CC-06

UNIT-4

# BIOSYNTHESIS AND DEGRADATION OF AMINO ACIDS

LECTURE DELIVERED BY


**NIRAJ KUMAR**

*DEPARTMENT OF BIOCHEMISTRY*

PATNA UNIVERSITY

Many amino acids are synthesized by pathways that are present only in plants and microorganisms. Since mammals must obtain these amino acids in their diets, these substances are known as essential amino acids.

The other amino acids, which can be synthesized by mammals from common intermediates, are termed nonessential amino acid.

# Metabolism of the Common Intermediates

1. ***Oxidation:*** all amino acids can be oxidized in **TCA** cycle with **energy** production
2. ***Fatty acids synthesis:*** some amino acids provide **acetyl CoA** e.g. leucine and lysine (ketogenic amino acids).
3. ***Gluconeogenesis:*** ketoacids derived from amino acids are used for synthesis of **glucose** (is important in starvation).

| ***Glucogenic*** | ***Ketogenic*** | ***Glucogenic & Ketogenic*** |
|---|---|---|
| Ala, Ser, Gly, Cys, Arg, His, Pro, Glu, Gln, Val, Met, Asp, Asn. | Leu , Lys | Phe, Tyr, Trp, Ile, Thr |

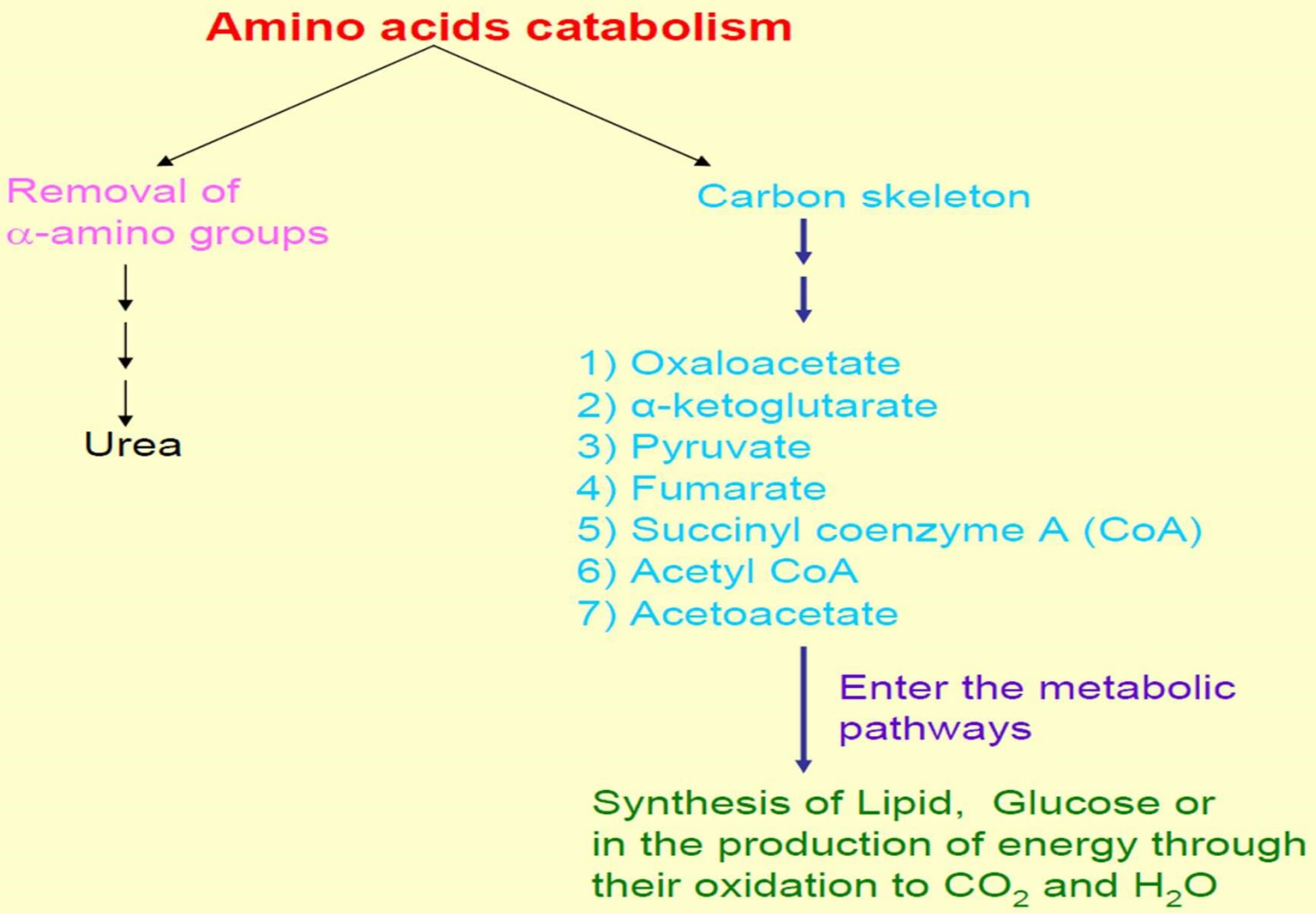
# Essential *versus* Nonessential Amino Acids

**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 | |

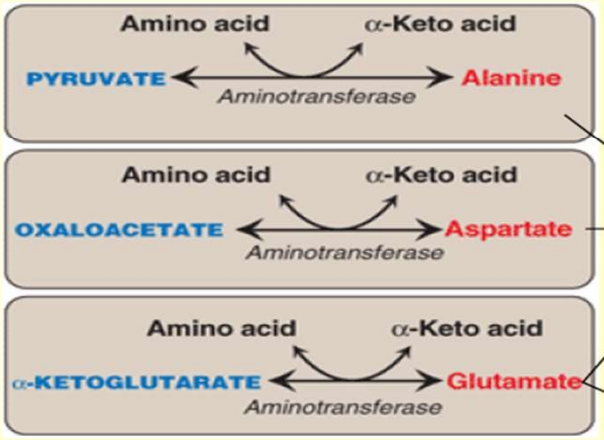
[a] Arginine is synthesized by mammalian tissues, but the rate is not sufficient to meet the need during growth.
[b] Methionine is required in large amounts to produce cysteine if the latter is not supplied adequately by the diet.
[c] Phenylalanine is needed in larger amounts to form tyrosine if the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


