Fate of Amino Acid carbon Skeleton
Catabolism of 3C, 4C, 5C

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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

Body proteins

α-amino groups

Other nitrogen containing compounds

NH4+

Disposal of Nitrogen

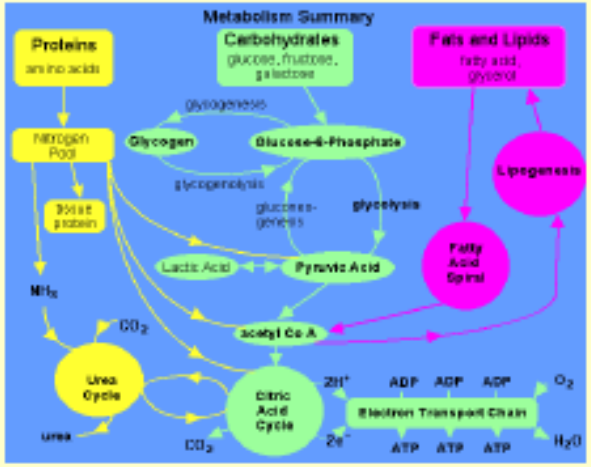
Urea

excreted

Carbon skeletons

Amino acids synthesis & degradation

Enters various metabolic pathways



Amino acids catabolism

Removal of α-amino groups

Urea

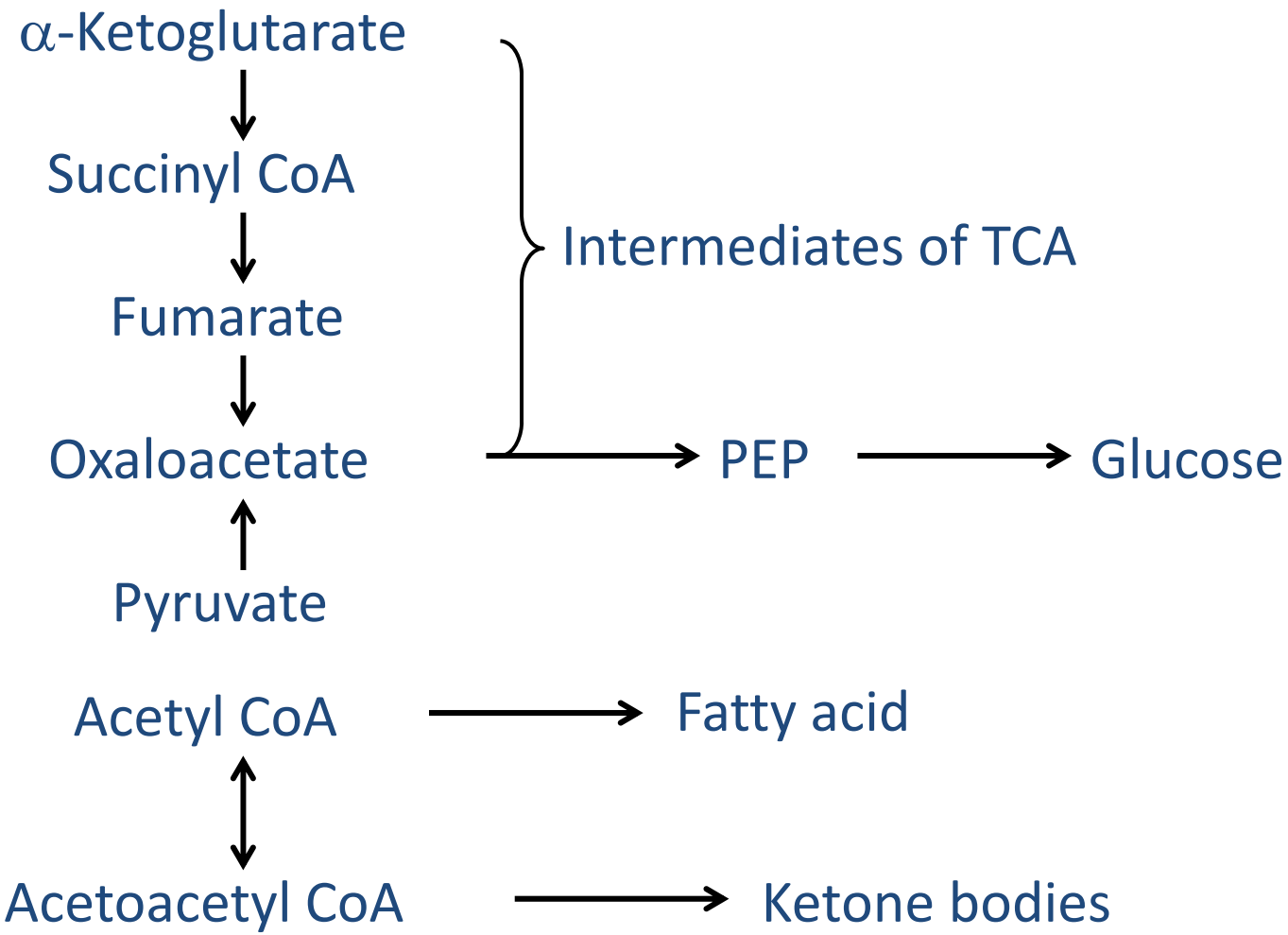
Carbon skeleton

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

catabolites of amino acid



Amino Acid Carbon Skeletons

Amino acids, when deaminated, yield **α-keto acids** that, directly or via additional reactions, feed into major metabolic pathways (e.g., Krebs Cycle).

Amino acids are grouped into 2 classes, based on whether or not their carbon skeletons can be converted to glucose:

- **glucogenic**
- **ketogenic**.

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

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

Carbon skeletons of **glucogenic** amino acids are degraded to:

- **pyruvate**, or
- a **4-C or 5-C intermediate of Krebs Cycle**. These are precursors for gluconeogenesis.

Glucogenic amino acids are the major carbon source for **gluconeogenesis** when glucose levels are low.

They can also be catabolized for **energy**, or converted to glycogen or fatty acids for energy **storage**.

Ketogenic

Amino acids that can be converted into ketone bodies through ketogenesis

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

Carbon skeletons of **ketogenic** amino acids are degraded to:

- **acetyl-CoA**, or
- **acetoacetate**.

Acetyl CoA, & its precursor acetoacetate, cannot yield net production of oxaloacetate, the gluconeogenesis precursor.

For every 2-C acetyl residue entering Krebs Cycle, 2 C leave as CO_2.

Carbon skeletons of ketogenic amino acids can be catabolized for **energy** in Krebs Cycle, or converted to **ketone bodies** or **fatty acids**.

They **cannot be converted to glucose**.

