بسم الله الرحمـٰن الرحيم

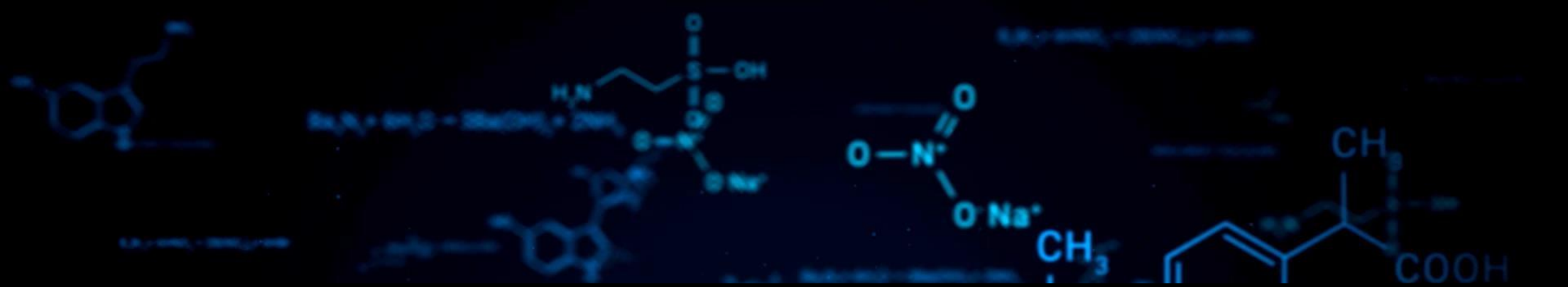
(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Metabolism | Lecture 17

Carbon Skeletons

Written by : NST member

Reviewed by : NST



Carbon Skeletons of Amino Acids

Prof. Nafez Abu Tarboush

After dealing with amino group (by transamination and oxidative deamination then urea cycle) , now we have to deal with the rest of the carbon skeleton in the amino acids.

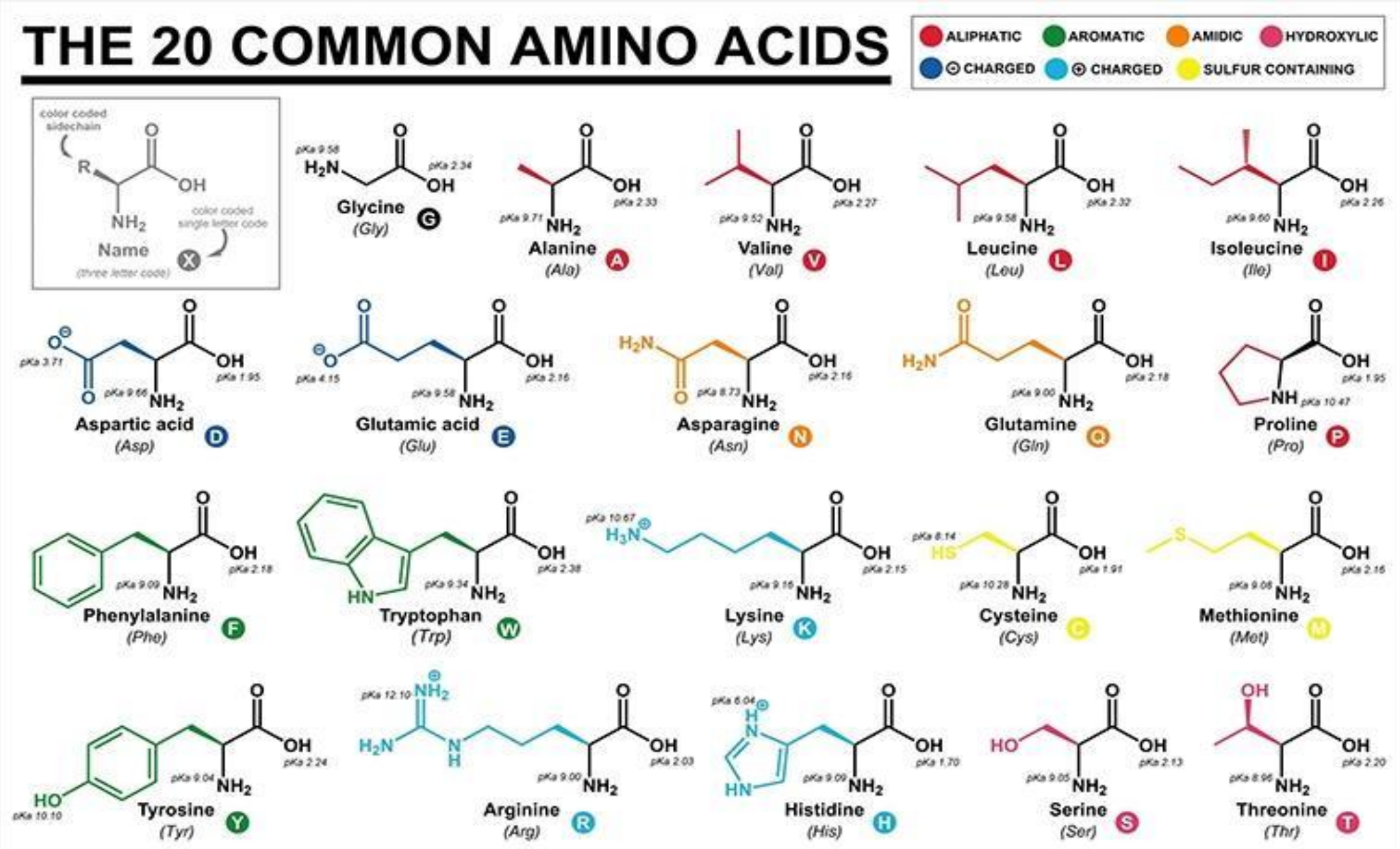
Metabolism of the carbon skeleton will give us some molecules that are glucogenic (related to glucose) or ketogenic (related to ketone bodies)

Glucogenic molecules include intermediates like **pyruvate** and some **citric acid cycle intermediates (Zaloaceteate, α-ketoglutarate, succinyl-CoA and fumarate)**

Ketogenic products include **acetyl-CoA**, **acetoacetate** or **acetoacetyl-CoA**

Some amino acids give us molecules which are glucogenic and ketogenic. (Mixed amino acids)

Recalling the structures of amino acids is **important** for this lecture.



OVERVIEW

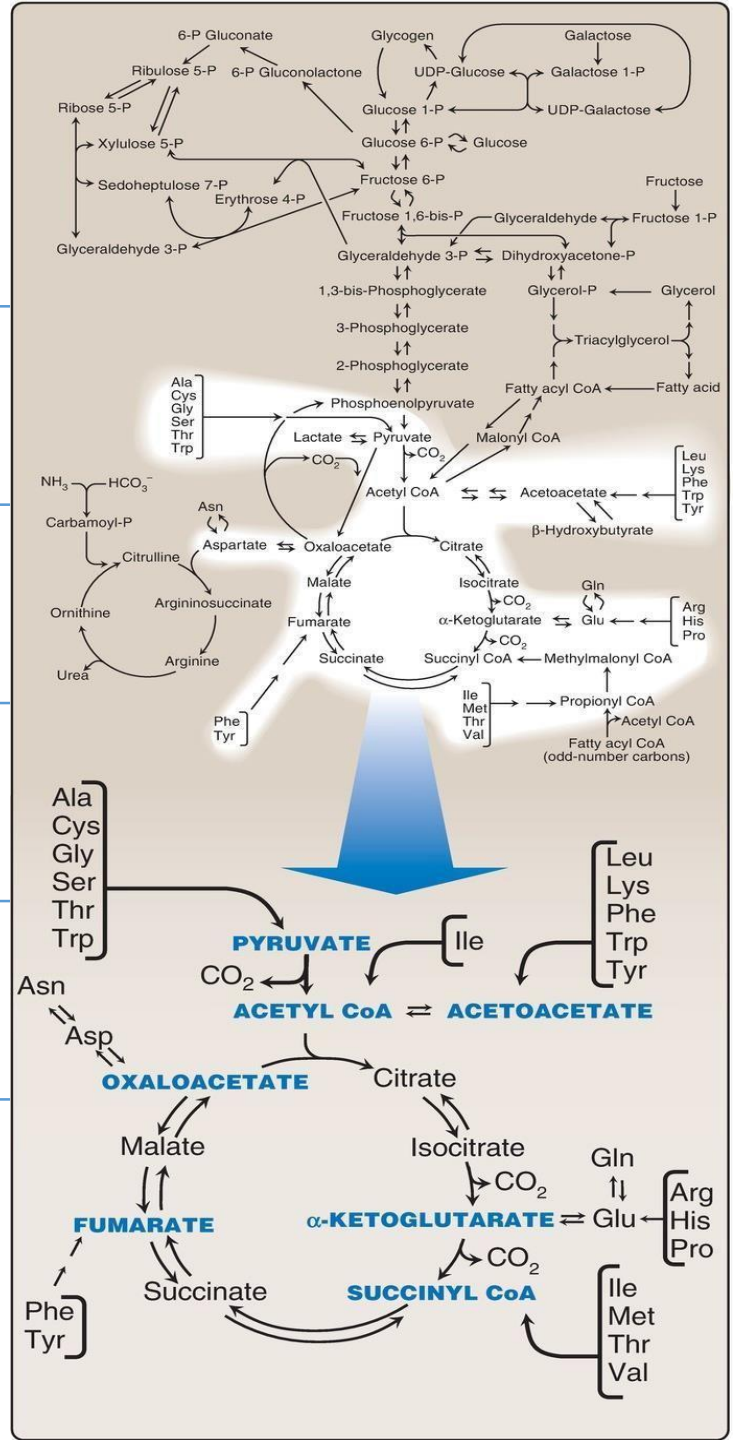
Removal of the α-amino group → Catabolism of α-keto acids (carbon skeletons)

Seven intermediate products: pyruvate, oxaloacetate, α-ketoglutarate, fumarate, succinyl-CoA, acetyl-CoA, & acetoacetate

Resulting either in the synthesis of glucose, ketone bodies, or lipids or in the production of energy (TCA)

Nonessential amino acids can be synthesized in sufficient amounts

Genetic defects in the pathways of amino acid metabolism can cause serious disease