Amino acids catabolism
Removal of
α-amino groups
Urea
Carbon skeleton
1) Oxaloacetate
2) α-ketoglutarate
3) Pyruvate
4) Fumarate
5) Succinyl coenzyme A (CoA)
6) Acetyl CoA
7) Acetoacetate
Enter the metabolic pathways
Synthesis of Lipid, Glucose or
in the production of energy through
their oxidation to $CO_2$ and $H_2O$

# 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



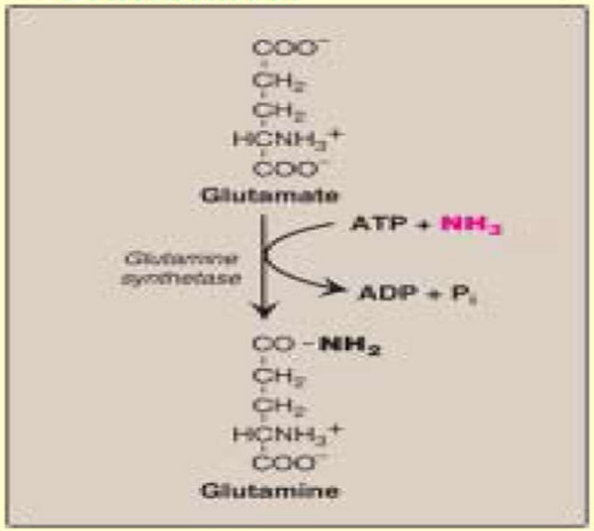

Ala, Asp and Glu are synthesized by transfer of an amino group to the α-keto acids pyruvate, oxaloacetate, and a-ketoglutarate respectively.

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

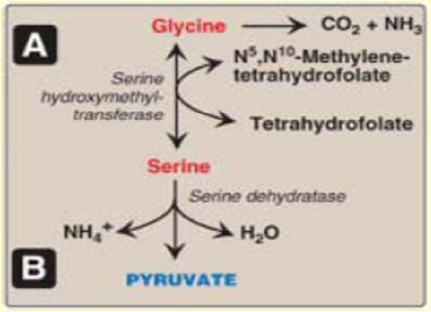
## Proline:

Glutamate is converted to proline by cyclization and reduction reactions.

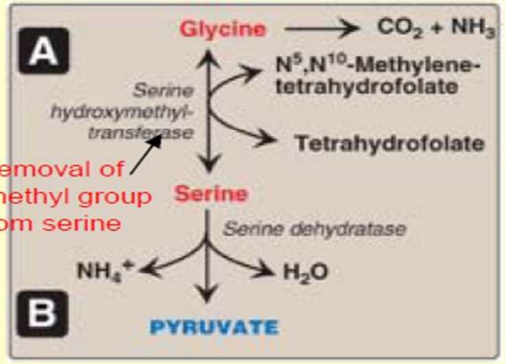
## Serine:

Synthesized from glycolysis intermediate 3-phosphogylcerate.

Or




## Glycine:




## Cysteine:

Is synthesized by two consecutive reactions

1) Homocysteine + serine ⟶ Cystathionine

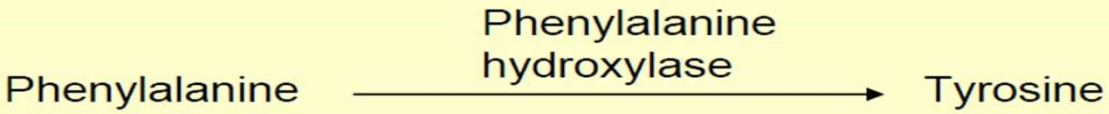
2) | hydrolysis

↓

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.**

# 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

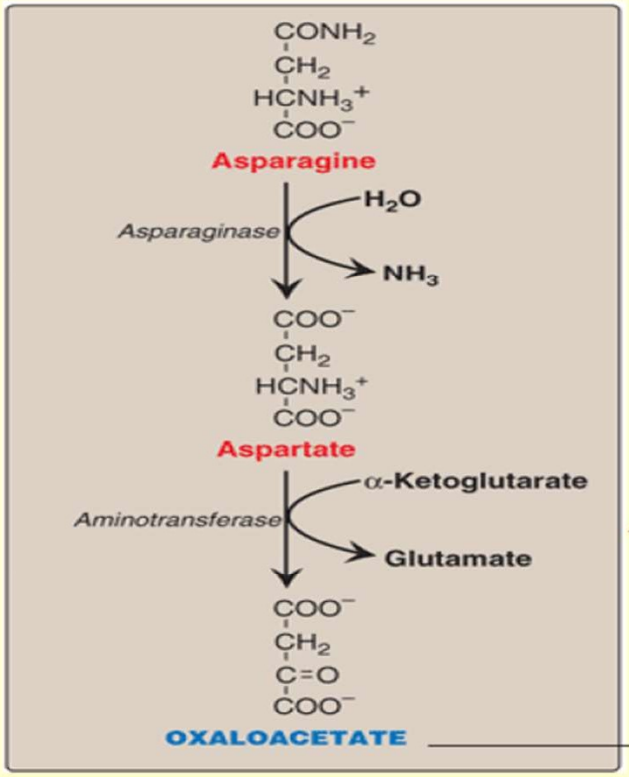
Amino acids whose catabolism yields pyruvate or one of the intermediates of the citric acid cycle are termed glucogenic or glycogenic

