, Isoleucine and Threonine



1) Valine and Isoleucine → Metabolism of Isoleucine
Also give Acetyl CoA and hence
Is both glucogenic and ketogeic

Valine and Isoleucine

↓

Propionyl CoA

↓ Requires vitamin B12 and Biotin

Succinyl CoA ⟶ TCA cycle

2) Threonine

Threonine

↓ dehydrated

Propionyl CoA

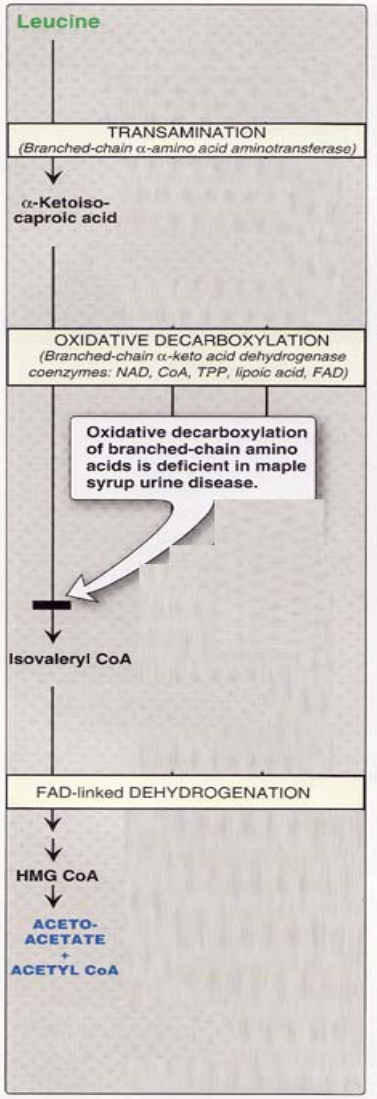
↓

Succinyl CoA ⟶ TCA cycle

Amino acids that form acetyl CoA or acetoacetyl CoA

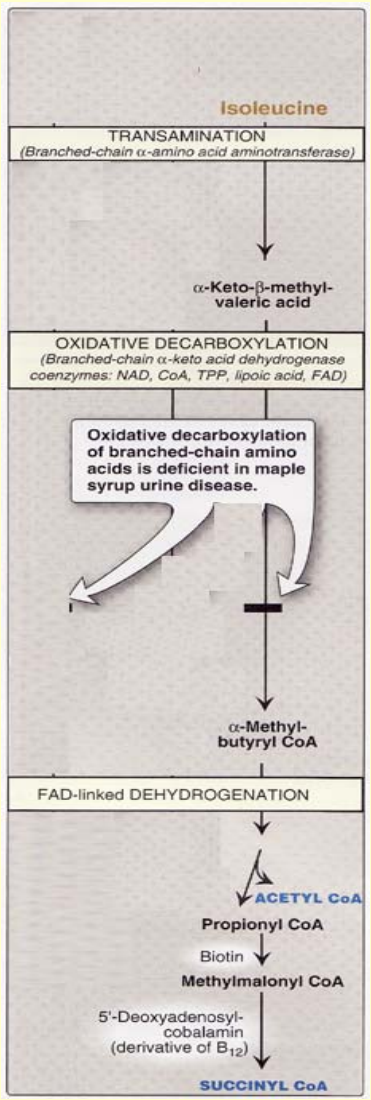
1) Leucine

Exclusively Ketogenic



2) Isoleucine

Ketogenic and glucogenic



3) Lysine

Exclusively Ketogenic

↓

Acetyl CoA

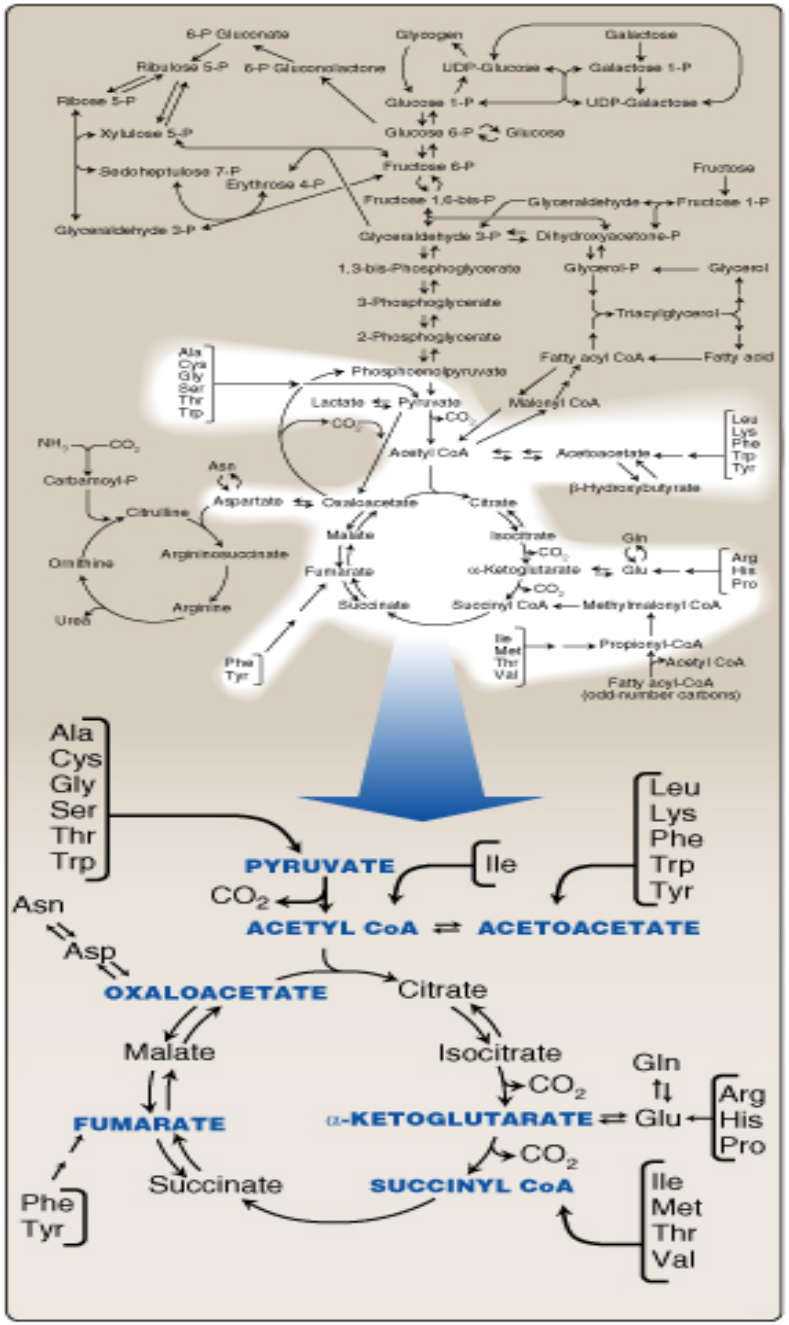
Lysine is unusual in that neither of its amino groups undergoes transamination as the first step of in catabolism

4) Tryptophan