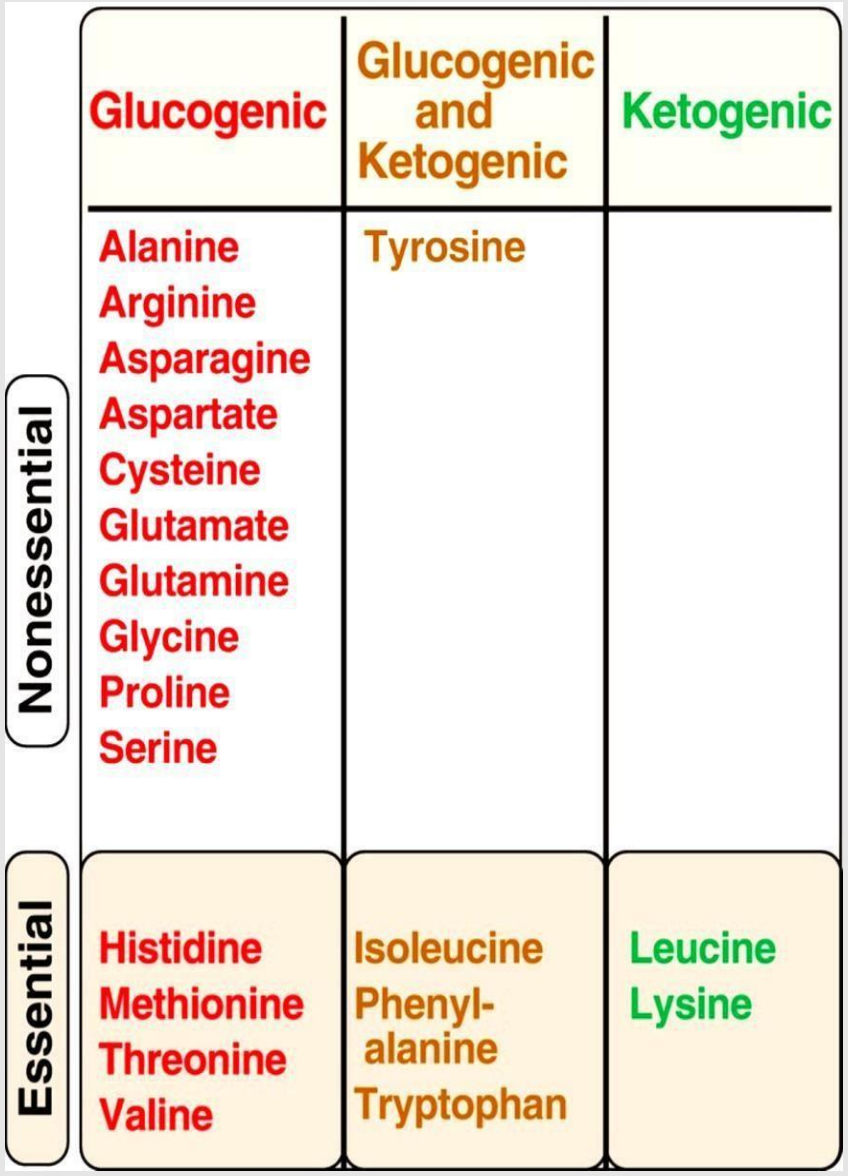


GLUCOGENIC AND KETOGENIC AMINO ACIDS

Glucogenic: substrates for gluconeogenesis (pyruvate and TCA intermediates)

Ketogenic: acetoacetate or its precursors (acetyl CoA or acetoacetyl CoA)

Both



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

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

* You have to memorize this figure.

How to memorize them?

Ketogenic amino acids start with letter 'L'

Mixed amino acids are the **aromatic + Isoleucine**

The rest of them are glucogenic

* Essential amino acids in this lecture are underlined, to help you in memorizing them.

Catabolism to OxaloAcetate

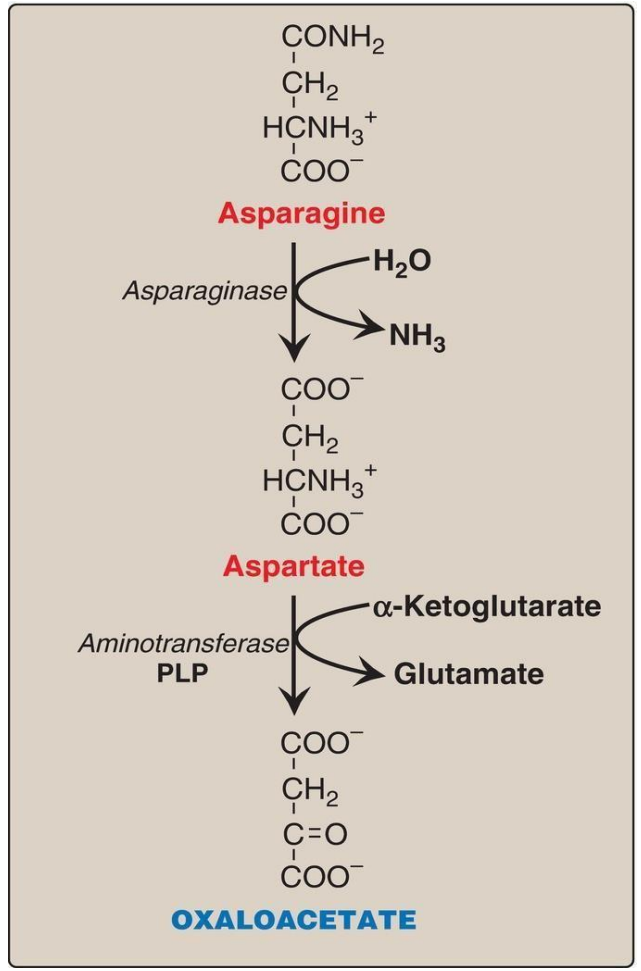
- Asparagine and aspartate
- Asparaginase systemically to treat leukemia!

OAA is one of the Krebs cycle intermediates.

OAA is the corresponding keto acid for **aspartate**

Aspartate is converted to OAA through a **transamination** reaction catalyzed by **aspartate transaminase**

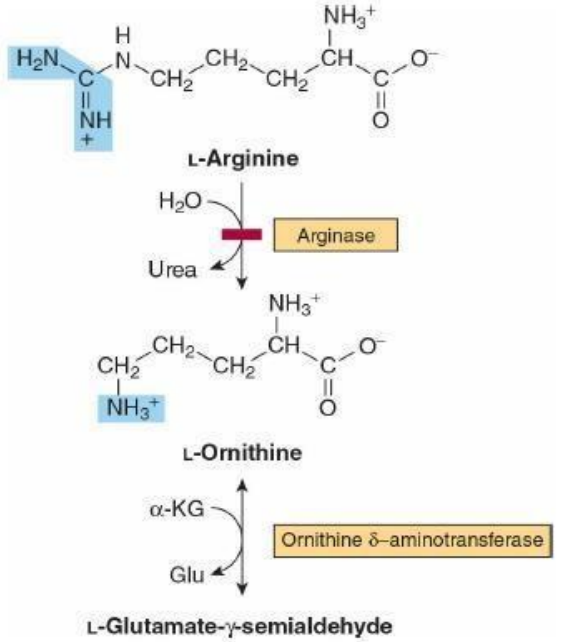
Asparagine is converted to aspartate through a **hydrolysis** reaction breaking down the ammonia group using a **lyase** enzyme (**asparaginase**)

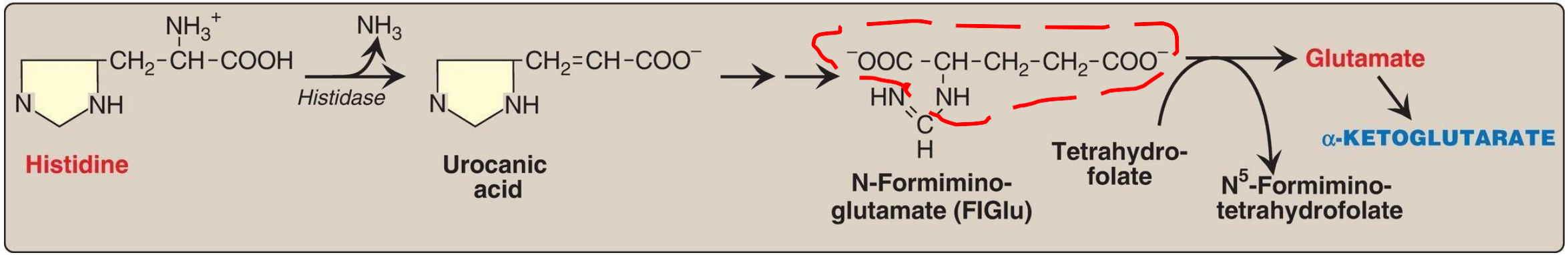


Catabolism to α-KetoGluterate (via Glu) - QHRP

Glutamine – Histidine– Arginine – Proline

- Glutamine: glutaminase and GDH
- Proline: oxidized to Glu
- Arginine: arginase
- Histidine:
  - Folic acid deficiency
  - Impaired histidase: histidinemia and urocanic aciduria





Glutamate is related to α-ketoglutarate through **transamination** reaction and **oxidative deamination** reaction.

Glutamine is converted to glutamate through **deamination** reaction by **glutaminase**

Proline is **oxidized** to **Glutamate**

Arginase breaks down arginine to urea and ornithine, ornithine can be converted to glutamate related molecule (an aldehyde form) through a **transamination** reaction, finally, this molecule can be converted to **glutamate**.

Histidine has a special side chain in its structure (one carbon and a five membered imidazole ring) which will become an open chain molecule.

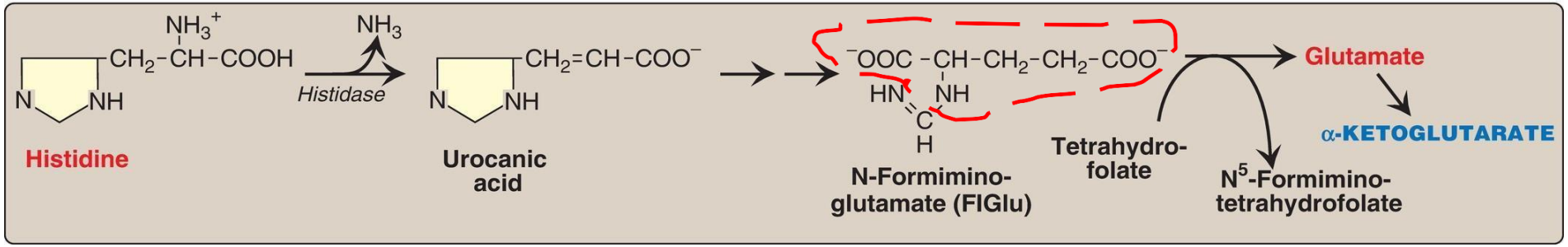
It is converted to **urocanic acid** by **histidase**, further converted to **N-Formimino-glutamate** (A glutamate molecule coupled to a formyl group, which has one carbon atom)

This one carbon unit is coupled to nitrogen attached to the glutamate.