Ketone bodies

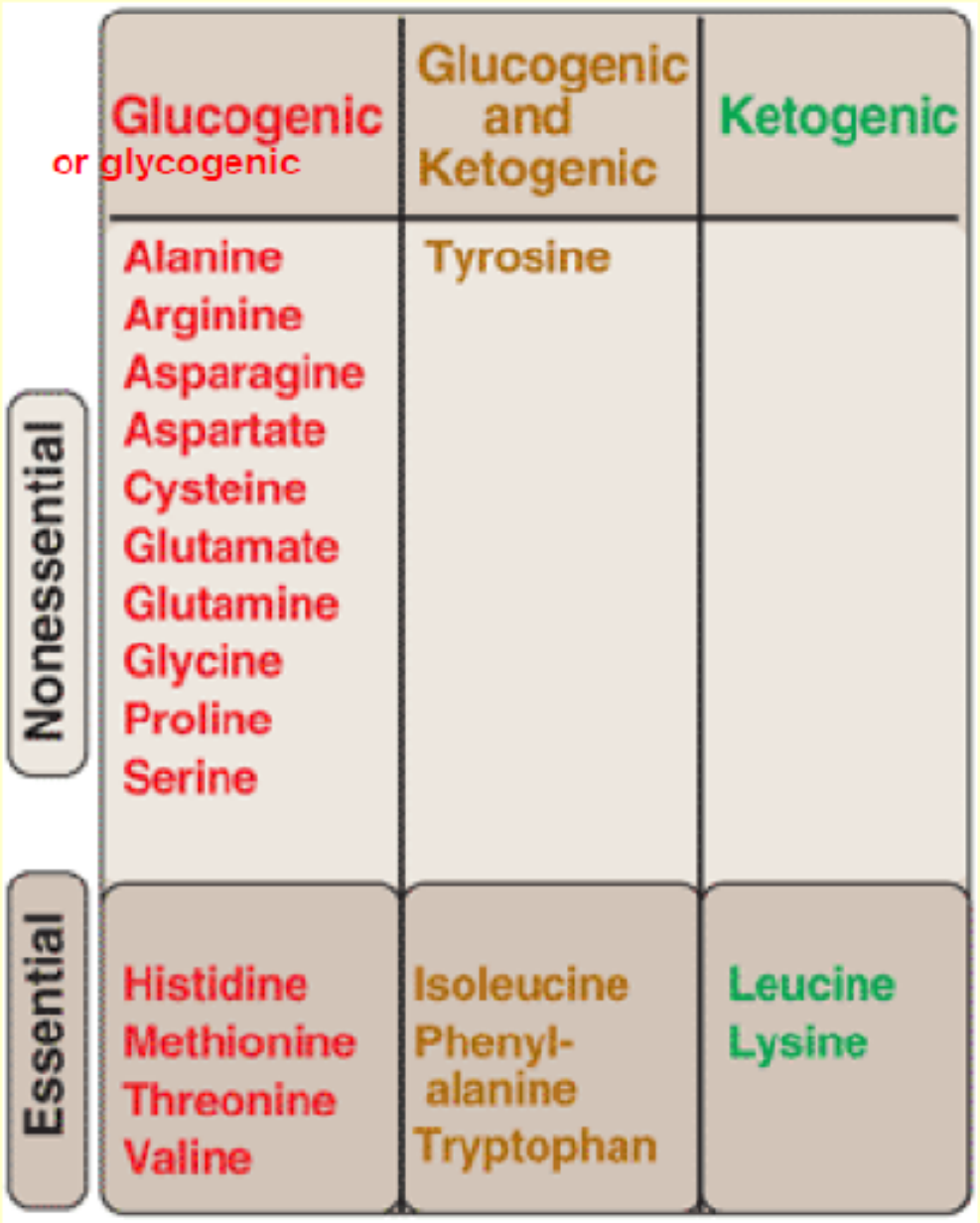
Ketone bodies are three water-soluble compounds that are produced as by-products when fatty acids are broken down for energy in the liver and kidney.

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.

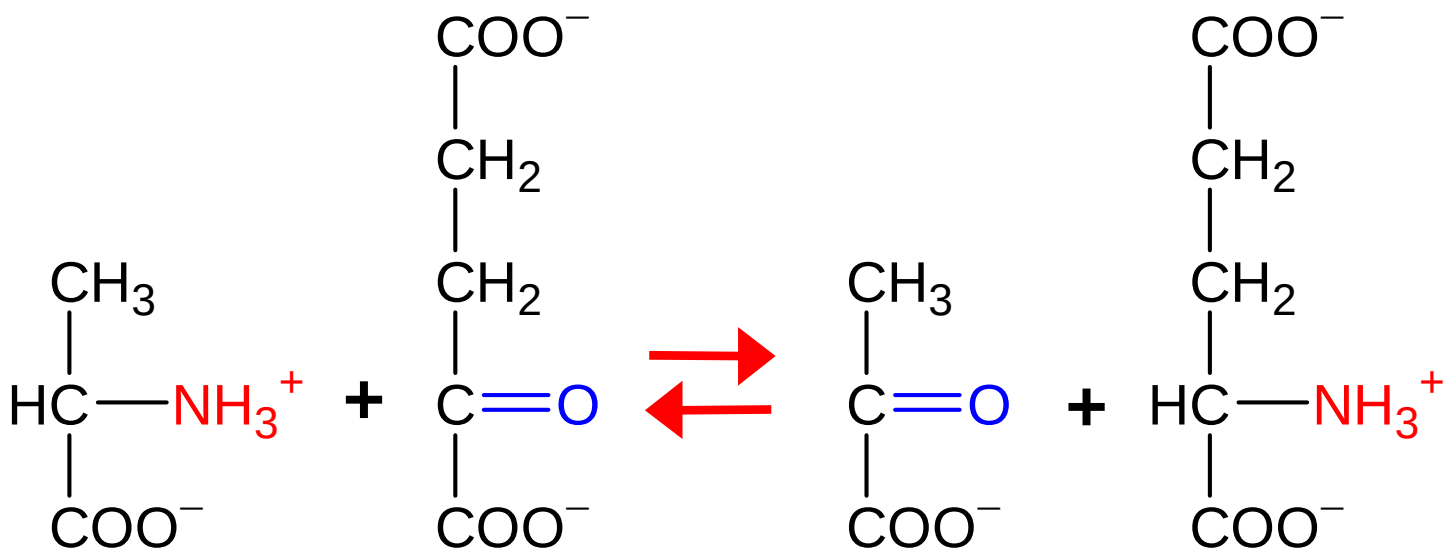
Excess ketone bodies accumulate, this abnormal (but not necessarily harmful) state is called Ketosis

Glucogenic and Ketogenic Amino acids



The **3-C** α-keto acid **pyruvate** is produced from **alanine, serine, glycine, cysteine & threonine**.

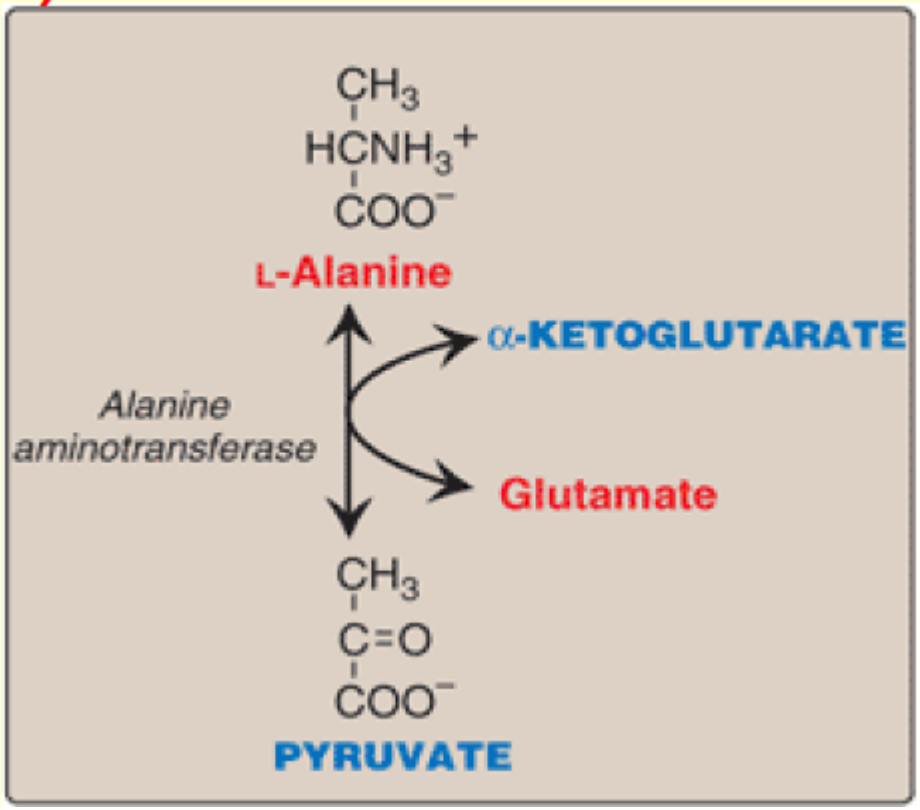
Alanine deamination via Transaminase directly yields pyruvate.