Glucogenic and ketogenic

Since its metabolism yields both alanine and Acetoacetyl CoA

Overview of Amino Acid Catabolism



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

Enter as acetoacetate intermediates

Enter as both TCA cycle and acetyl derived intermediates

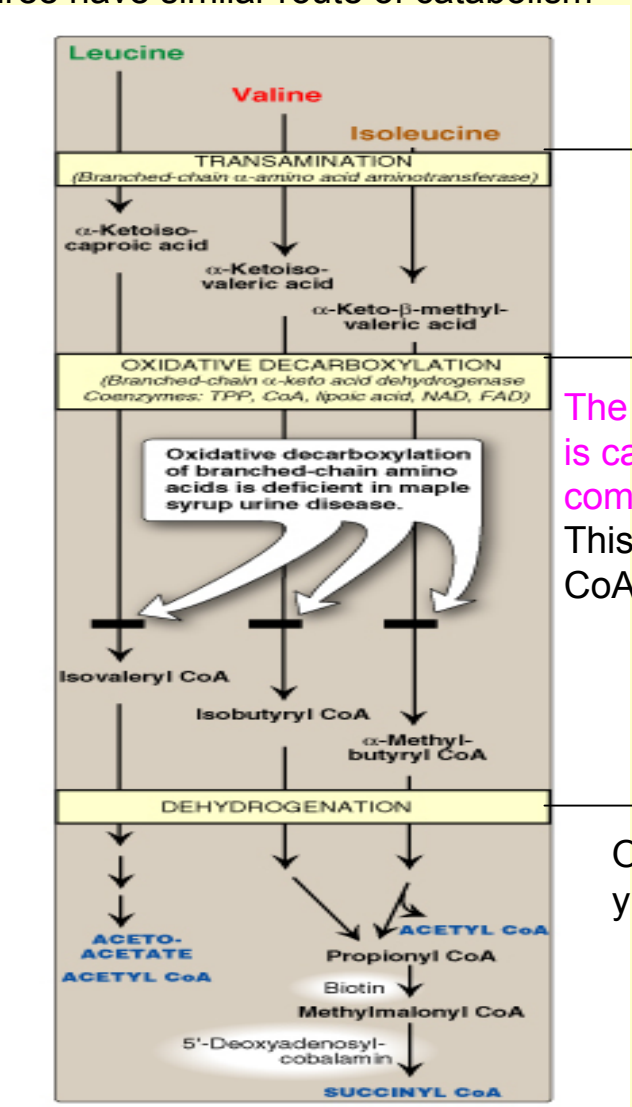
Enter as TCA cycle intermediates

Seven central products of amino acid metabolism

Catabolism of the branched chain amino acids

Branched chain AA are: Isoleucine, Leucine, Valine

* Essential AA
•Metabolized primarily by the peripheral tissues (muscles) and not In the liver like other amino acids.
*All three have similar route of catabolism



Transamination

Catalyzed by a single Vitamin B6-requiring enzyme, Branched-chain α-amino acid aminotransferase.