Formimino group will be cleaved by a **folic acid dependent enzyme (Tetrahydrofolate) ,vitamin B9 dependent,** leaving a glutamate molecule

Histidinemia:

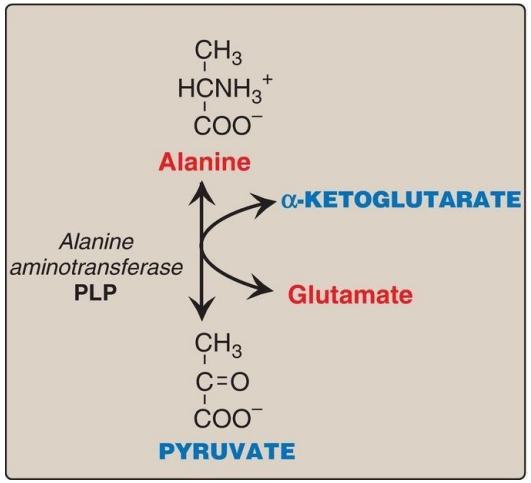
An elevation in histidine, may be a result from a deficiency in histidase or other enzymes following in the pathway depending if there is urocanic acid in the urine or not which is a diagnostic marker.

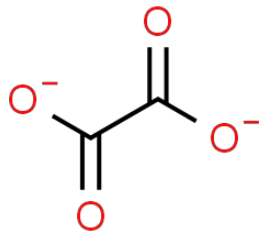


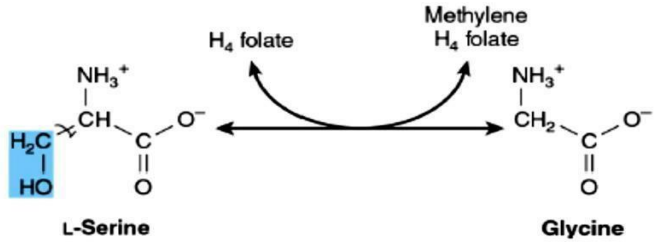
Catabolism to pyruvate – (GSCAT²)

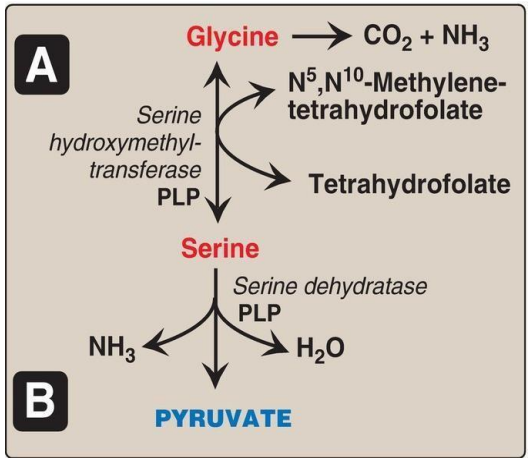
GSCAT²:
Glycine – Serine – Cysteine– Alanine – Threonine – Tryptophan

- Alanine: ALT **(Alanine Transaminase)**
- Tryptophan catabolism produces alanine
- Serine: glycine or pyruvate
- Glycine:
  - Reverse or CO_2 and NH_3 (glycine cleavage system)
  - Transaminated to glyoxylate → oxidized to oxalate or transaminated back to glycine
  - Deficiency of transaminase causes oxalate stones





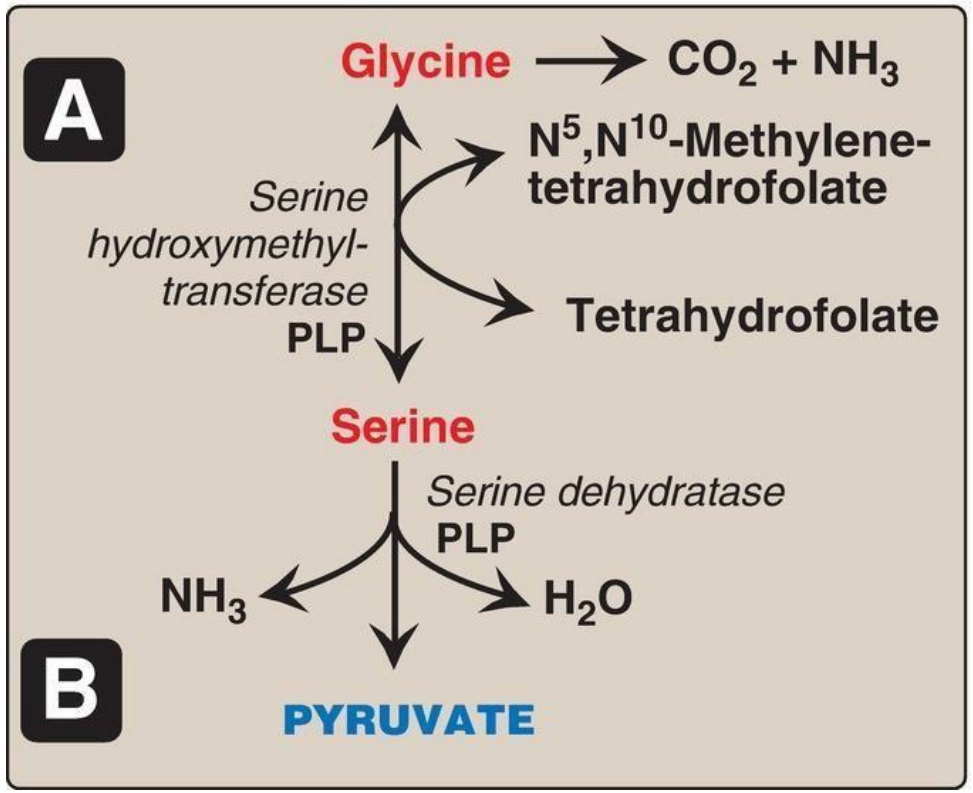




Serine has two pathways:

1- It can be converted to **glycine** through **hydroxymethyl transferase (reversible step)**

2- It can be converted to **pyruvate** through **serine dehydratase** which produces an ammonia group and converts serine to the keto acid associated with it.



Serine side chain contains one carbon atom and an OH group, cleaving OH gives alanine which can be converted to pyruvate.

Glycine is the simplest amino acid, logically, it will be converted to a simple molecule which is pyruvate.

Glycine must be converted to serine, this is done by an enzyme called **hydroxymethyl transferase** which transfers a **hydroxymethyl** group in a reversible reaction.

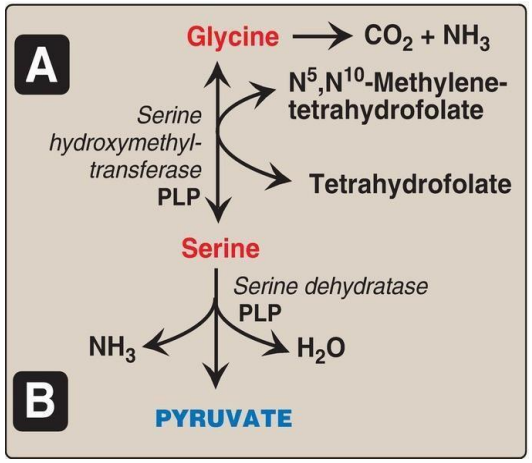
This enzyme is dependent on **PLP** (Vitamin B6) and **Folic acid** (Vitamin B9)

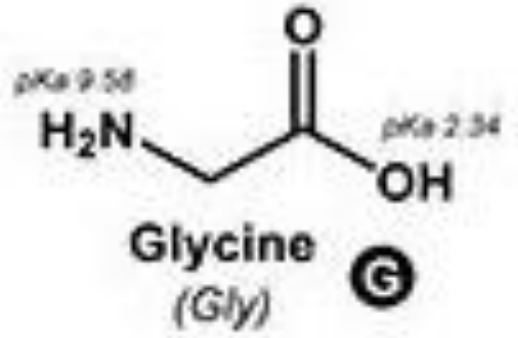
Glycine has many other pathways:

1- Glycine cleavage enzyme, which results in CO2 and NH3.

2- It can be **transaminated** to **glyoxylate**.

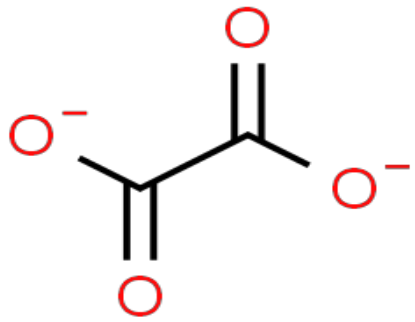
3- **Glyoxylate** can be reversed to glycine or it can be oxidized to **oxalate**



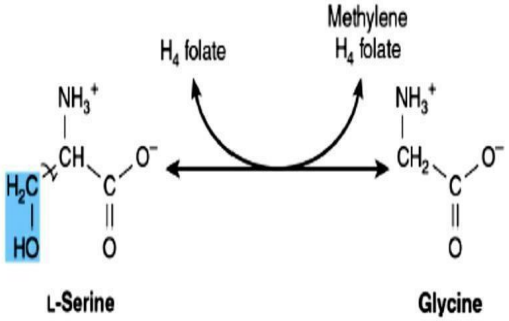


Oxalate is a molecule that contain 2 carboxylic group, consequently, it can attract calcium.

A deficiency in back transamination (glyoxylate to glycine) may cause oxalate stones.

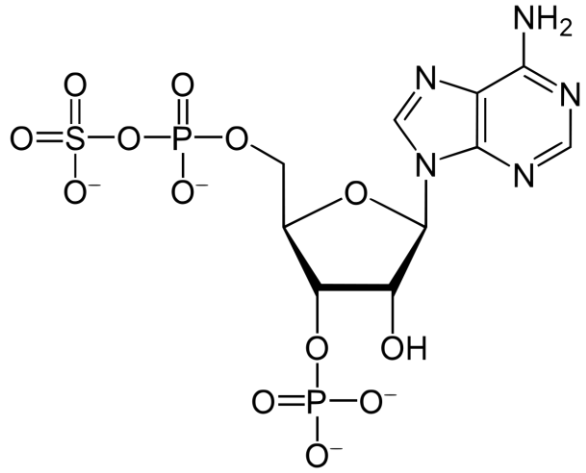


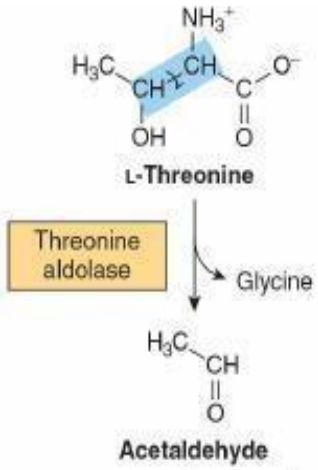
Vitamin B12 and Vitamin B9 are heavily involved nitrogen metabolism.