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**

# 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

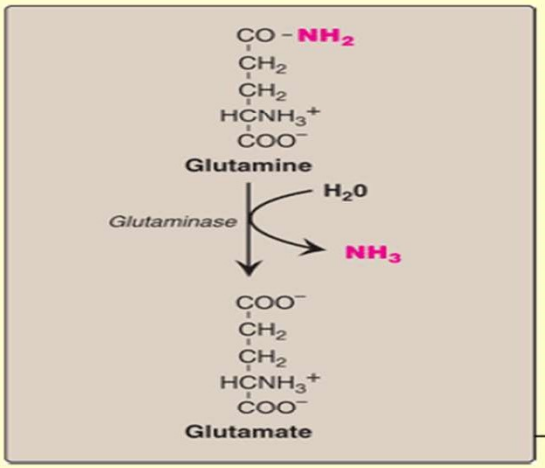
condenses with acetyl CoA to form citrate in the first reaction of the Krebs cycle. → **Glucogenic**

# Amino acids that form α-ketoglutarate

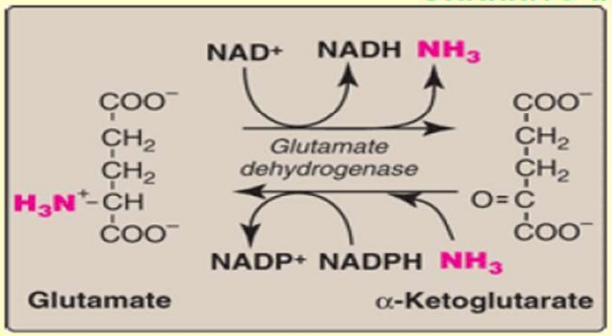
Glucogenic

## (Glutamine, Proline, Arginine, Histidine)

### 1) Glutamine:




Oxidative deamination




oxidative deamination by glutamine dehydrogenase → α-ketoglutarate

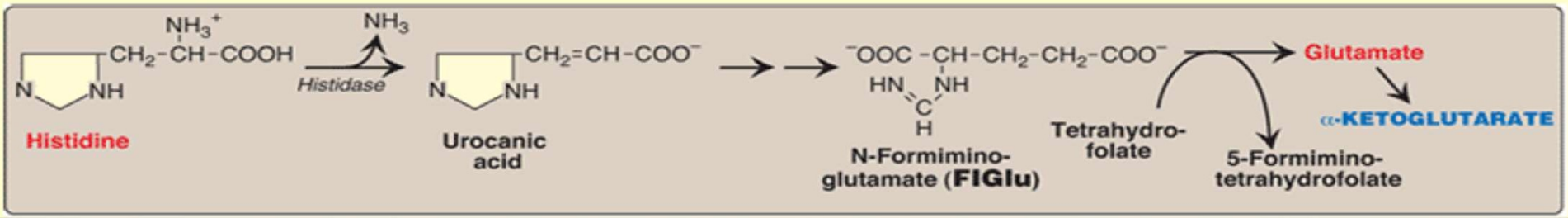
### 2) Proline:

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**

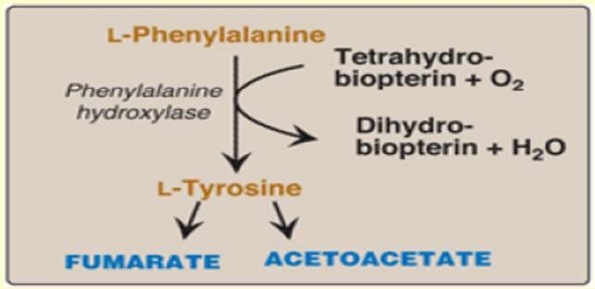
### 4) Histidine:

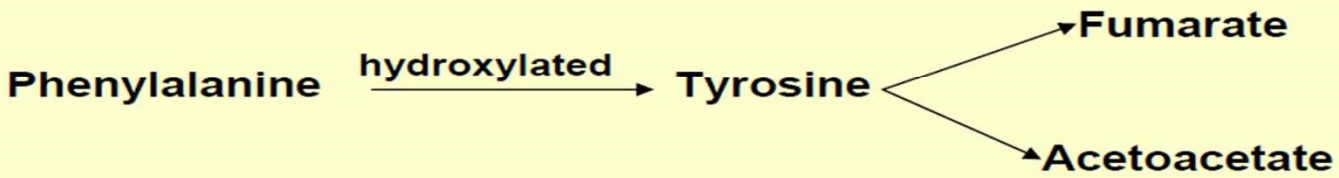


## Amino Acids that enter metabolism as fumarate

### Phenylalanine and Tyrosine

1) Phenylalanine and 2) Tyrosine



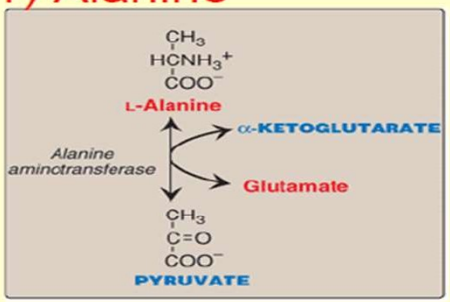

**Hence these two aa are both glucogenic and ketogenic**

## Amino acids that enter metabolism as pyruvate

Glucogenic

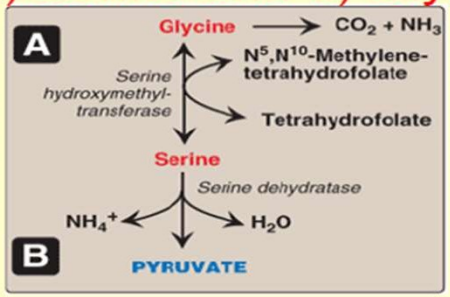
Alanine, Serine, Glycine, Cystine Threonine