Oxidative decarboxylation

The removal of carboxyl group of the α-keto acids from these three AAs is catalyzed by the same branched-chain α-keto acid dehydrogenase complex.

This enzyme uses thiamine pyrophosphate, lipoic acid, FAD, NAD+, and CoA as cooenzymes).

Dehydrogenase

Oxidation of the products formed in the decarboxylation reaction yields α-β-unsaturated acyl CoA derivatives.

Role of Folic aid in Amino acid metabolism

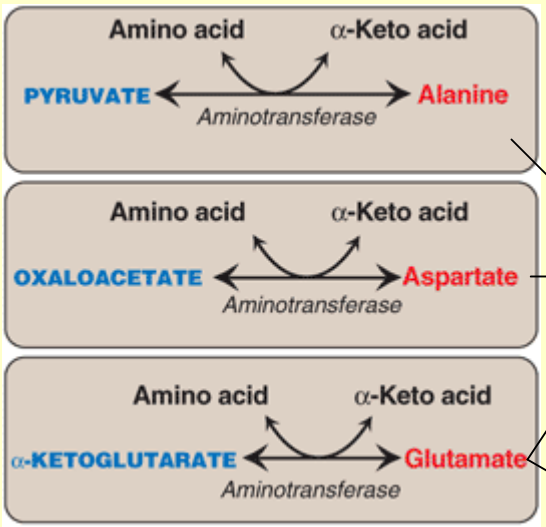
Tetrahydrofolic acid, an active form of Folic acid that carries single carbon unit. This carbon unit is transferred to specific structures that are being synthesized or modified.

One-carbon metabolism comprises a network of integrated biochemical pathways that donate, and regenerate, the **one-carbon** moieties needed for physiologic processes.

Biosynthesis of nonessential amino acids

Non essential amino acids are synthesized from intermediates of metabolism or, from essential amino acids.

Synthesis from α-keto acids



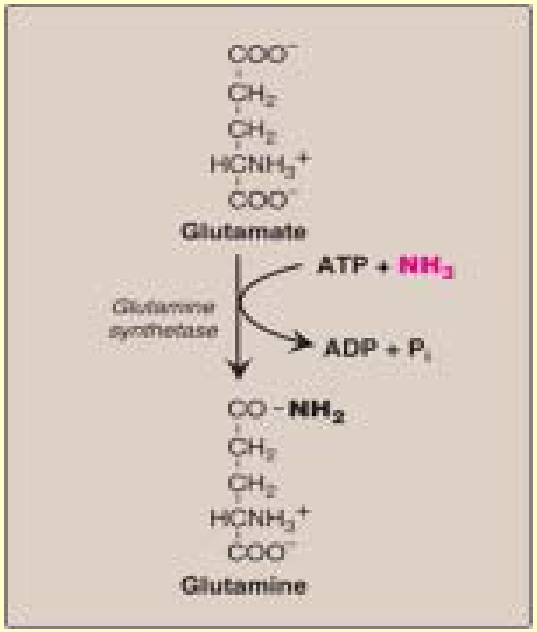
Ala, Asp and Glu are synthesized by transfer of an amino group to the α-keto acids pyruvate, oxaloacetate, and a-ketoglutarate respectively.

Glutamate can also be synthesized by Reverse of oxidative deamination, catalyzed by glutamate dehydrogenase.

Biosynthesis of nonessential amino acids

Synthesis by amidation

Glutamine:



Glutamine:

- contains an amide linkage with ammonia at the γ-carboxyl
- Is formed from glutamate
- Reaction is driven by glutamine synthetase
- Requires ATP
- Reaction serves as a major step for detoxification of ammonia in addition to the synthesis of Glutamine for protein synthesis.

Aspargine:

Aspargine:

- contains an amide linkage with ammonia at the β-carboxyl
- Is formed from Aspratate
- Reaction is driven by asparagine synthatase using glutamine as a amide donor.
- Requires ATP

Biosynthesis of nonessential amino acids

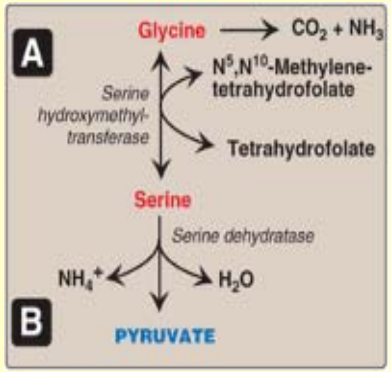
Proline:

Glutamate is converted to proline by cyclization and reduction reactions.

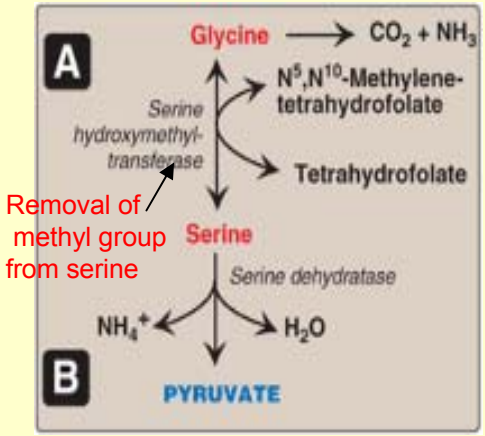
Serine:

Synthesized from glycolysis intermediate 3-phosphogylcerate.