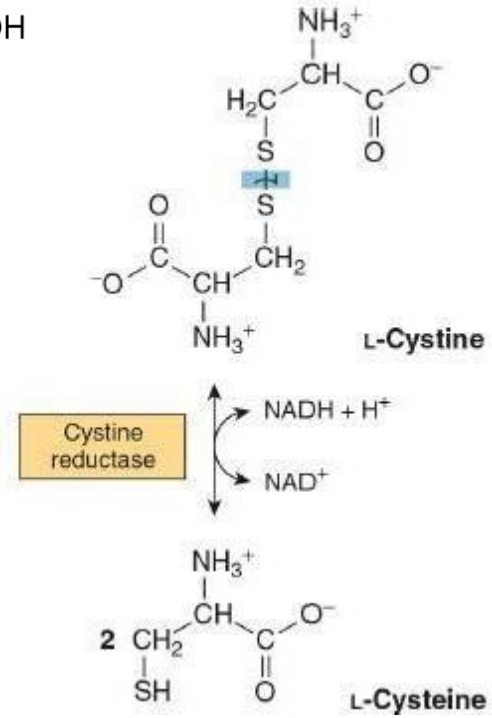


Catabolism to pyruvate – (GSCAT²)

- Cysteine: desulfurization to yield pyruvate (desulfinase)
  - Sulfate released can be used to synthesize 3′- phosphoadenosine-5′-phosphosulfate (PAPS), an activated sulfate donor
  - Oxidized to its disulfide derivative, Cystine
- Threonine: minor pathway in humans







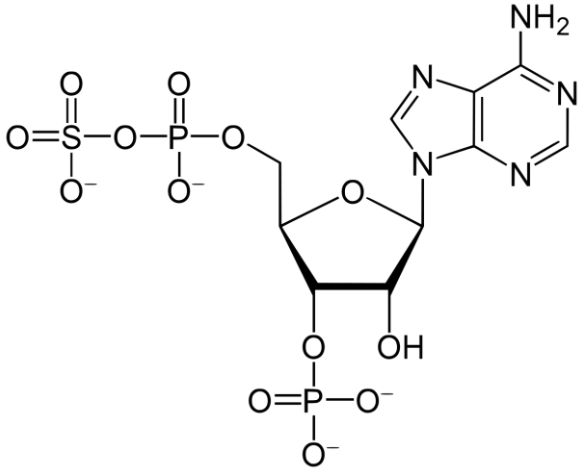
Cysteine side chain contains one carbon attached to a **thiol** group.

Removing the thiol group will produce alanine.

Desulfinase is the enzyme that removes the sulfur.

Sulfate group will be added to an adenosine molecule coupled with a phosphate group.

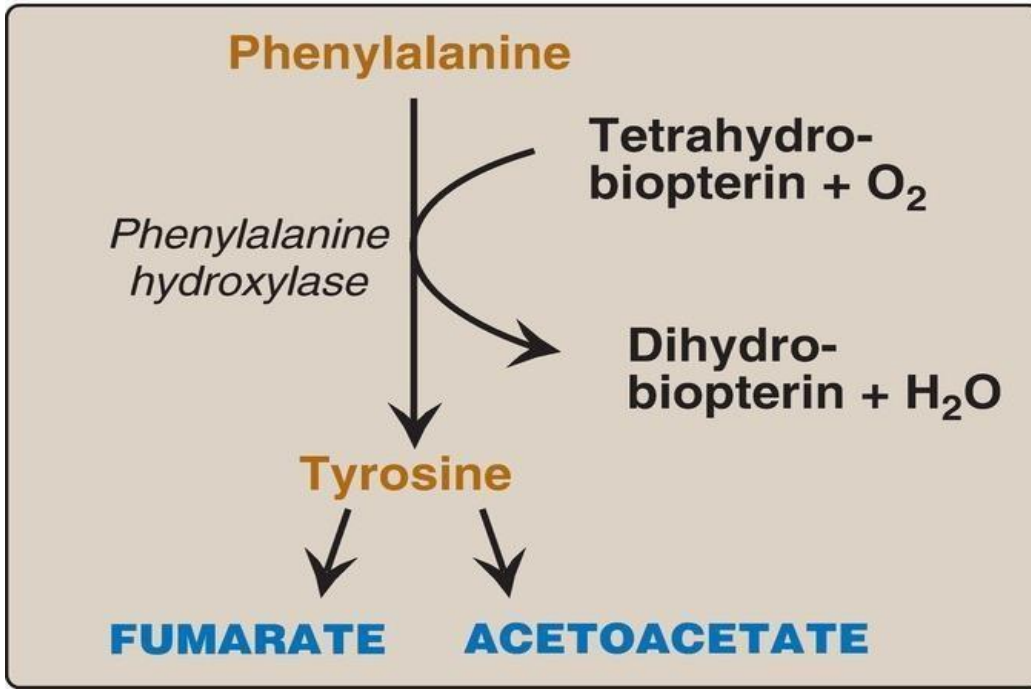
This resulting molecule is called **3′-phosphoadenosine-5′-phosphosulfate (PAPS)** which is a sulfate donor.



Threonine minor pathway in humans for the degradation to alanine.

Catabolism to fumarate

- Phenylalanine and tyrosine — Mixed amino acids
  - Irreversible reaction
  - Phenylalanine hydroxylase (PAH)
  - Tetrahydrobiopterin
  - Fumarate and acetoacetate
- Inherited deficiencies: phenylketonuria (PKU), tyrosinemia, alkaptonuria as well as the condition of albinism



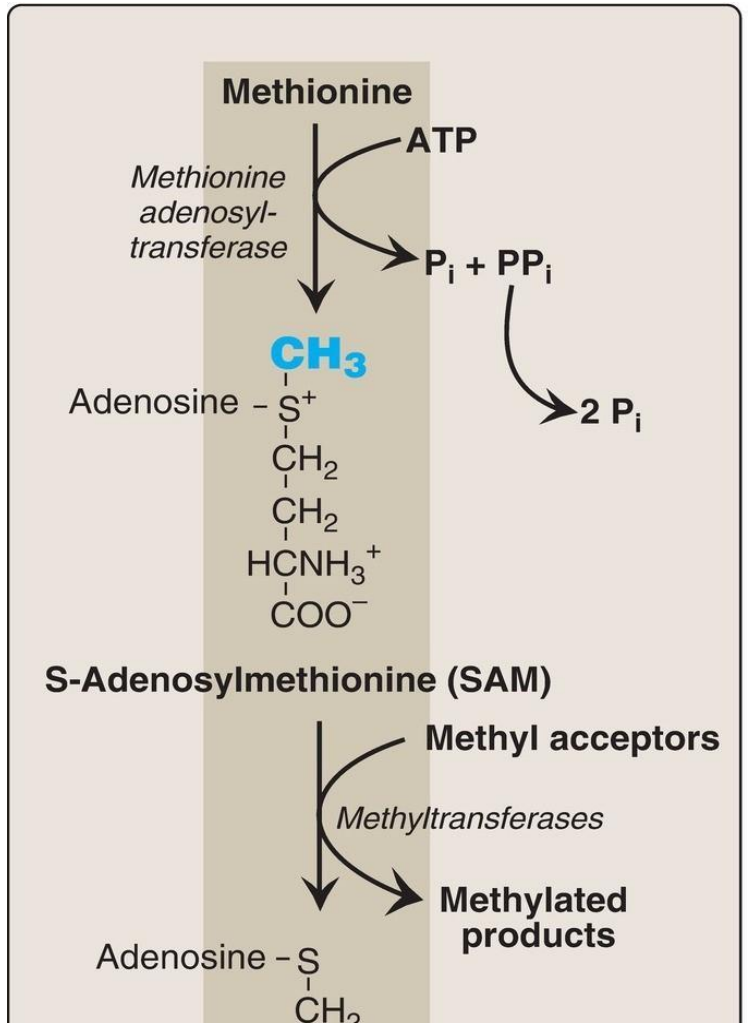
Glucogenic Ketogenic

Tetrahydrobiopterin is a coenzyme used in hydroxylation reactions.

Dihydrobiopterin can be reduced again to tetrahydrobiopterin using an enzyme called **dihydropteridine reductase** which we can synthesize it in our bodies from GTP synthesis

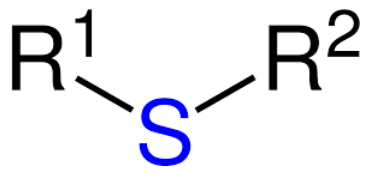
Catabolism to succinyl CoA: Methionine

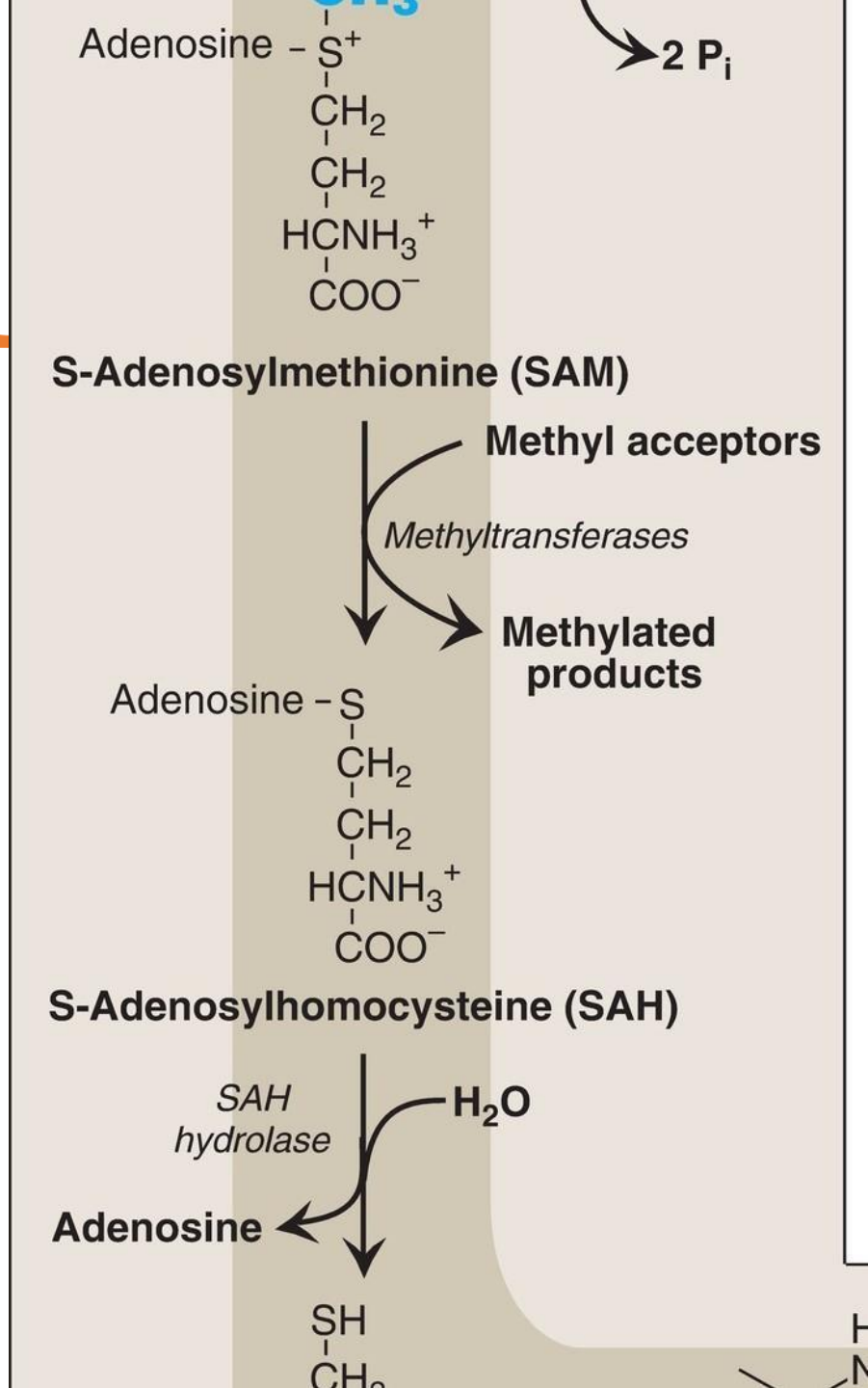
- S-adenosylmethionine (SAM)
- The major methyl group donor in one-carbon metabolism
- Source for homocysteine (Hcy)
- Atherosclerotic vascular disease and thrombosis
- SAM synthesis: Met condenses with ATP
- A high-energy compound that is unusual (no P)
- Hydrolysis of all three phosphate bonds