### 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

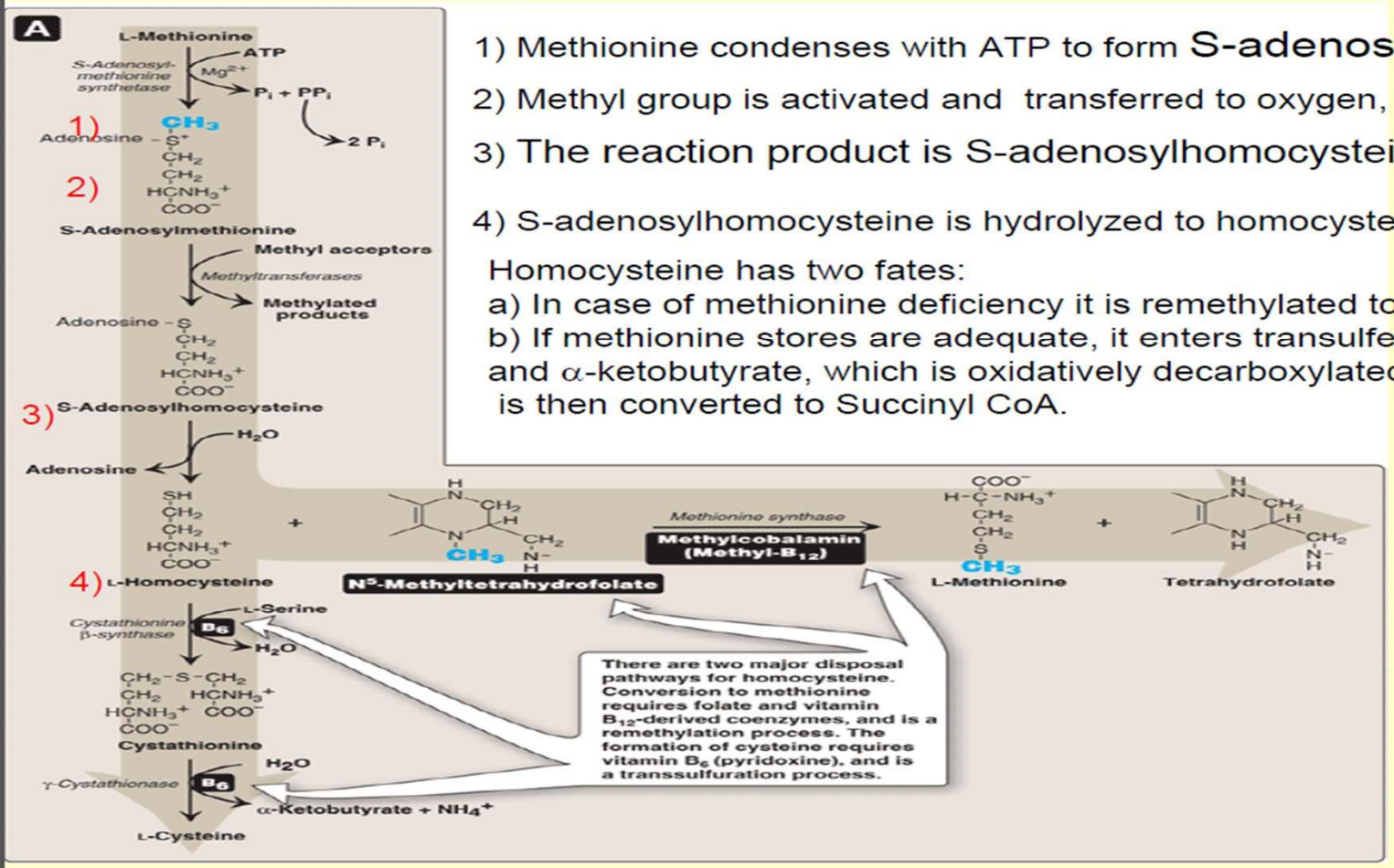
Threonine → pyruvate

Threonine → α-ketobutyrate → Succinyl CoA

# Amino acids that enter metabolism as 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

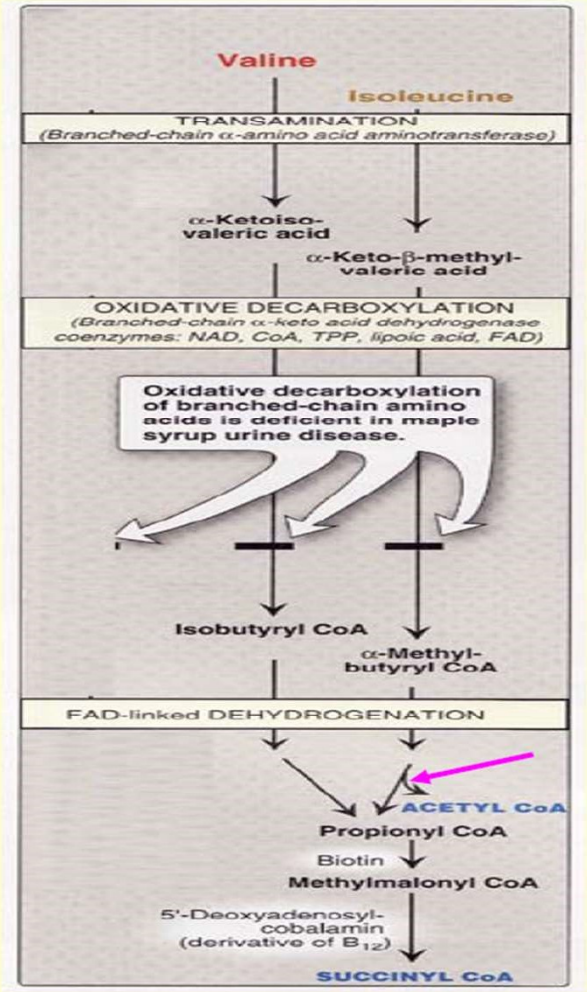
4) S-adenosylhomocysteine is hydrolyzed to homocysteine.