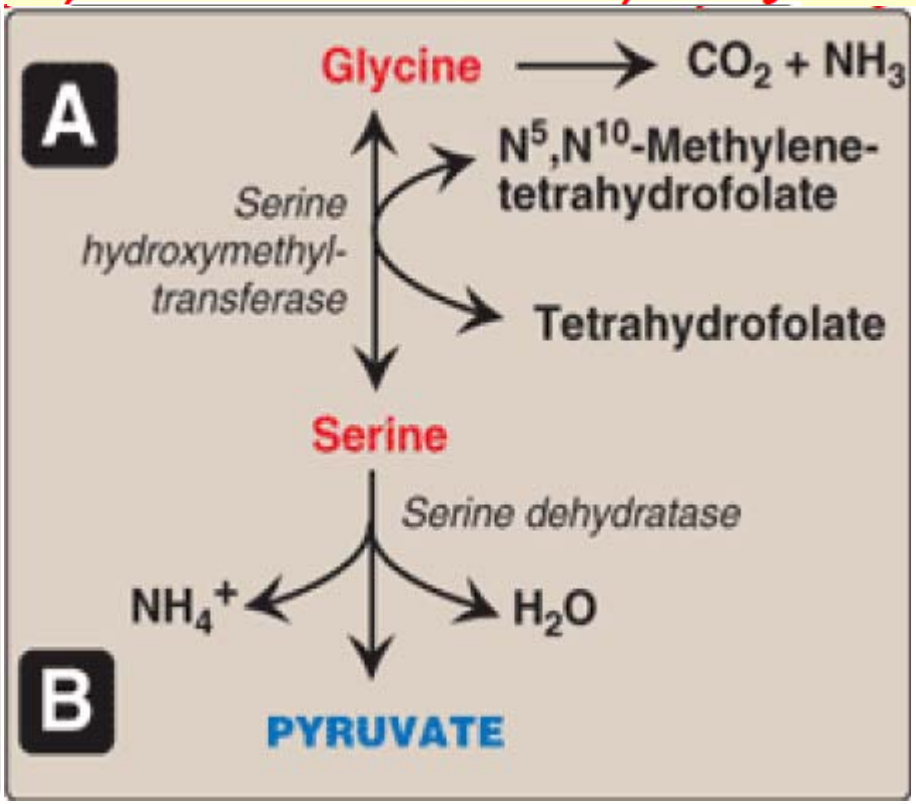
Amino acids that enter metabolism as pyruvate

Alanine, Serine, Glycine, Cystine Threonine

1) Alanine



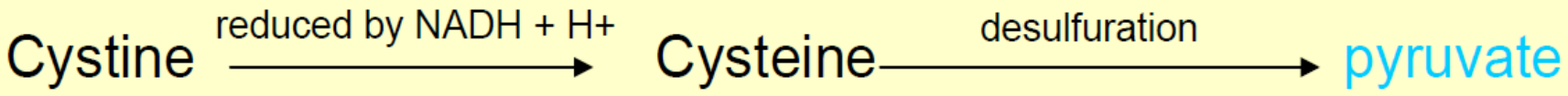
2) Serine and 3) Glycine



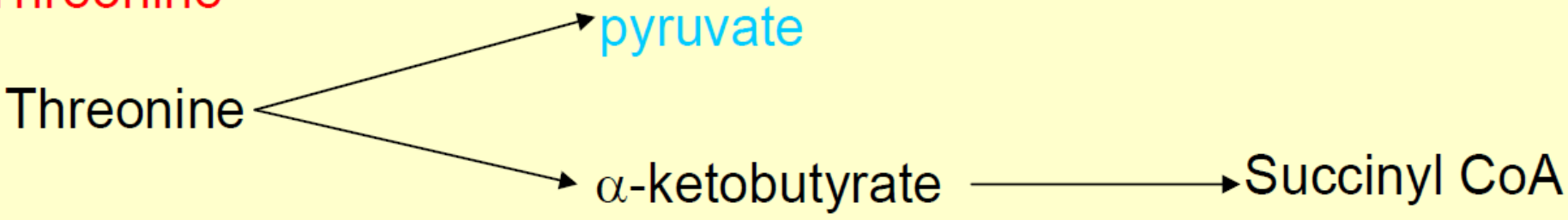
Amino acids that enter metabolism as pyruvate

Alanine, Serine, Glycine, Cystine Threonine

4) Cystine



5) Threonine



The **4-C** Krebs Cycle intermediate **oxaloacetate** is produced from **aspartate & asparagine**.

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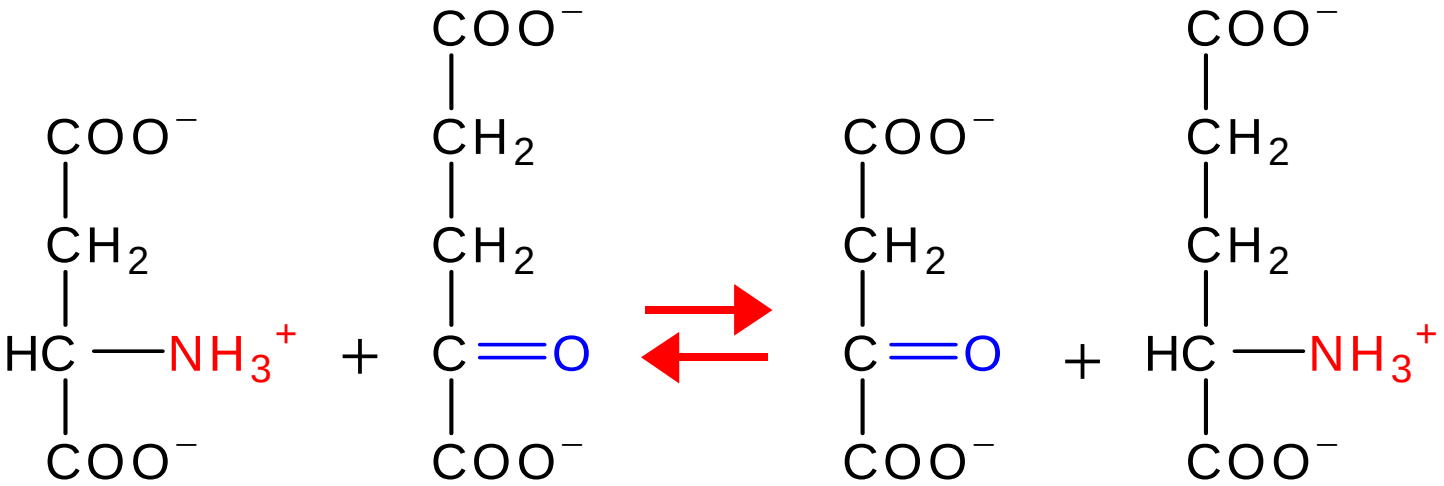
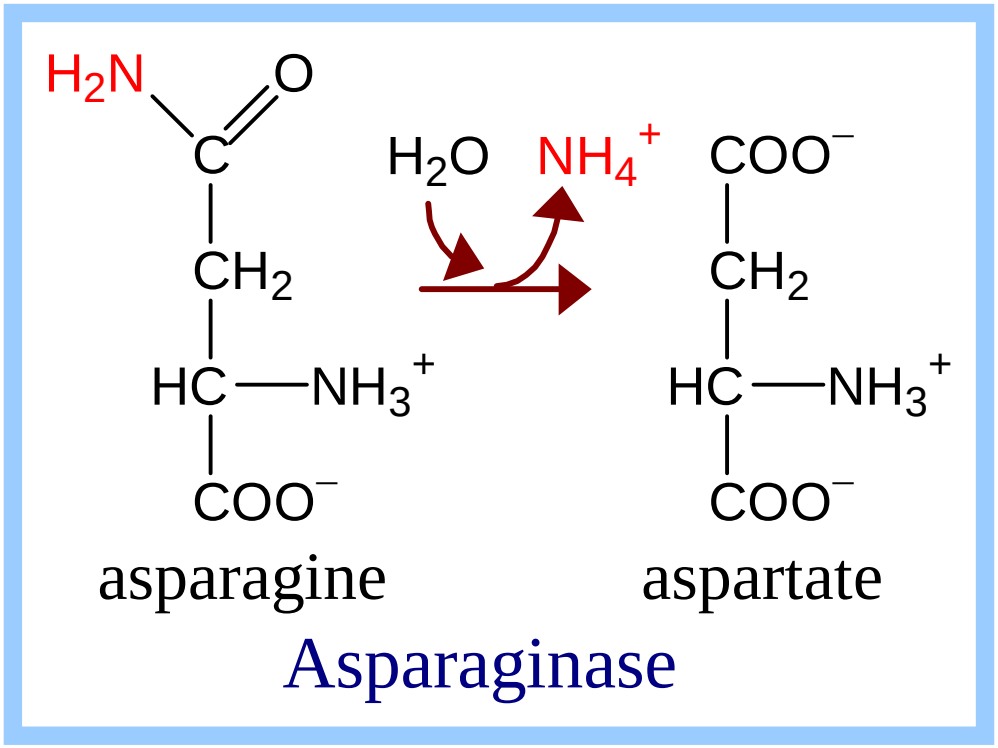
Aspartate transamination yields **oxaloacetate**.