Catabolism to succinyl CoA: Methionine

- Activated methyl group:
  - Can be transferred by methyltransferases
  - Nitrogen or oxygen atoms and sometimes to carbon atoms
  - The reaction product, S-adenosylhomocysteine (SAH), analogous to methionine (thioether)
  - Methyl transfer essentially irreversible





Methionine is an essential amino acid which we can get from diet.

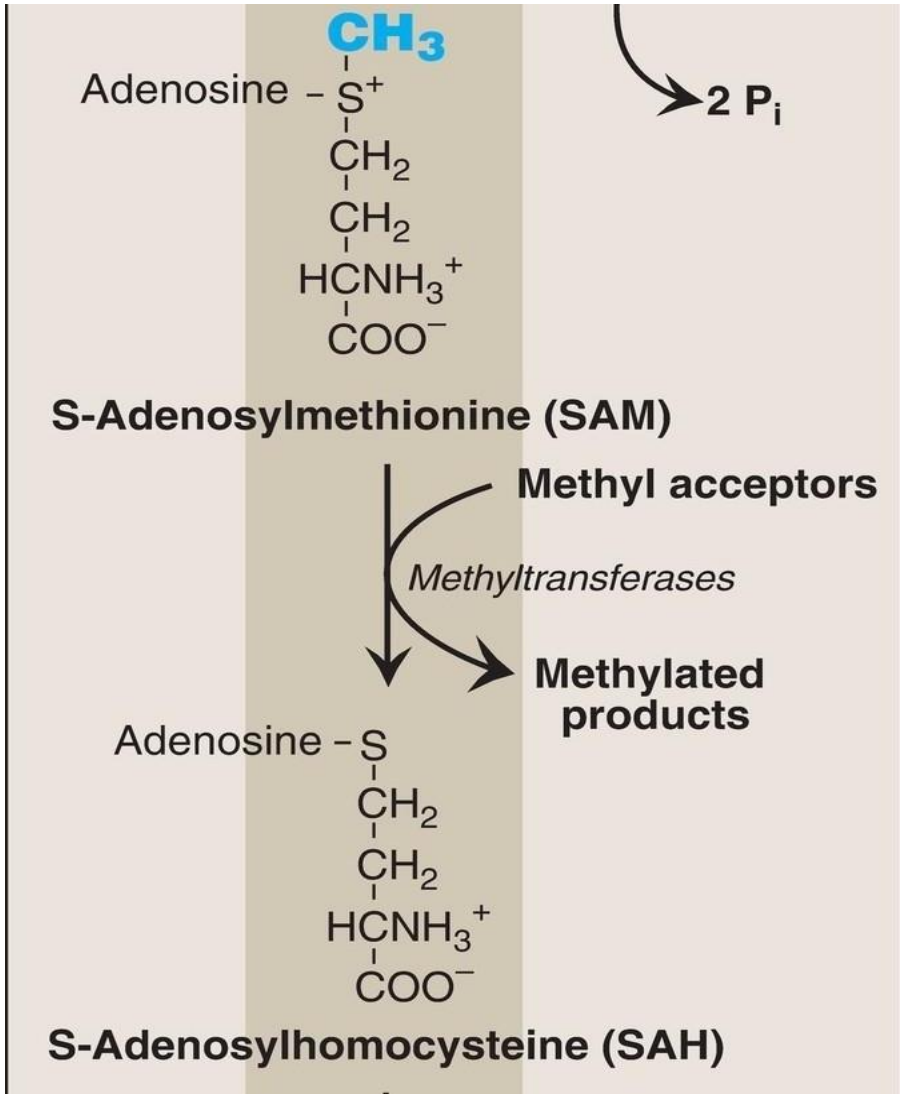
Methionine catabolism pathway:

1-Adenosine will be coupled to methionine at the sulfur atom producing a molecule called **S-adenosylmethionine "SAM"** (S stands for sulfur atom where the adenosine molecule binds).

2- Methyl group will be transferred to other molecules using **methyltransferases** enzymes.

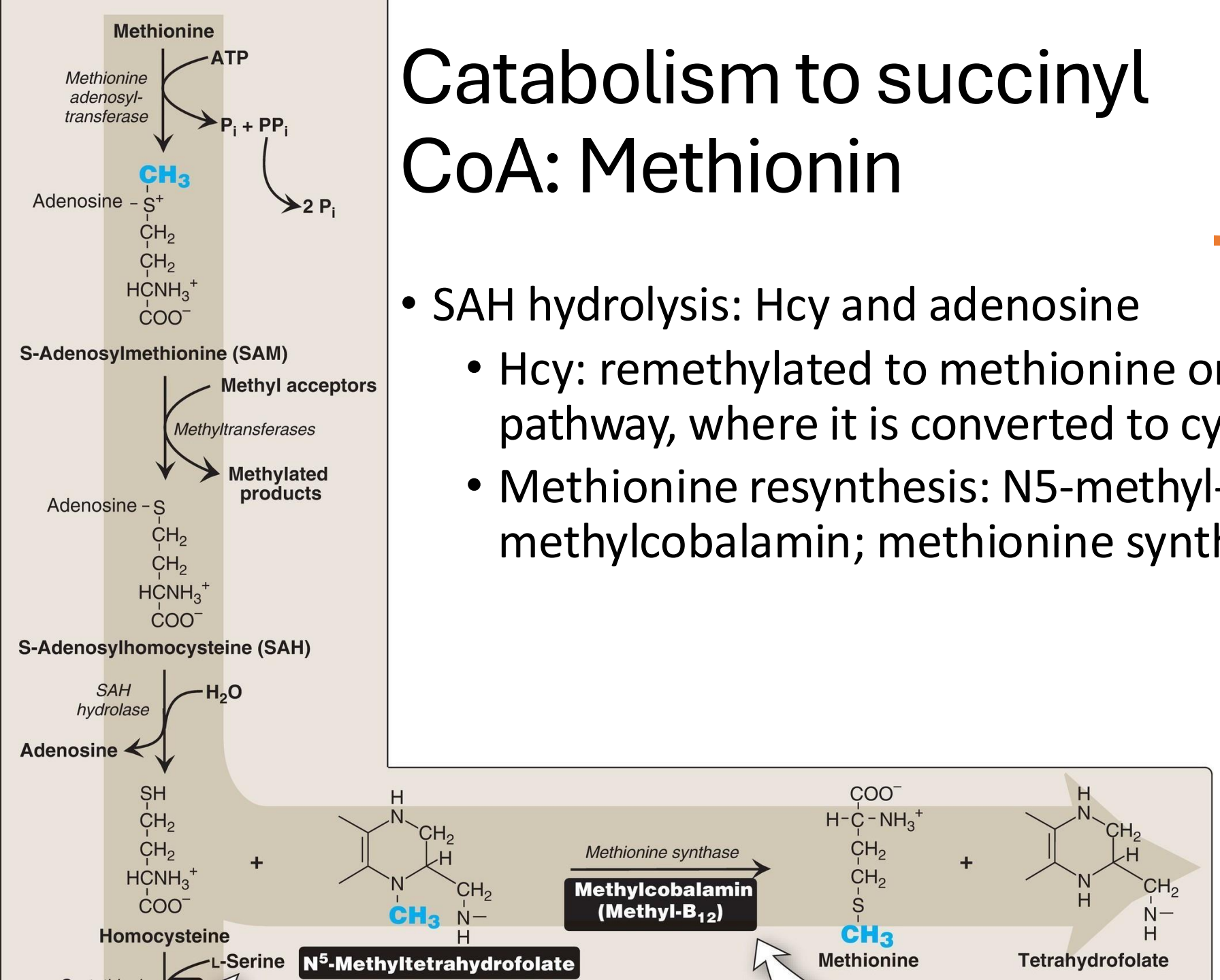
3- After cleavage of methyl group, the remaining molecule resemble cysteine with one more carbon. This molecule is called **S-adenosylhomocysteine "SAH"**.

SAM is an activated unstable molecule, because the sulfur atom is overloaded weakening the bond between methyl group and sulfur, this makes SAM a main methyl donor alongside with tetrahydrofolate (folic acid).