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 $\alpha$-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

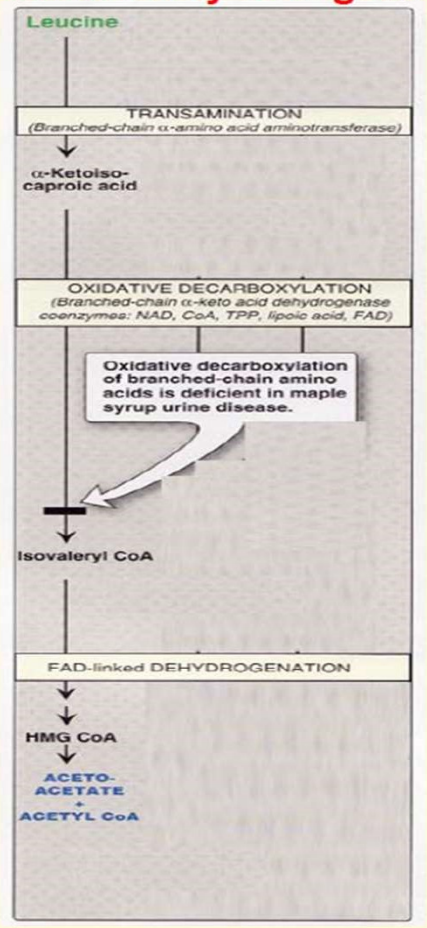
↓

Succinyl CoA → TCA cycle

# Amino acids that form acetyl CoA or acetoacetyl CoA

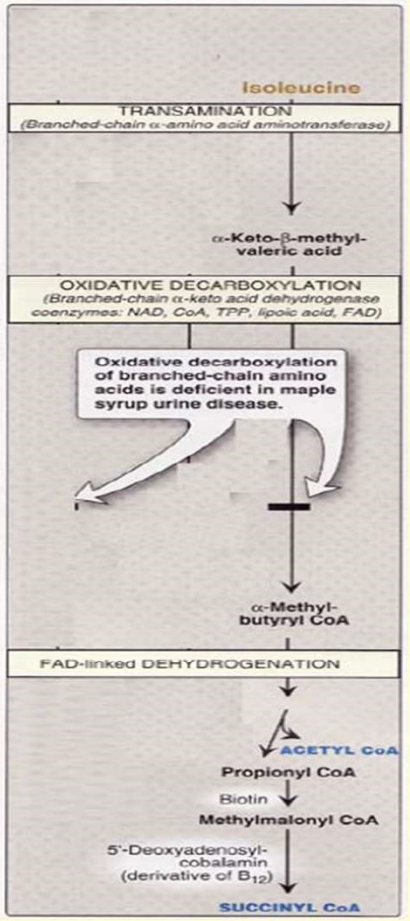
## 1) Leucine

**Exclusively Ketogenic**




## 2) Isoleucine

**Ketogenic and glucogenic**




## 3) Lysine

**Exclusively Ketogenic**

↓

Acetyl CoA

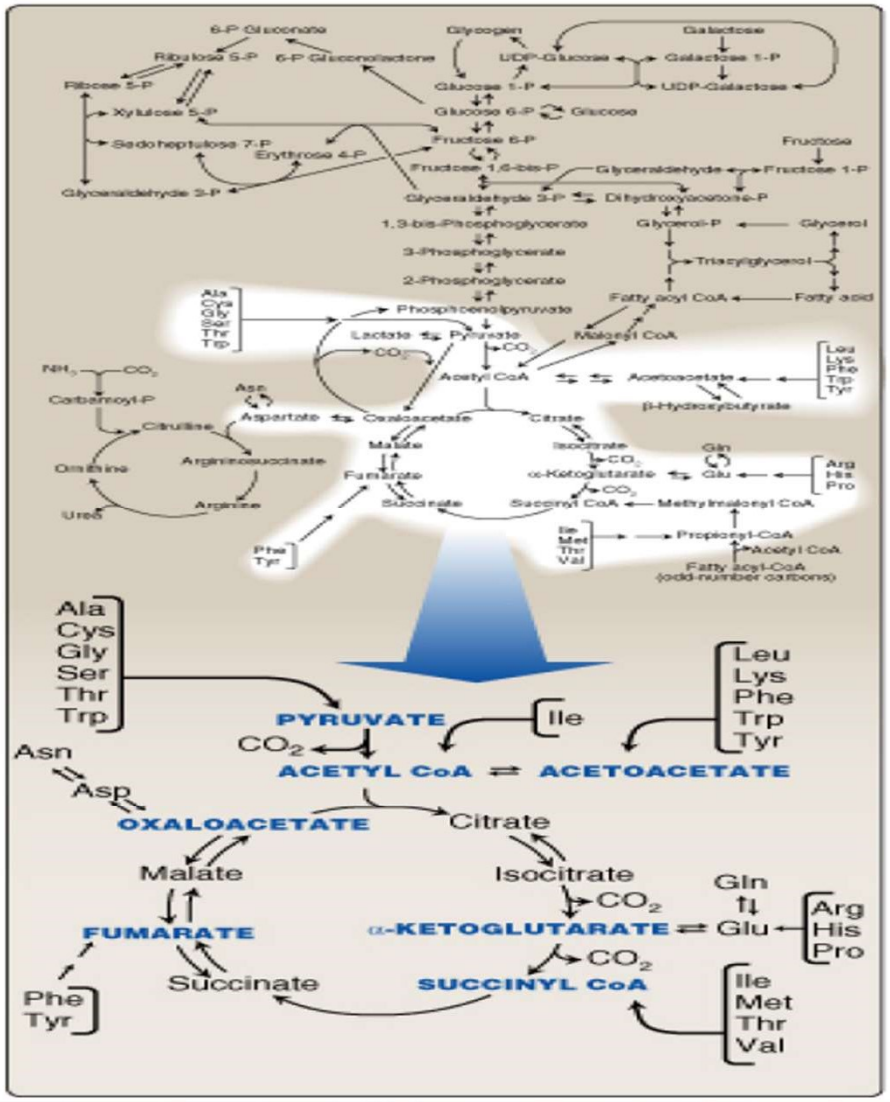
## 4) Tryptophan

**Glucogenic and ketogenic**

Since its metabolism yields both alanine and Acetoacetyl CoA