Or



Glycine:



Cysteine:

Is synthesized by two consecutive reactions

1) Homocysteine + serine ⟶ Cystathionine

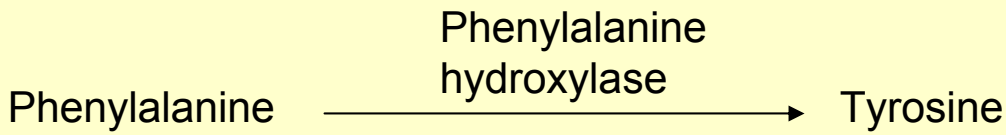
2) hydrolysis

↓

α-ketobutyrate + cysteine

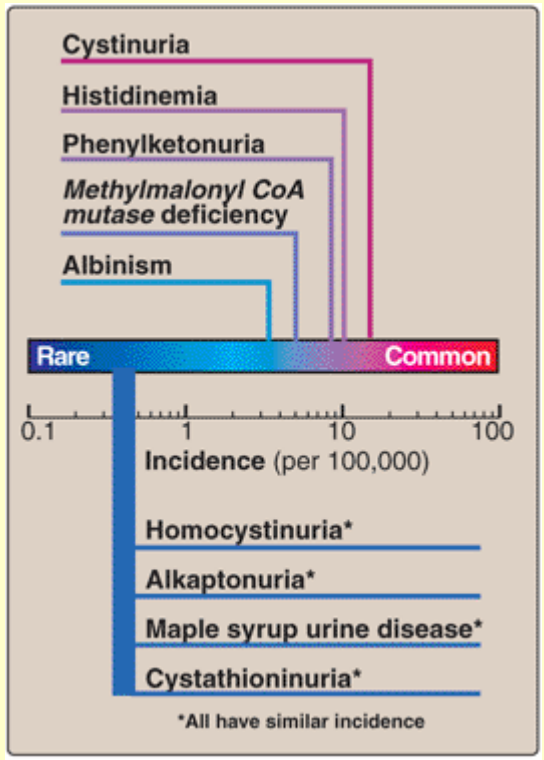
Biosynthesis of nonessential amino acids

Tyrosine



Tyrosine and Cysteine are non essential AA. But there synthesis is dependent on the essential AAs phenylalanine and methionine resp.
Hence, these AAs are non essential only when there is an adequate supply of essential AA.

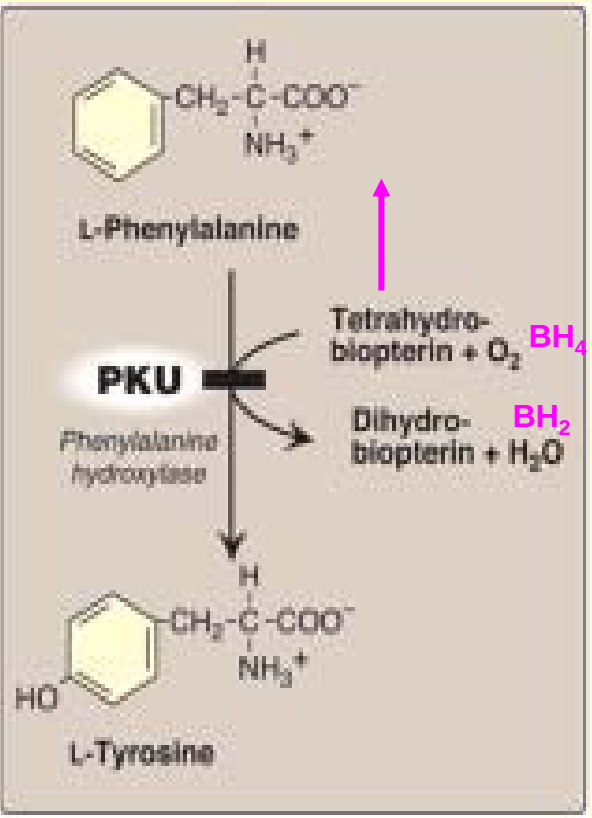
Metabolic defects in Amino acid metabolism