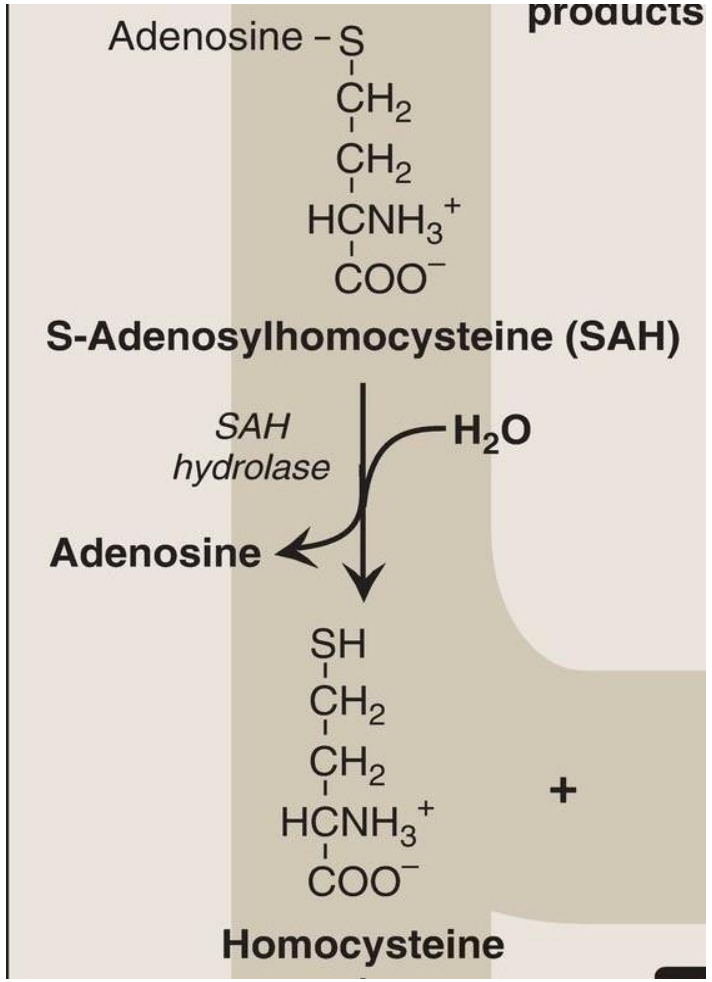


Catabolism to succinyl CoA: Methionin

- SAH hydrolysis: Hcy and adenosine
  - Hcy: remethylated to methionine or transsulfuration pathway, where it is converted to cysteine
  - Methionine resynthesis: N5-methyl-THF; methylcobalamin; methionine synthase



4- SAH will be **hydrolyzed** into adenosine and homocysteine.



After intensive research in the last two decades, homocysteine has been identified as a very bad molecule.

It is linked to myocardial infarctions, strokes and cardiovascular diseases.

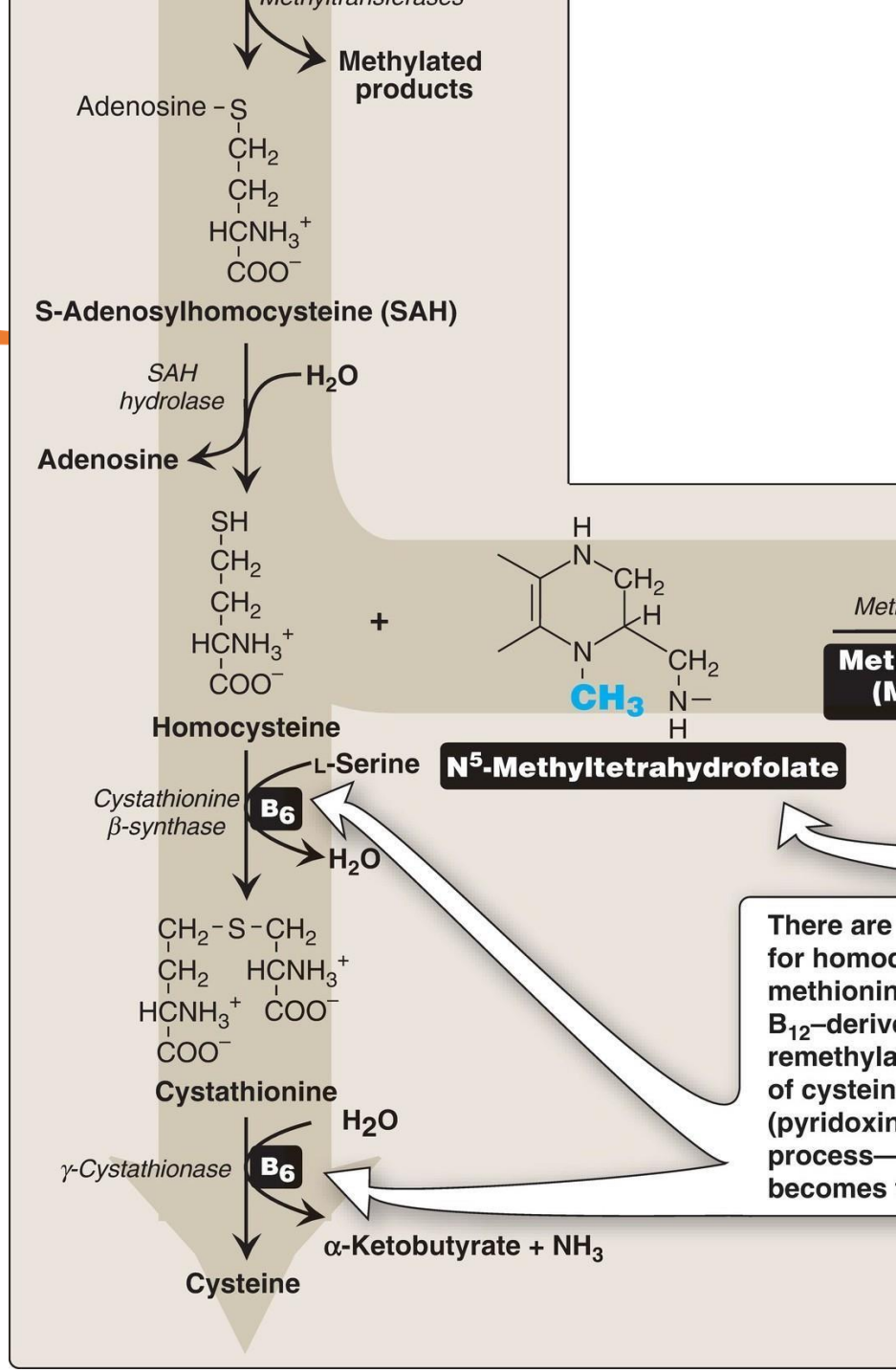
Its concentration is getting elevated in the population.

About 7% of the population shows high levels of homocysteine.

This elevation is due to a change in the lifestyle of the population. (More dense protein food and less vitamins).

Catabolism to succinyl CoA: Methionine

- SAH hydrolysis: Hcy and adenosine
  - Cysteine synthesis: condensation; Ser; cystathionine (α-ketobutyrate and cysteine); B6; oxidatively decarboxylated to form propionyl CoA. Propionyl CoA is converted to succinyl CoA
  - Cysteine is conditionally essential



5- Homocysteine should be degraded by two pathways:

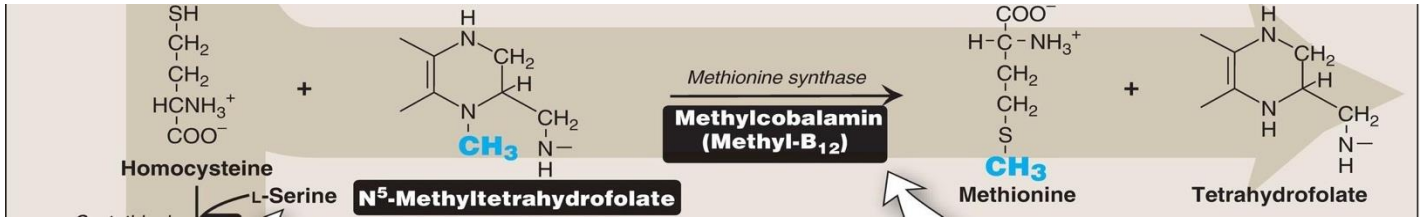
A) "**Re-methylation**": converting it to methionine by adding one methyl group transferred from tetrahydrofolate.

This reaction is catalyzed by **methionine synthase** aided by **Vitamin B12** as a coenzyme

Re-methylation also requires Vitamin B9

Methionine is an essential amino acid that is used for synthesizing protein. Also, it can be used to produce other essential amino acid like cysteine.

* The number over 'N' in tetrahydrofolate means that the methyl group is linked to tetrahydrofolate on nitrogen number 5.
It can be N^5 , N^{10} or both (when it is linked to 2 methyl groups) .



B) "**Transsulfuration**" Converting homocysteine to cysteine by adding one carbon before the sulfur.

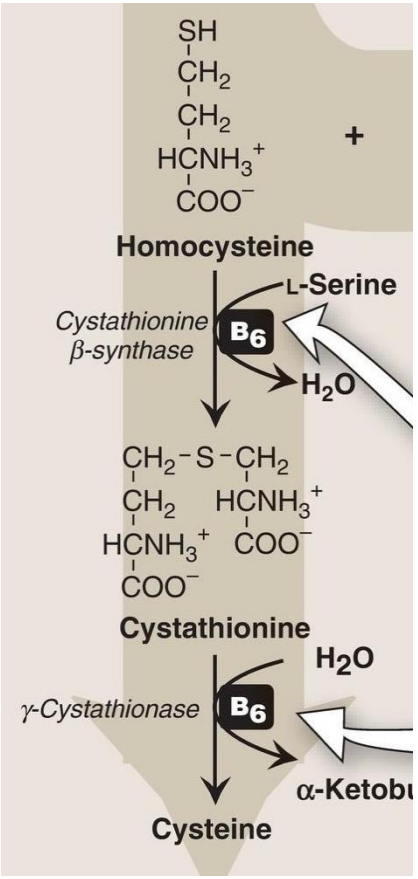
How is it done?