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

# Overview of Amino Acid Catabolism




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

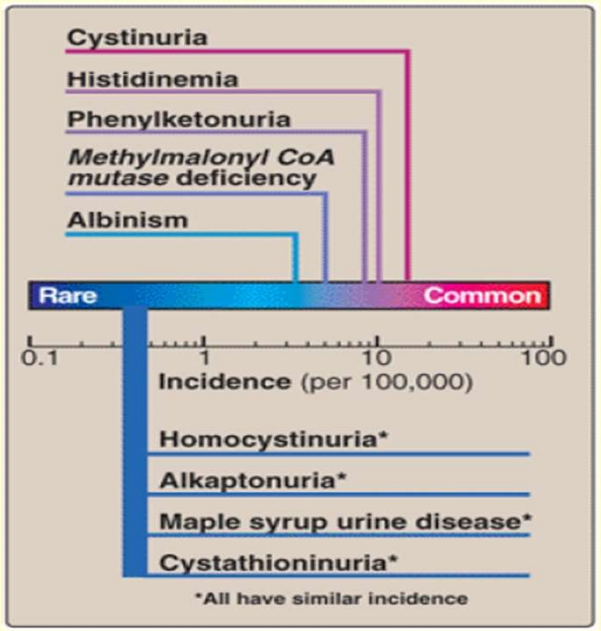
Enter as acetoacetate intermediates

Enter as both TCA cycle and acetyl derived intermediates

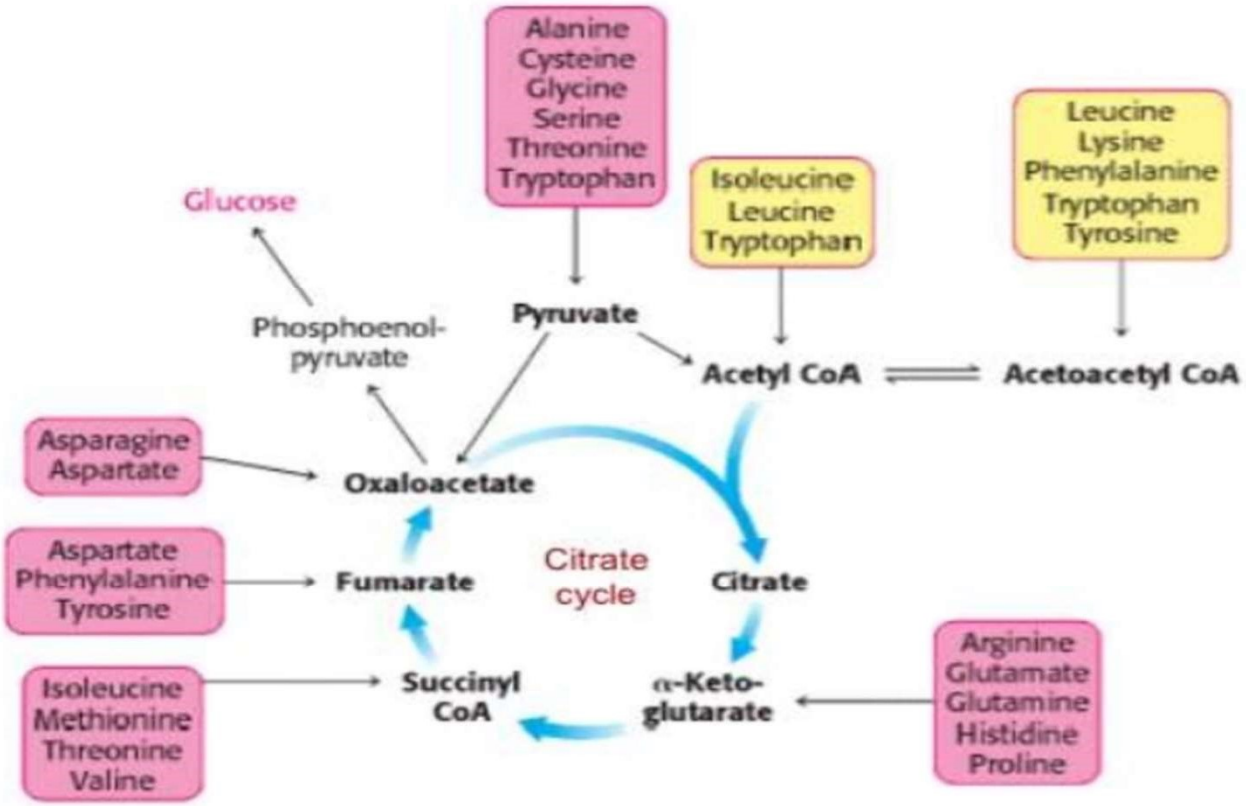
Enter as TCA cycle intermediates

Seven central products of amino acid metabolism

# Metabolic defects in Amino acid metabolism

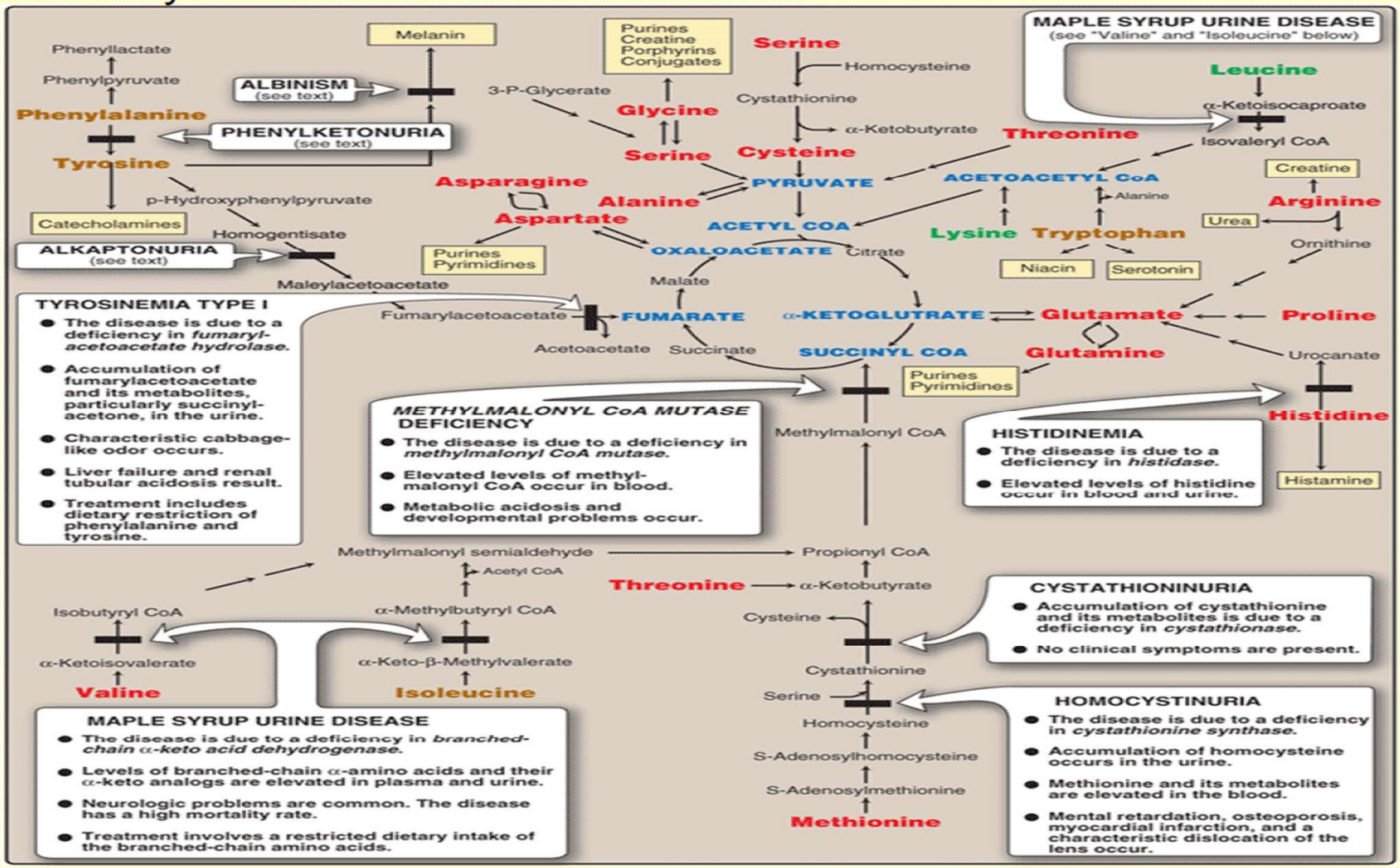


# The common metabolic intermediates that arised from the degradations of amino acids are: acetyl CoA, pyruvate, one of the krebs cycle intermediates (α-ketoglutarate, succinyl CoA, fumarate& oxaloacetate)




**Fates of the Carbon Skeletons of Amino Acids.** Glucogenic amino acids are shaded red, and ketogenic

# 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 |

| *classified 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*

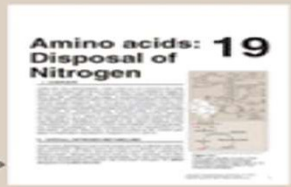
Accumulation of substrate and a deficiency in product of defective enzyme — *can result in* → Characteristic smell of the urine