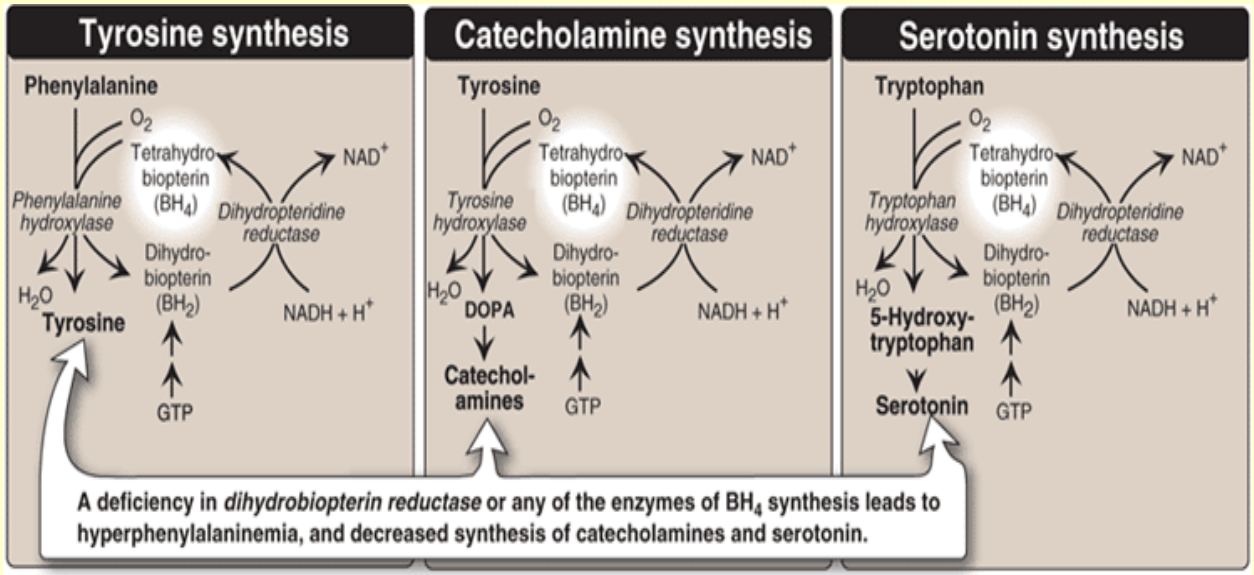
Phenylketonurea (Prevalence of 1:15,000)

A deficiency in phenylalanine hydroxylase results in the disease phenylketonuria (PKU).

More than 400 mutations in gene that code for PKU has been identified and the disease is often heterozygous.



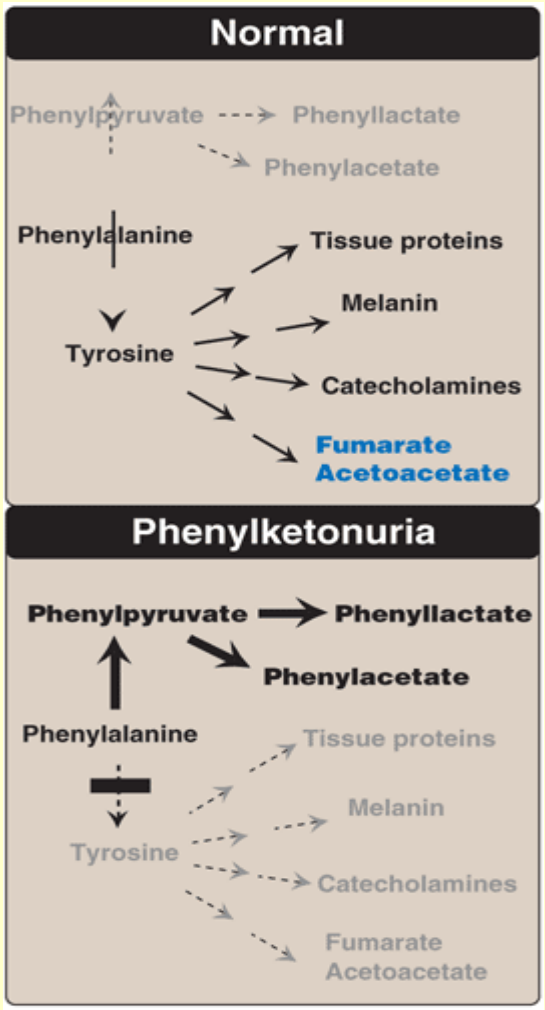
Deficiency of enzymes required for the synthesis of BH4 and dihydropterine (BH2) Reductase which regenerates BH4 from BH2 also leads to hyperphenylalaninemia.



BH4 is also required for tyrosine hydroxylase and tryptophan hydroxylase

Treatment: replacement therapy with BH4 or generated products

Pathways of phenylalanine metabolism in normal individuals and in patients with phenylketonuria.



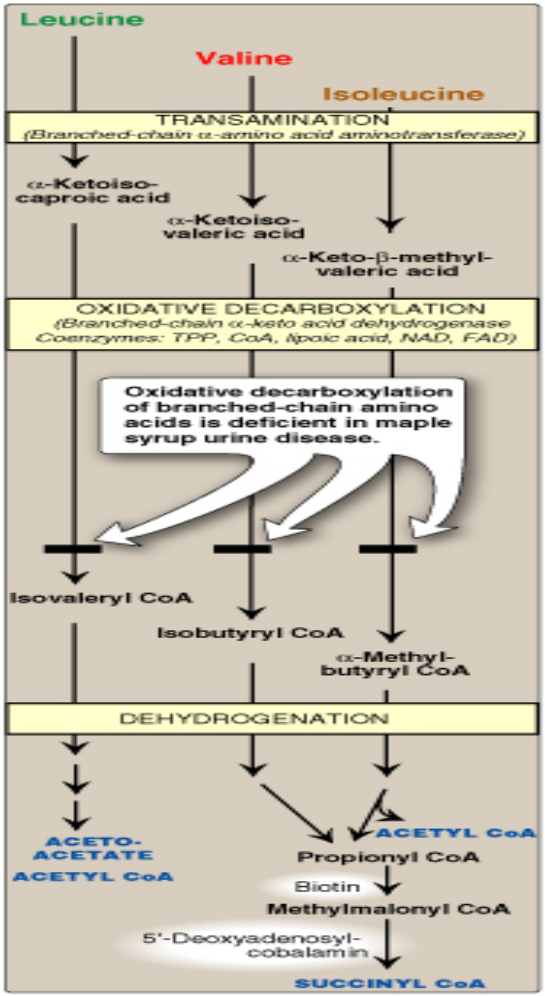
Characteristics of classic PKU:

1) Elevated phenylalanine, phenylpyruvate, phenyllactate and phenylacetate in tissues, plasma and urine.
2) CNS symptoms: Mental retardation, failure to walk or talk, seizures, hyperctivity, tremor etc.
3) Hypopigmentation: deficiency in the formation of Melanin lead to the deficiency of pigmentation (fair hair, light skin, color, and blue eyes.

Treatments: Synthetic nutrient with low phenylalanine content supplemented with tyrosine

Maple syrup urine disease (MSUD) (rare, prevalence of 1:185,000)

Autosomal recessive disease in which there is a partial or complete deficiency of Branched chain α-keto acid dehydrogenase, an enzyme that decarboxylates leucine, Isoleucine, and Valine.



Disease leads to accumulation of these amino aids and branched chain α-keto acid substrates causing abnormalities in brain functions.

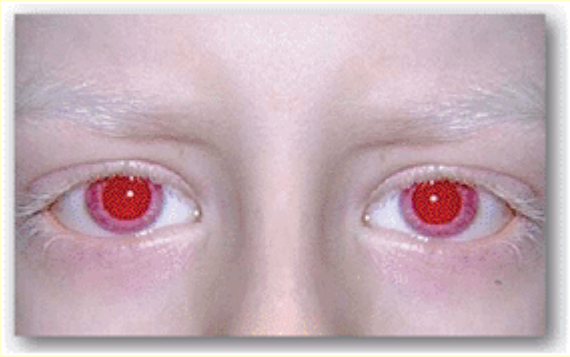
Characteristics of MSUD

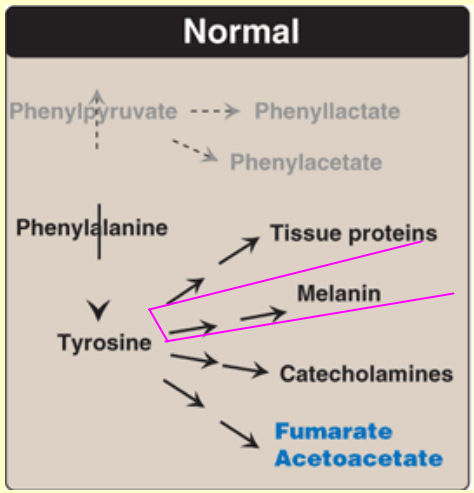
Patients show feeding problems, vomiting, dehydration, severe metabolic acidosis and Classic maple syrup odor to the urine.

Treatments:

Giving a synthetic formula that contains limited amount of leucine, Isoleucine, and Valine.

Albinism





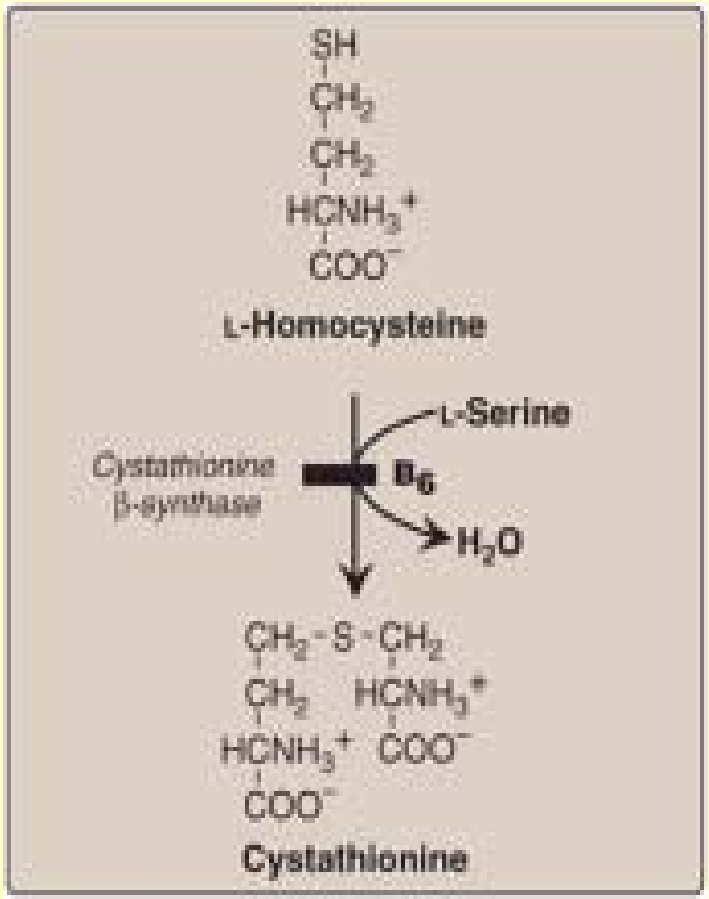
Condition in which defect in tyrosine metabolism results in deficiency in the production of melanin.