Aspartate is also converted to **fumarate** in Urea Cycle.
Fumarate is converted to oxaloacetate in Krebs cycle.



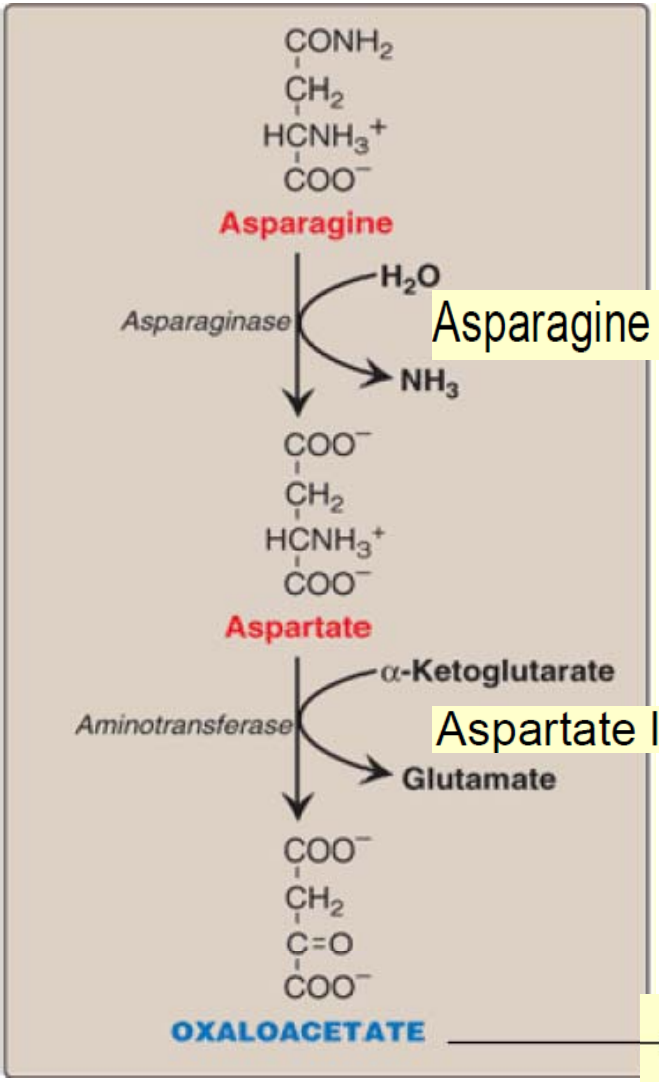


Asparagine loses the amino group from its R-group by hydrolysis catalyzed by **Asparaginase**.

This yields aspartate, which can be converted to oxaloacetate, e.g., by transamination.

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

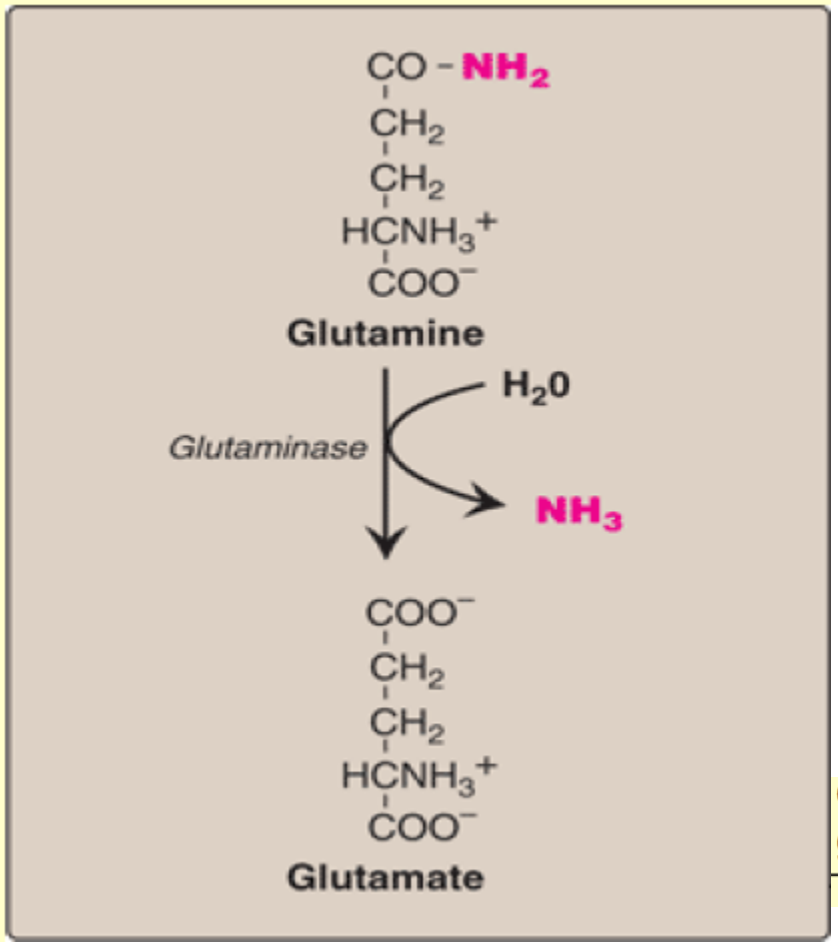
Aspartate loses its amino group by transamination to form oxaloacetate