1) By adding another amino acid (serine) that has one carbon in its side chain and can bind to the sulfur using **cycstathionine B-synthase**

2) Cut the molecule using **cystathionase**

Both of these enzymes are **pyridoxine-dependent (Vitamin B6)**

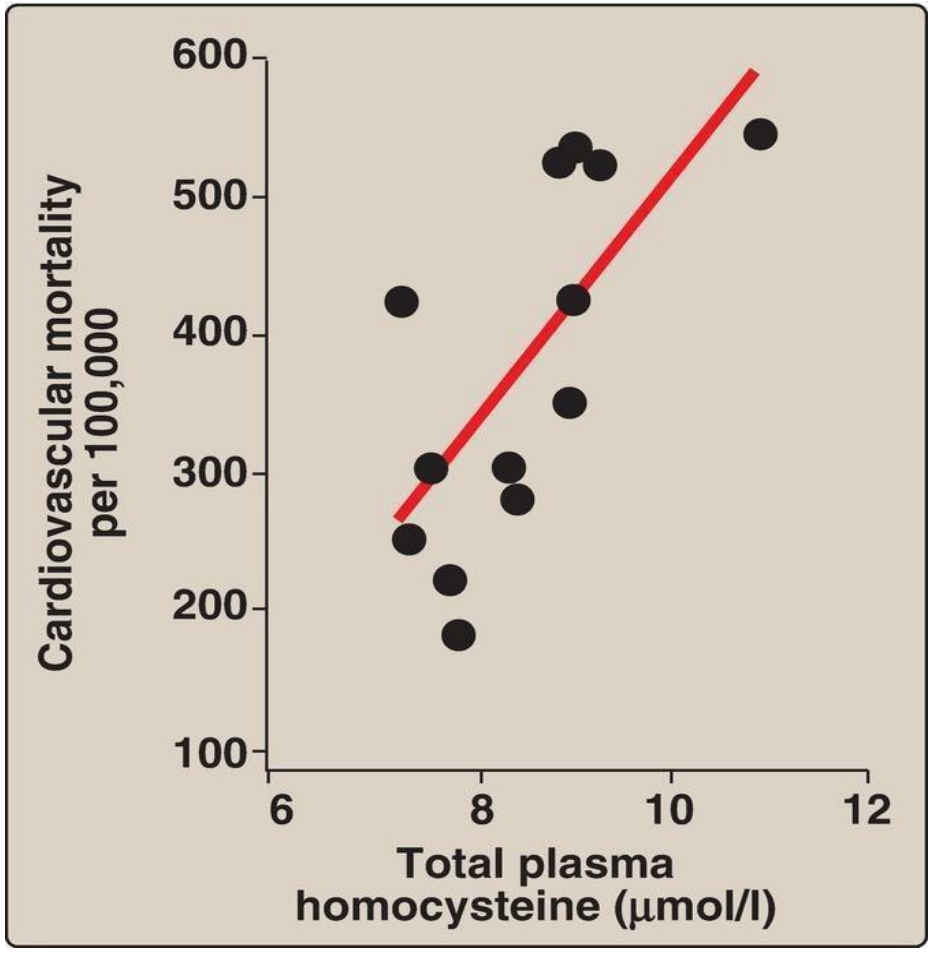
NH3 will leave and the rest of carbons will leave as **α-ketobutyrate** which is a source of energy.



α-ketobutyrate is then converted to propionyl-CoA then to succinyl-CoA

Relationship of homocysteine to vascular disease

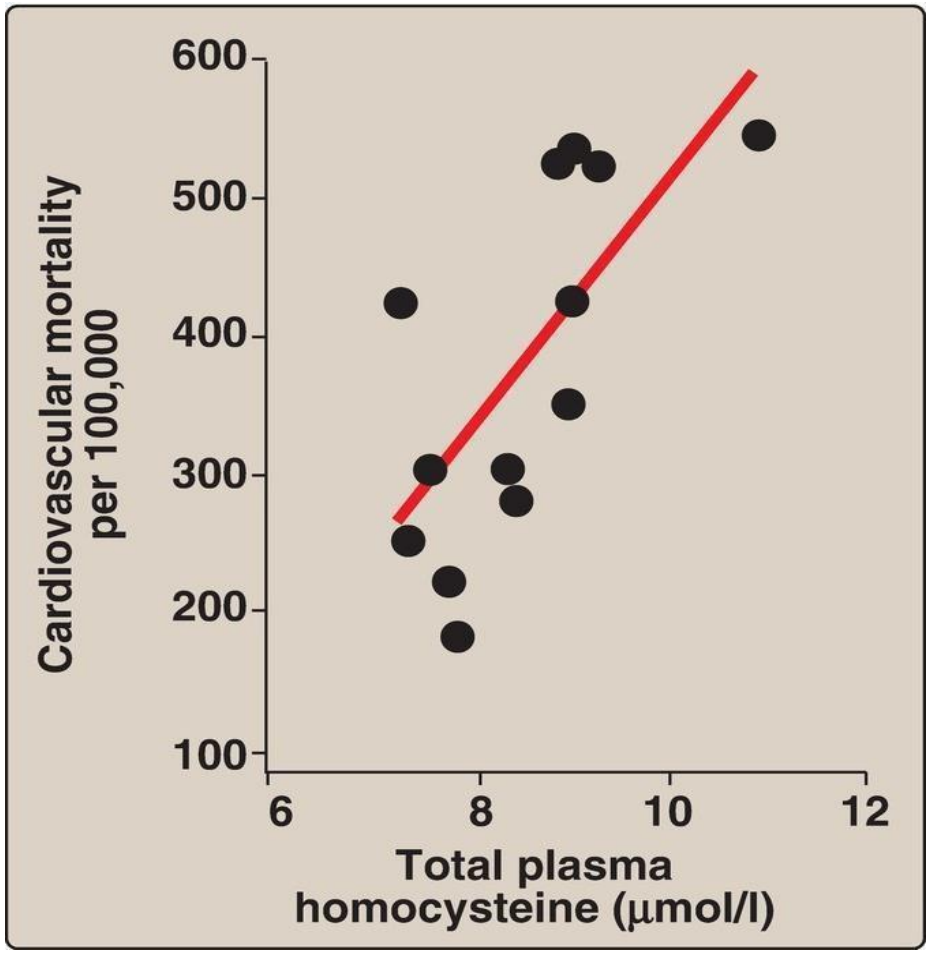
- Promotes oxidative damage, inflammation, and endothelial dysfunction
- Independent risk factor: CVD, stroke
- Mild elevations (hyper-homocysteinemia): ~7% of the population
- Inversely related to plasma levels of folate, B12, B6
- Supplementation therapy
- Whether Hcy is a cause or a marker of such damage



Deficiency in vitamins in our lifestyle causes accumulation of homocysteine which leads to cardiovascular diseases.

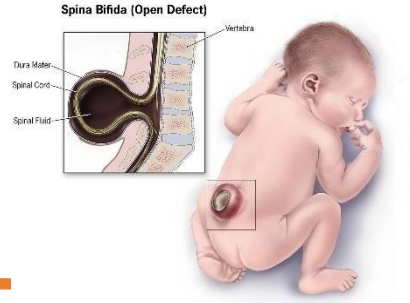
Vitamins B6, B9 and B12 are prescribed for people who are suffering from high homocysteine levels as a supplementation therapy.

It works by encouraging the routs of homocysteine degradation.

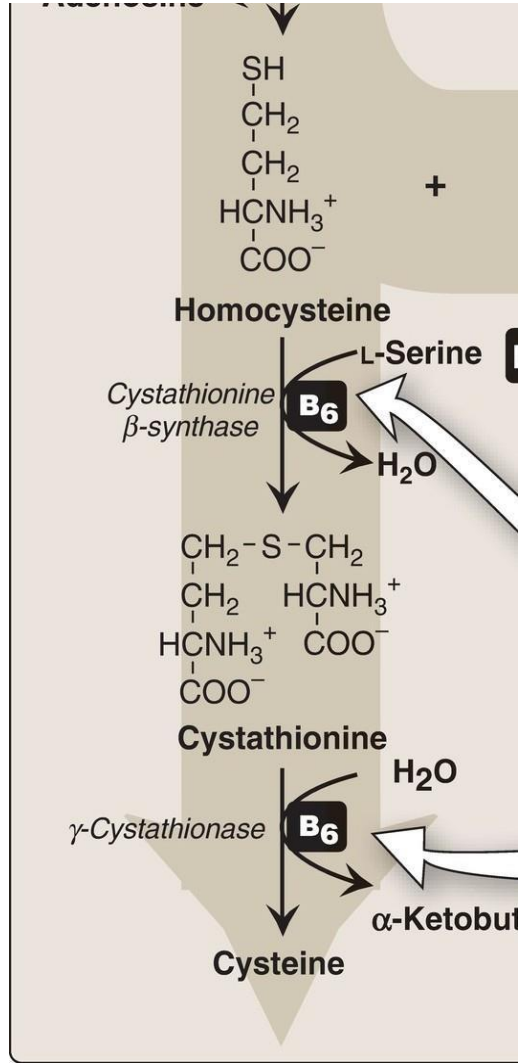


This figure shows a direct relationship between Total plasma homocysteine and cardiovascular mortality rates

Relationship of homocysteine to vascular disease



- Deficiencies in cystathionine β-synthase (transsulfuration):
  - Rare
  - Severe hyperhomocysteinemia (>100 µmol/L)
  - Classic homocystinuria
- Deficiencies in the remethylation reaction: rise in Hcy
- Elevated homocysteine and decreased folic acid: associated with increased incidence of neural tube defects (improper closure as in spina bifida) in the fetus
  - Periconceptual supplementation with folate reduces such defects



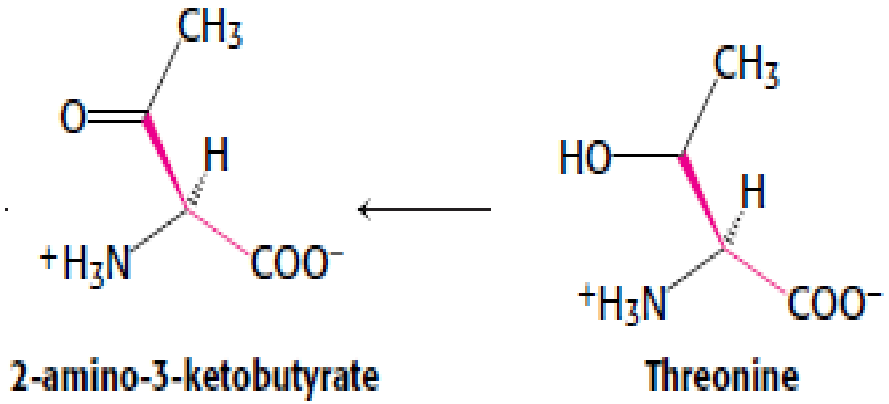
It is a common practice for all women planning for pregnancy to take folic acid.

(400µg/day) which is ×10 normal level.