*which leads to*

Disturbances in metabolism, particularly the CNS

*which leads to*

Seizures, mental retardation, other CNS effects

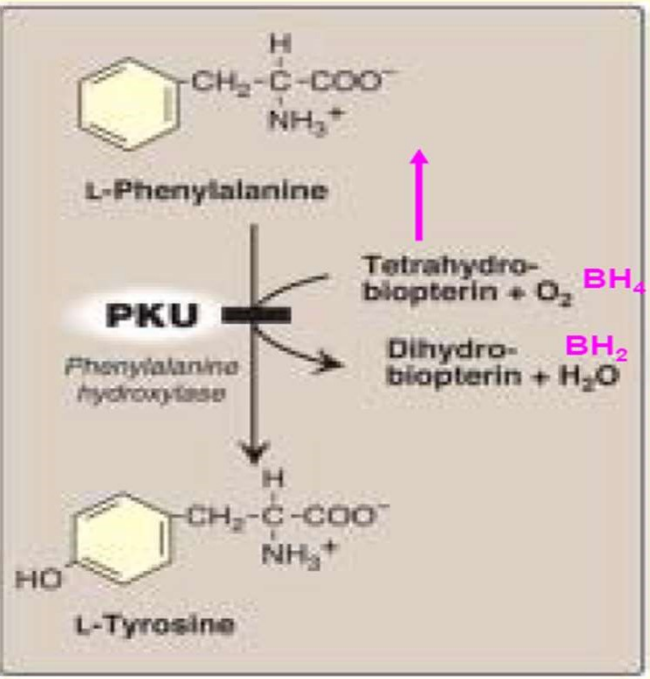



Concept connect

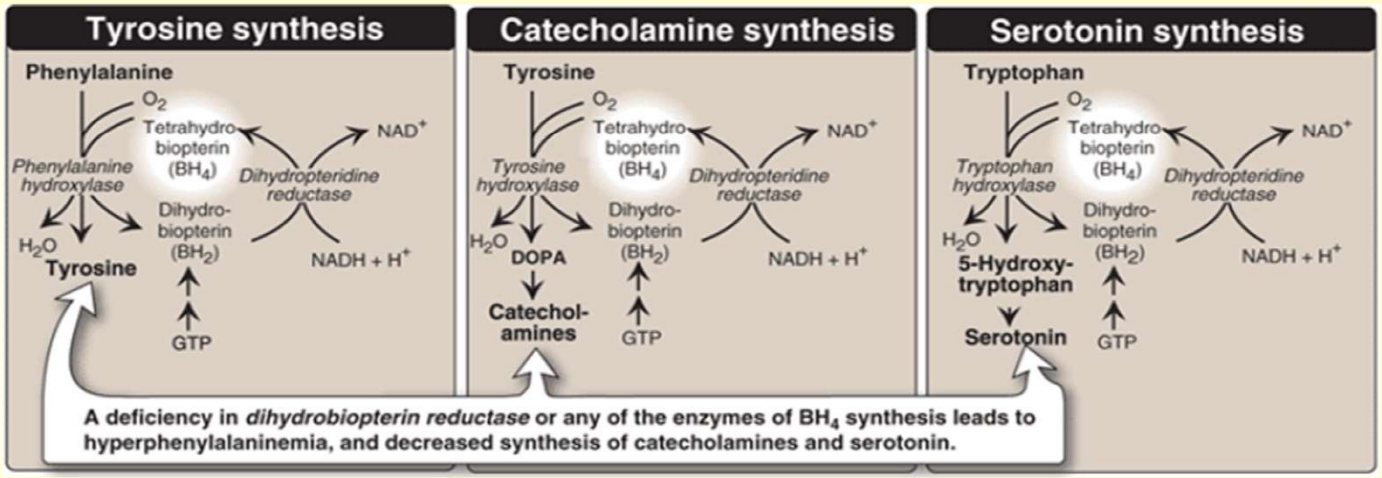
## Phenylketonurea (Prevalence of 1:15,000)

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.



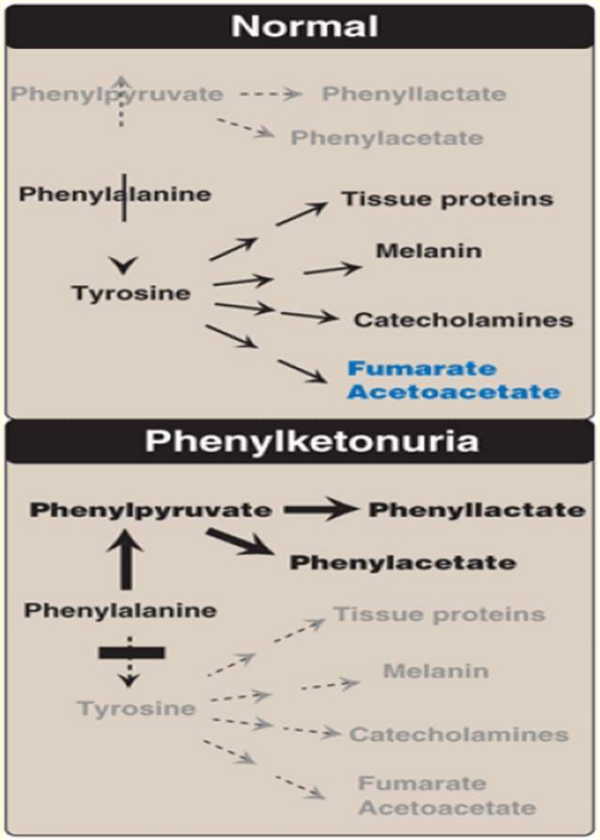

Deficiency of enzymes required for the synthesis of BH4 and dihydropterine (BH2) Reductase which regenerates BH4 from BH2 also leads to hyperphenylalaninemia.




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.



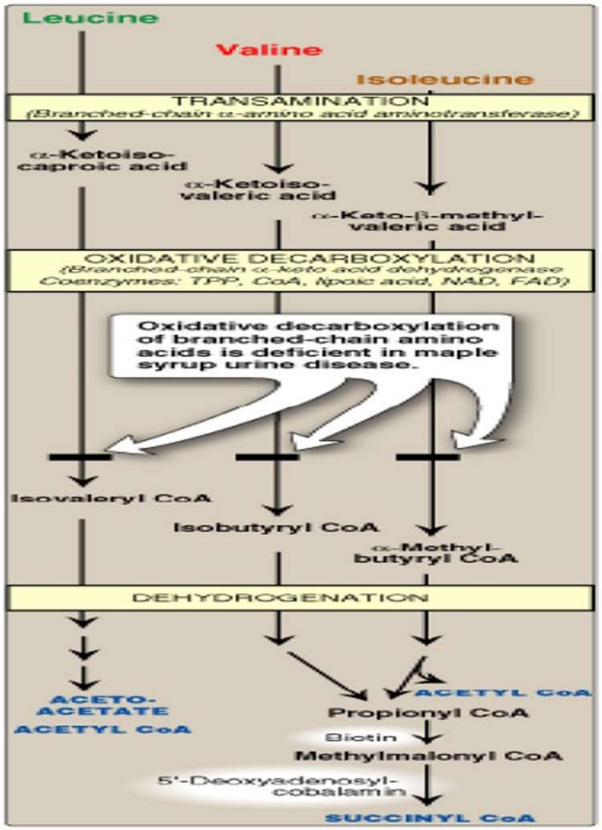

## Characteristics of classic PKU:

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.

# THANK YOU