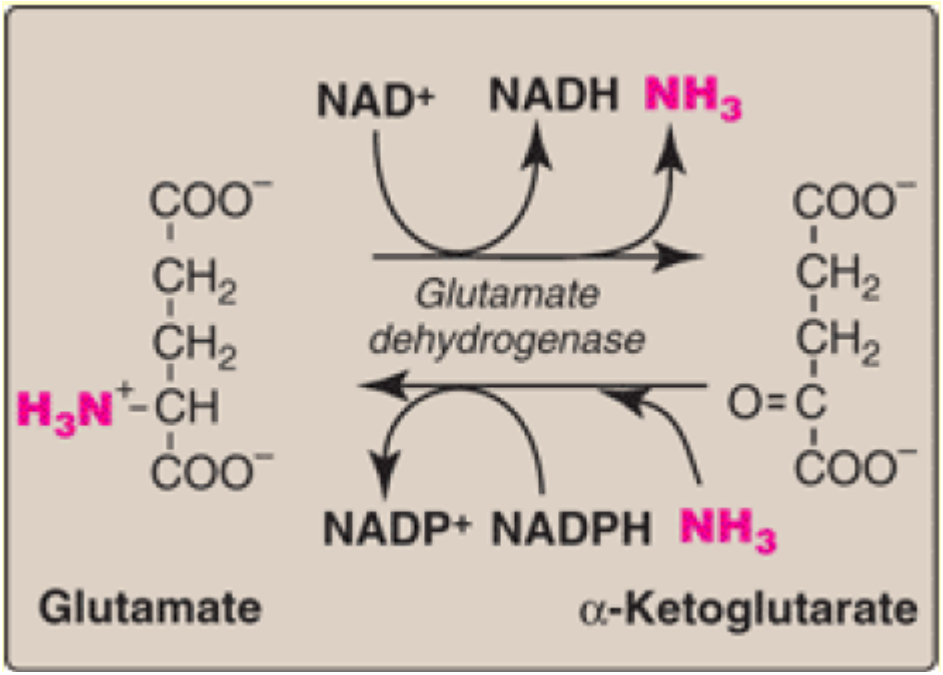
OXALOACETATE → condenses with acetyl CoA to form citrate in the first reaction of the Krebs cycle. → **Glucogenic**

The **5-C** Krebs Cycle intermediate **α-ketoglutarate** is produced from **glutamine, glutamate, arginine, histidine, & proline**.

Amino acids that form α-ketoglutarate

1. Glutamine and Glutamate catabolism

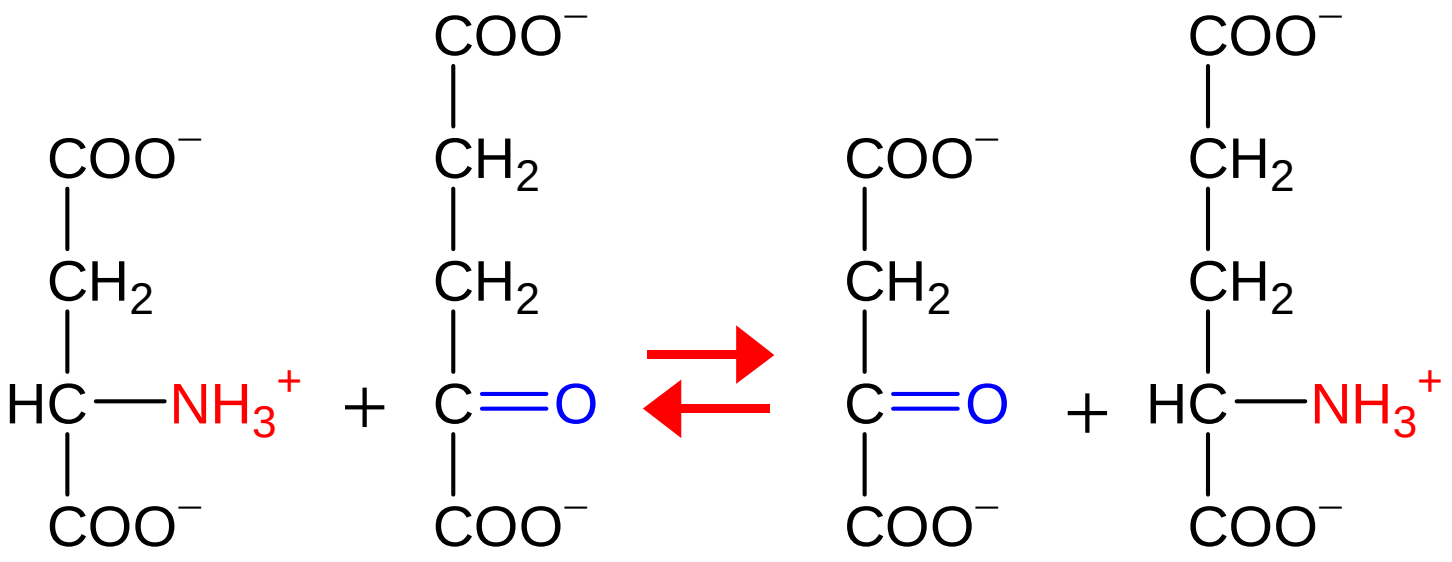




oxidative deamination by glutamine dehydrogenase → α-ketoglutarate

Glutamate deamination through two ways:

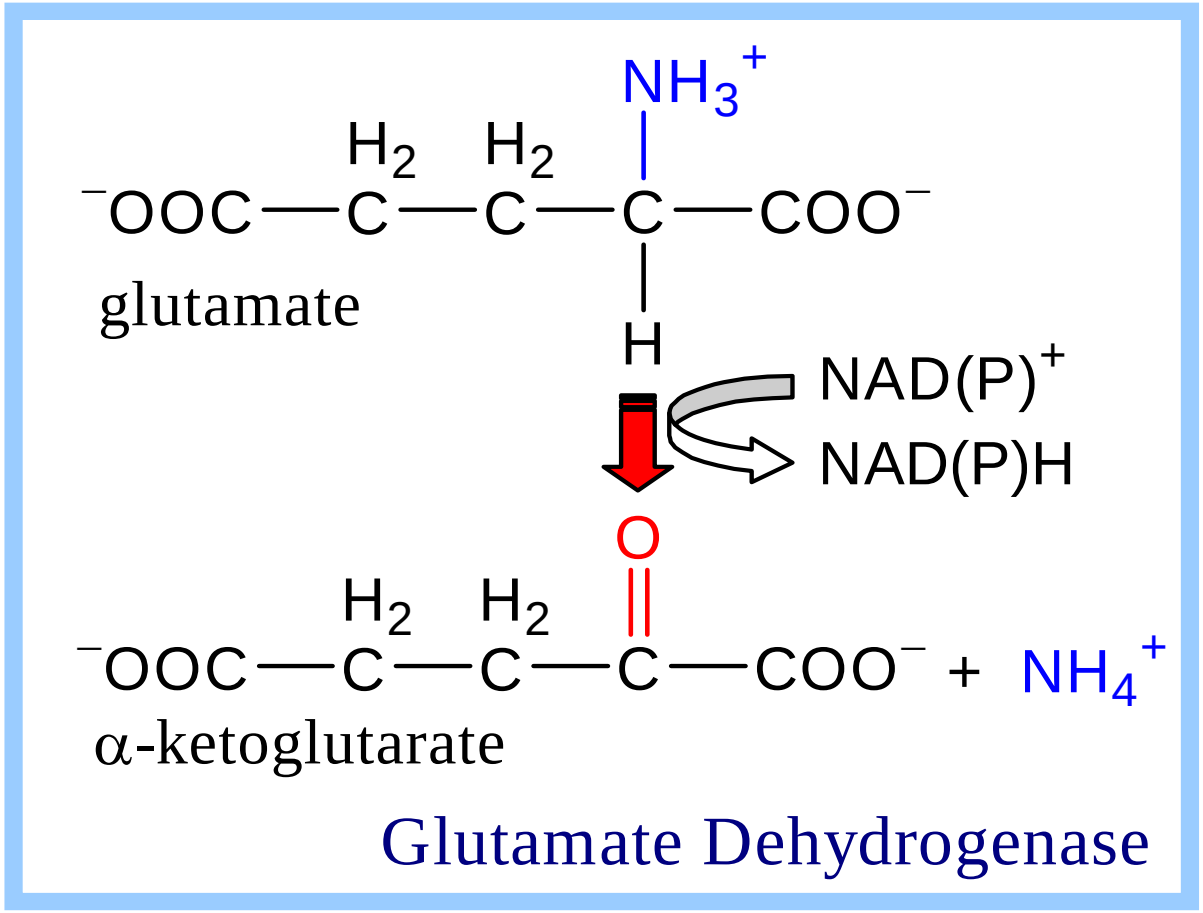
i) via Transaminase directly yields α-ketoglutarate.