Characteristics: hypopigmentation caused due to the deficiency in the formation of melanine results in partial or full absence of pigment from the skin, hair, and eyes.

Homocystinuria

Caused due to the defect in the metabolism of homocysteine. Most common cause is A defect in the enzyme cystathionine β-synthatase.

Results in elevation of homocysteine, methionine, and low levels of cysteine in plasma



Charactristics:

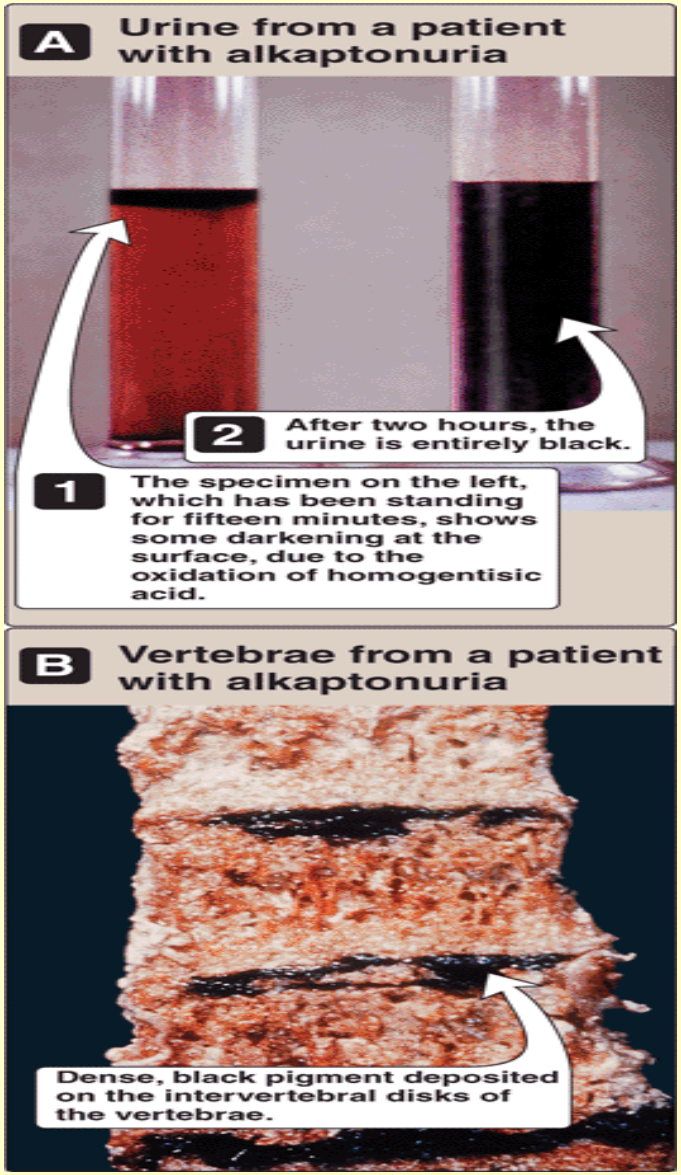
1) High levels of homocysteine and methionine in plasma and urine.
2) Patients exhibit ectopia (displacement of the lens of the eye)
3) Skeletal abnormalities
4) Premature arterial disease
5) Osteoporosis
6) Mental retardation

Treatment:

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

Alkaptonuria

Rare disease involving deficiency in homogentisic acid oxidase, enzyme in tyrosine degradation pathway.