Aminotransferase (Transaminase)

Glutamate deamination:

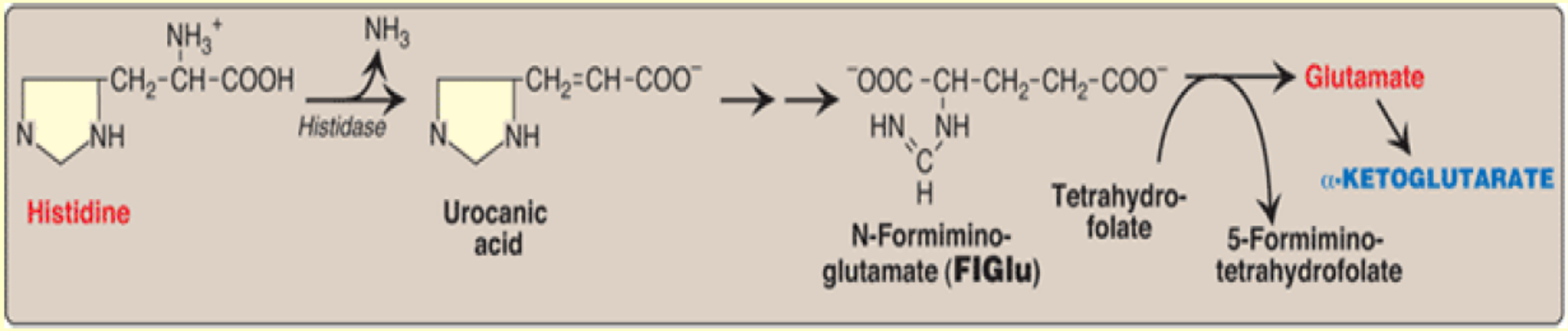
ii) by Glutamate Dehydrogenase also directly yields **α-ketoglutarate**.



2) Proline: It is oxidized to glutamate. Glutamate is then oxidatively deaminated to form α-ketoglutarate

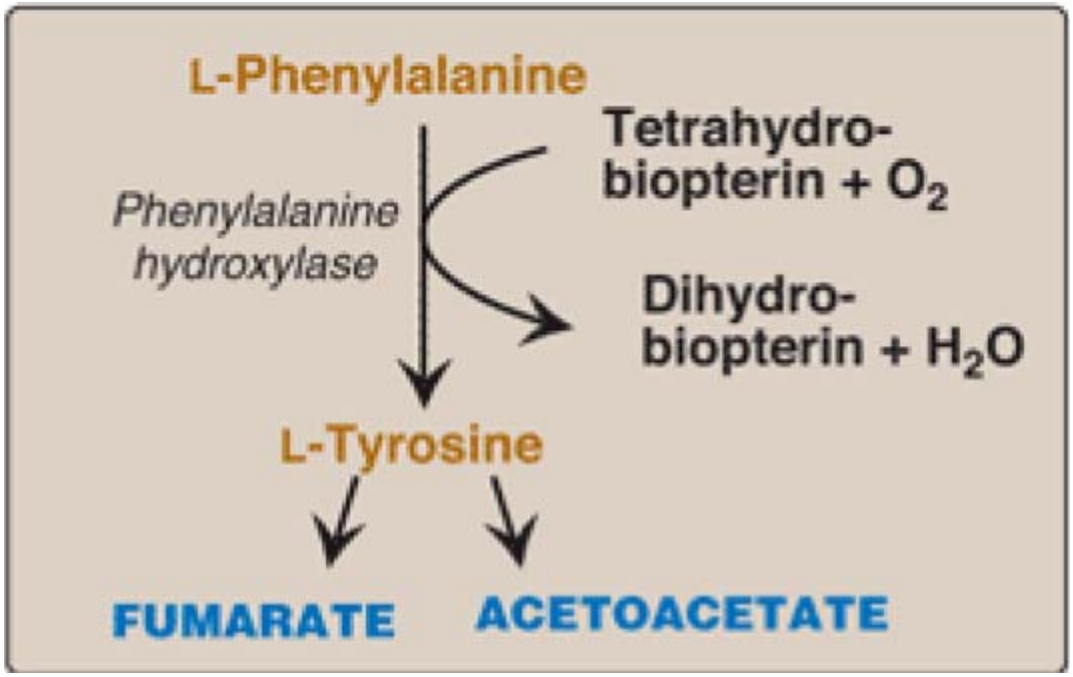
3) Arginine: This aa is cleaved by arginase to produce ornithine. Ornithine is subsequently converted to α-ketoglutarate

4) Histidine:



Amino Acids that enter metabolism as fumarate

Phenylalanine and Tyrosine



Phenylalanine —hydroxylated→ Tyrosine → Fumarate
Tyrosine → 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.

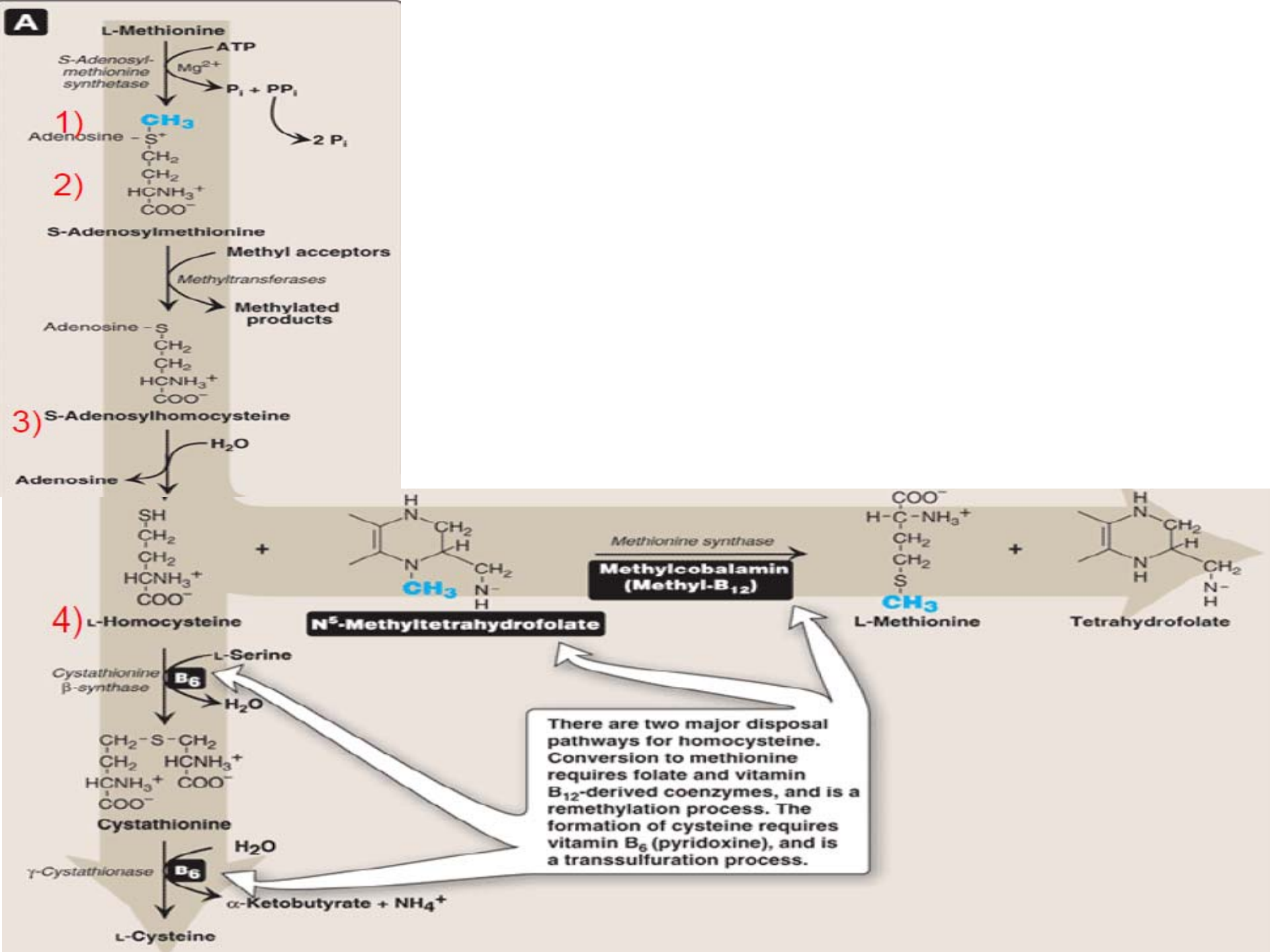
3) The reaction product is S-adenosylhomocysteine

4) S-adenosylhomocysteine is hydrolyzed to homocysteine.

Homocysteine has two fates:

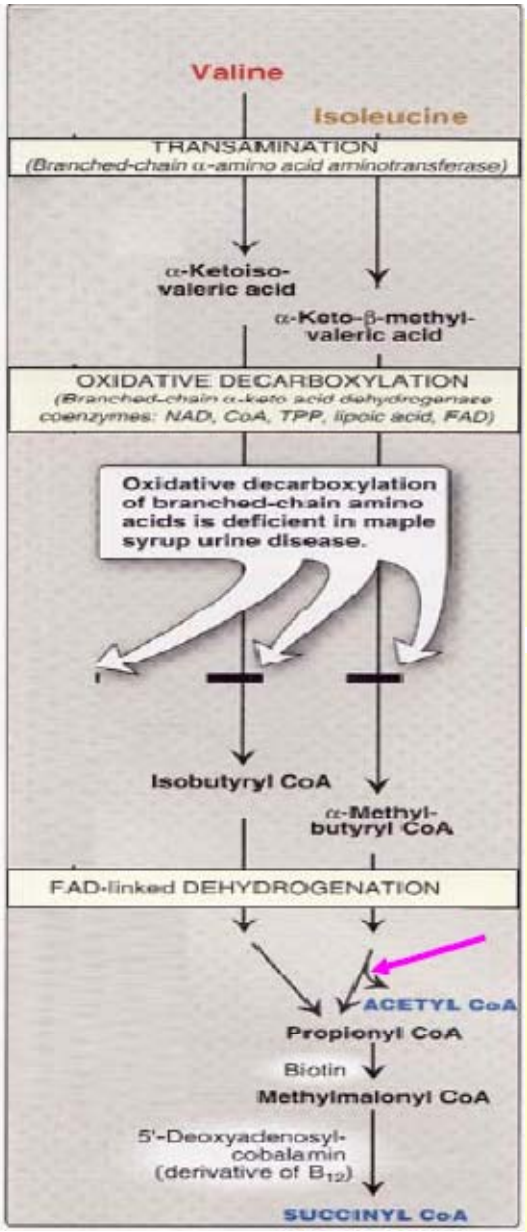
a) In case of methionine deficiency it is remethylated to methionine

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.


A
L-Methionine
ATP
S-Adenosyl-methionine synthetase
Mg2+
Pi + PPi
2 Pi
1)
2)
Adenosine
S-Adenosylmethionine
Methyl acceptors
Methyltransferases
Methylated products
3)
S-Adenosylhomocysteine
H2O
Adenosine
4)
L-Homocysteine
N5-Methyltetrahydrofolate
Methionine synthase
Methylcobalamin (Methyl-B12)
L-Methionine
Tetrahydrofolate
L-Serine
Cystathionine β-synthase
B6
H2O
Cystathionine
γ-Cystathionase
B6
H2O
α-Ketobutyrate + NH4+
L-Cysteine
There are two major disposal pathways for homocysteine. Conversion to methionine requires folate and vitamin B12-derived coenzymes, and is a remethylation process. The formation of cysteine requires vitamin B6 (pyridoxine), and is a transsulfuration process.