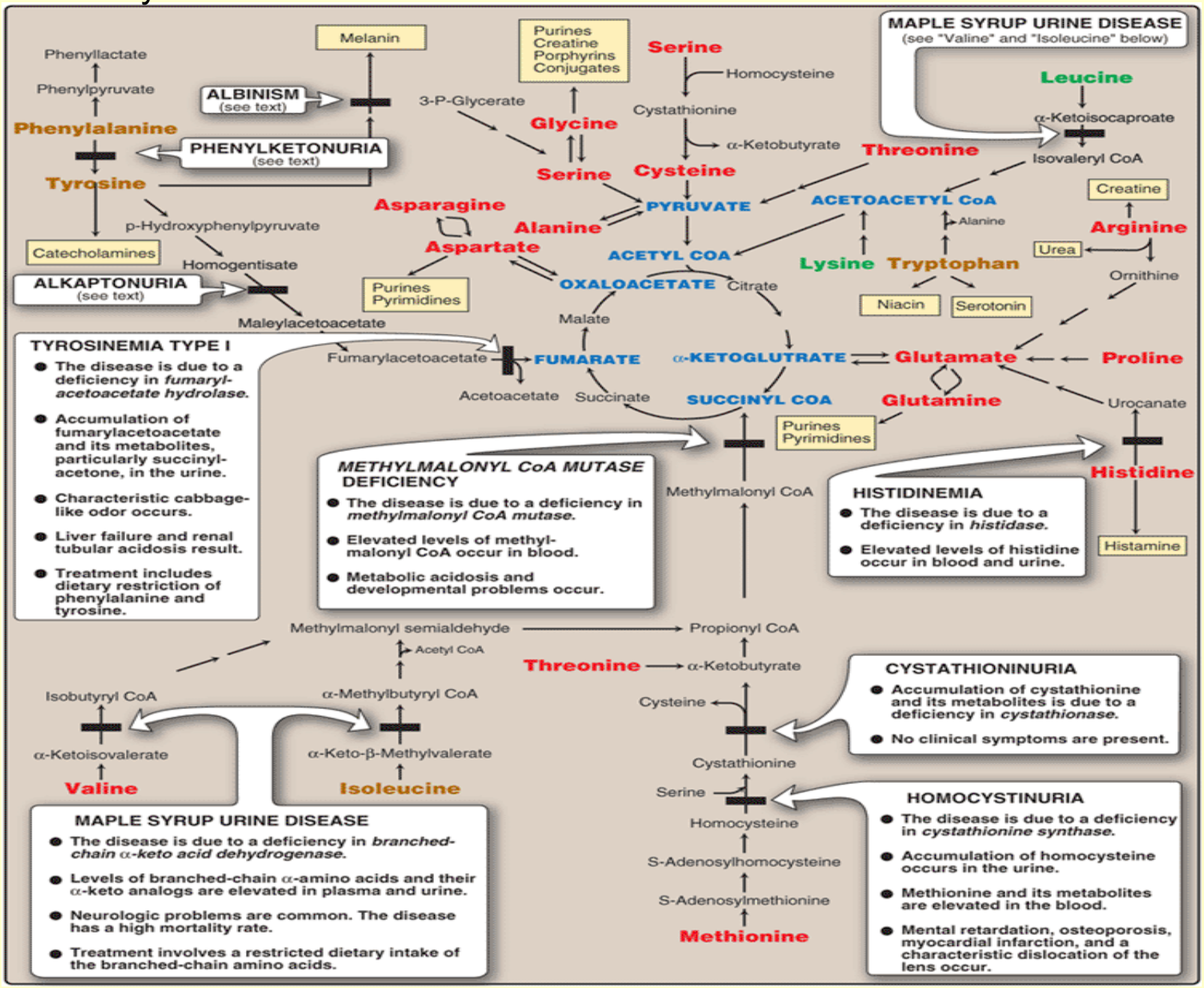
Characteristics:

1) Results in accumulation of homogentisic acidurea.
2) Large joint arthritis
3) Dense, black pigments deposited on the intravetebral disks of the vertebrae.

Treatment:

Low protein (low in phenylalanine and tyrosine) diet
Help reduce the levels of homogenistic acid.

Summary of the metabolism of amino acids



Metabolism of amino acids

Catabolism of amino acids

involves

- Removal of α-amino group
- Metabolism of carbon skeletons

converges to produce

Seven products

consisting of

ACETYL CoA	PYRUVATE
ACETOACETYL CoA	OXALOACETATE
	FUMARATE
	α-KETOGLUTARATE
	SUCCINYL CoA

cassified as	*classified as*
Ketogenic	Glucogenic
provide	*provide*
Lipids	Lipids
Energy	Energy
	Glucose

Synthesis of amino acids

involves

- Transamination of α-keto acids, for example, pyruvate → alanine
- Amidation, for example, asparate → asparagine
- Synthesis from other amino acids, for example, phenylalanine → tyrosine

Some clinically important amino acids

Methionine
- Source of methyl groups in metabolism
- Precursor of cysteine

Arginine
- Member of urea cycle
- Precursor of nitric oxide

Glutamine
- Storage and transport form of ammonia
- Precursor of purines and pyrimidines

Phenylalanine
- Precursor of tyrosine
- Elevated in phenylketonuria

Histidine
- Precursor of histamine
- Elevated in histidinemia

Tryptophan
- Precursor of serotonin

Alanine
- Transport form of ammonia from muscle

Metabolic defects in amino metabolism

characterized by

Family of defects in enzymes of amino acid metabolism — *can be* → Screened for in neonates

caused by

Point mutations, deletions, splicing errors — *usually* → Inheritance is recessive; heterozygotes usually do not show symptoms

which can lead to

Partially or completely inactive enzyme — *treated by* → Dietary restriction

which leads to

Accumulation of substrate and a deficiency in product of defective enzyme — *can result in* → Characteristic smell of the urine

which leads to

Disturbances in metabolism, particularly the CNS

which leads to

Seizures, mental retardation, other CNS effects

Amino acids: Disposal of Nitrogen 19

Concept connect