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

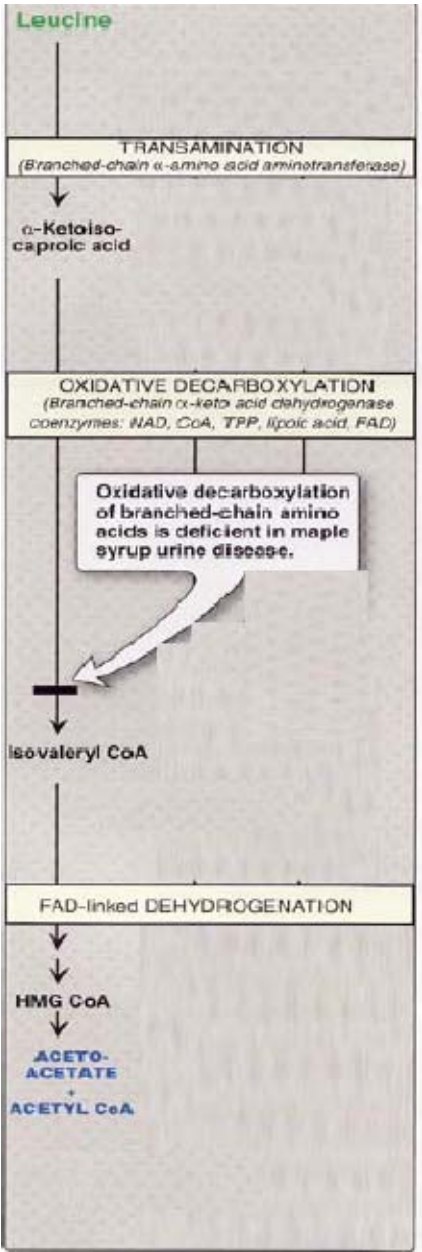
↓

Succinyl CoA ⟶ TCA cycle

Amino acids that form acetyl CoA or acetoacetyl CoA

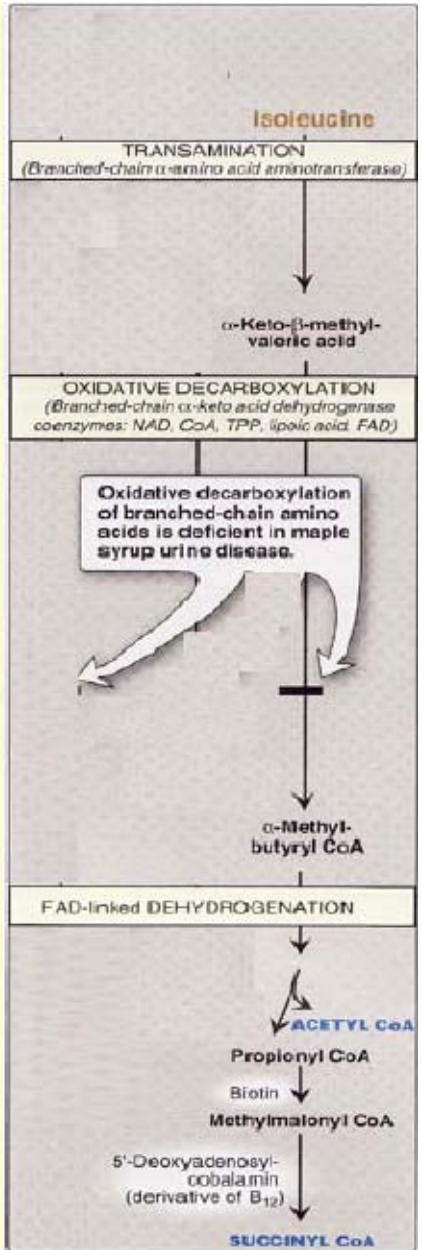
1) Leucine

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

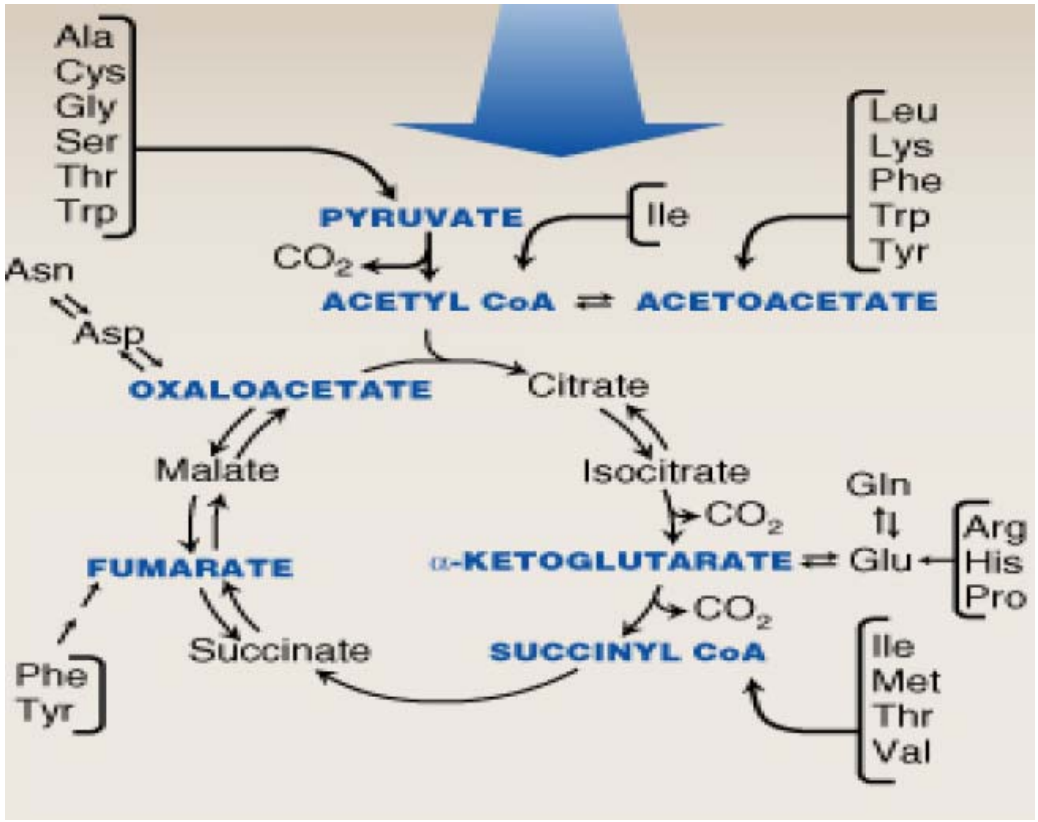
4) Tryptophan

Glucogenic and ketogenic

Since its metabolism yields both alanine and Acetoacetyl CoA

Overview of Amino Acid Catabolism

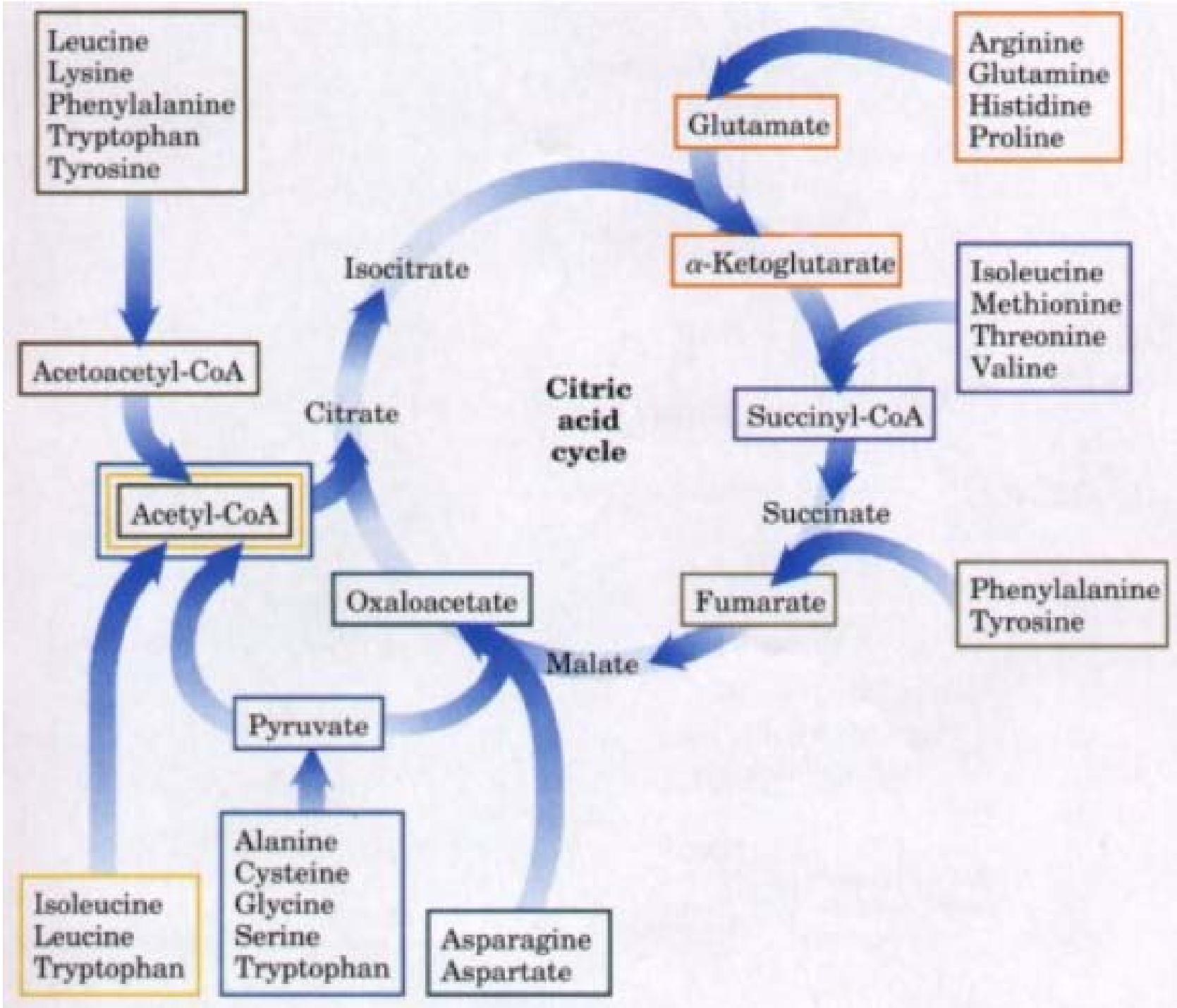
	Glucogenic	Glucogenic and Ketogenic	Ketogenic
Nonessential	Alanine Arginine* Asparagine Aspartate Cysteine Glutamate Glutamine Glycine Histidine* Proline Serine	Tyrosine	
Essential	Methionine Threonine Valine	Isoleucine Phenyl-alanine Tryptophan	Leucine Lysine



Enter as acetoacetate intermediates

Enter as both TCA cycle and acetyl derived intermediates

Enter as TCA cycle intermediates


Leucine
Lysine
Phenylalanine
Tryptophan
Tyrosine
Arginine
Glutamine
Histidine
Proline
Glutamate
Isocitrate
α-Ketoglutarate
Isoleucine
Methionine
Threonine
Valine
Acetoacetyl-CoA
Citrate
Citric acid cycle
Succinyl-CoA
Acetyl-CoA
Succinate
Oxaloacetate
Fumarate
Phenylalanine
Tyrosine
Malate
Pyruvate
Alanine
Cysteine
Glycine
Serine
Tryptophan
Isoleucine
Leucine
Tryptophan
Asparagine
Aspartate