Preconceptional folic acid supplementation should be started at least 3 months before conception

Other amino acids that form succinyl CoA

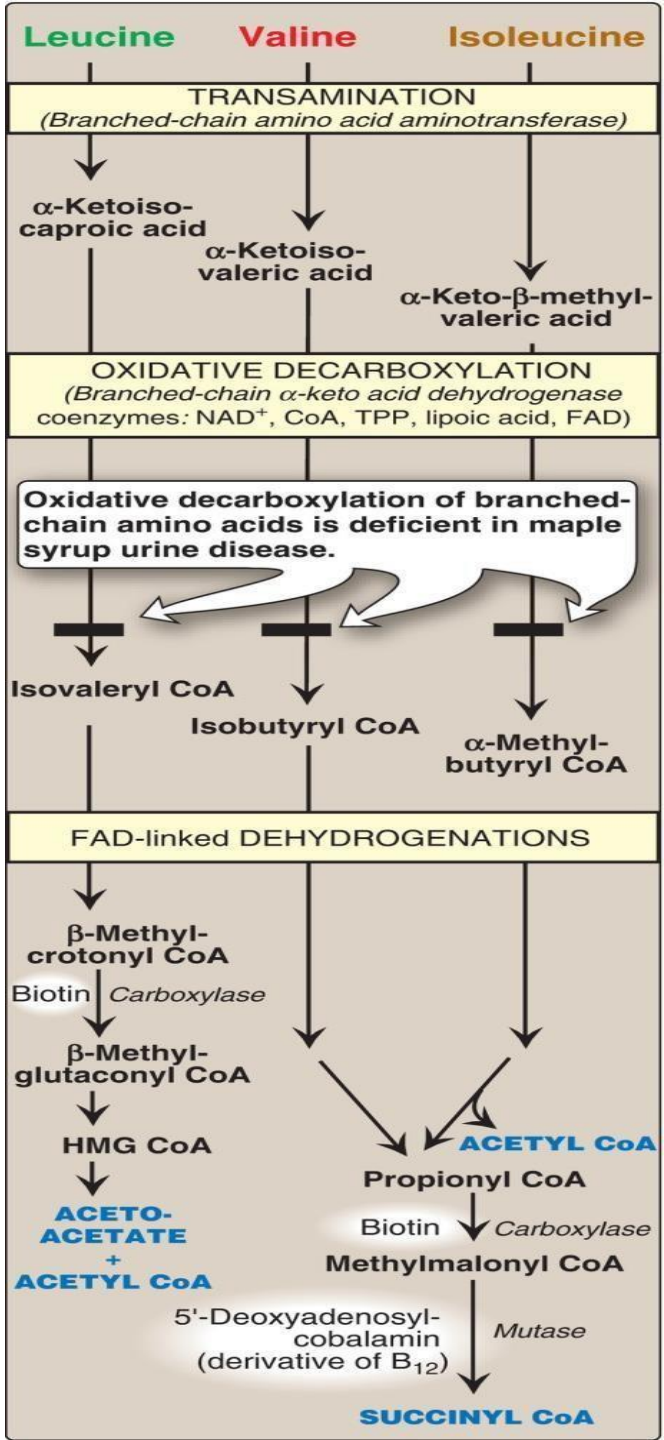
- Valine, isoleucine, and threonine
- Valine and isoleucine: BCAA
- Threonine: α-ketobutyrate → propionyl CoA → succinyl CoA



2-amino-3-ketobutyrate Threonine

Leucine is strictly ketogenic, it can't produce succinyl-CoA

Isoleucine and Valine produce propionyl-CoA then succinyl-CoA



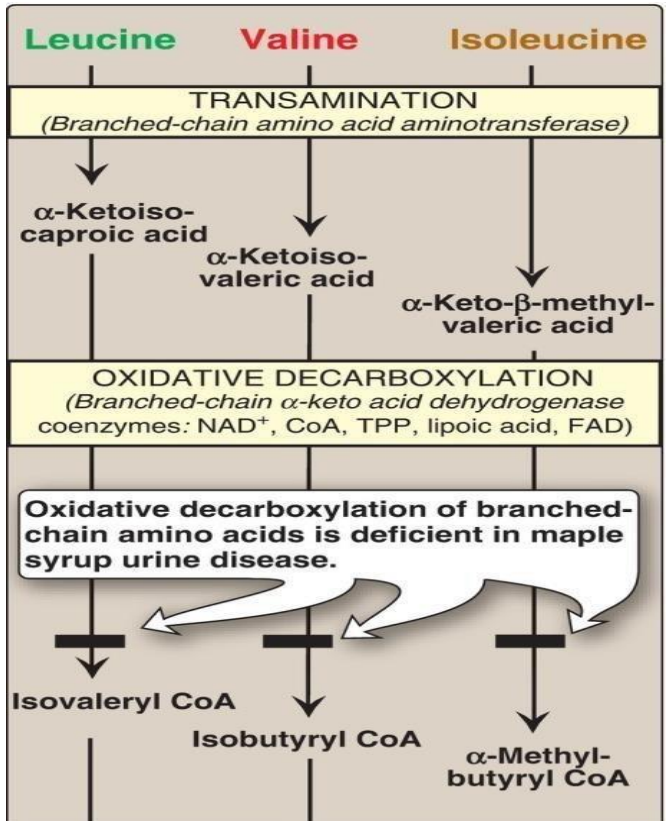
Branched chain keto acid dehydrogenase:

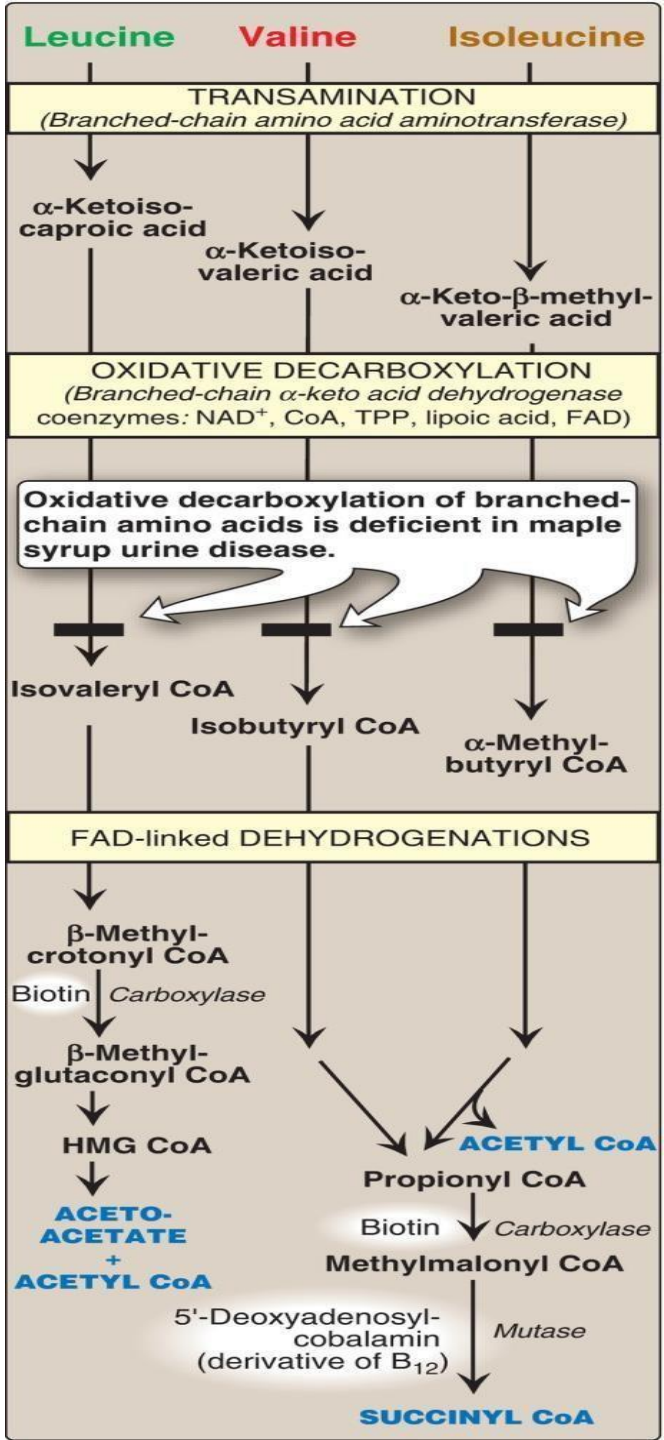
It is a complex enzyme (like pyruvate DH and α-ketodehydrogenase)

It consists of three separate enzymes combined to each other:

1- **Decarboxylase** 2- **Transacylase** 3- **Dehydrogenase**

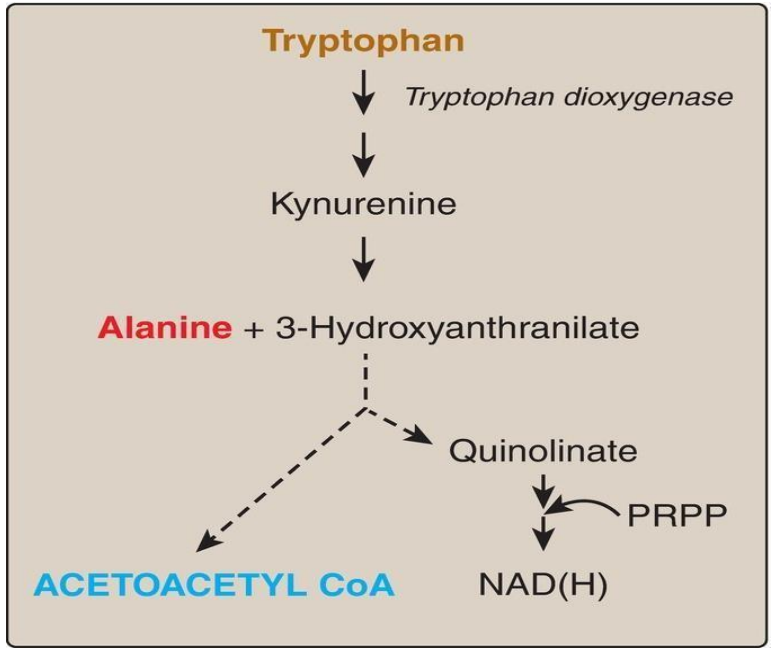
The output of this reaction are CO2 , NADH and the corresponding keto acid coupled to Co-A

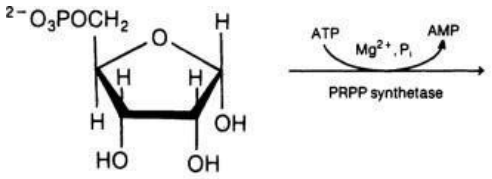




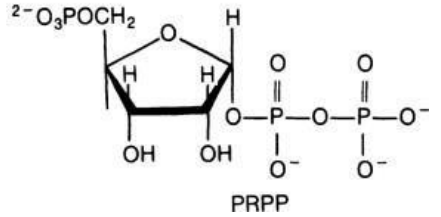
Catabolism to acetyl CoA or acetoacetyl CoA

- Tryptophan, leucine, isoleucine, and lysine form acetyl CoA or acetoacetyl CoA directly, without pyruvate serving as an intermediate
- Phenylalanine and tyrosine also give rise to acetoacetate
- Tryptophan: it produces alanine (glucogenic) and acetoacetyl CoA (ketogenic)
  - It produces Quinolinate which is used in the synthesis of NAD
  - NAD is called conditionally essential coenzyme, because it can be synthesized from Niacin (Vitamin B3) or it can be synthesized from Tryptophan in case of good Tryptophan input.
  - Niacin and Tryptophan are essential.





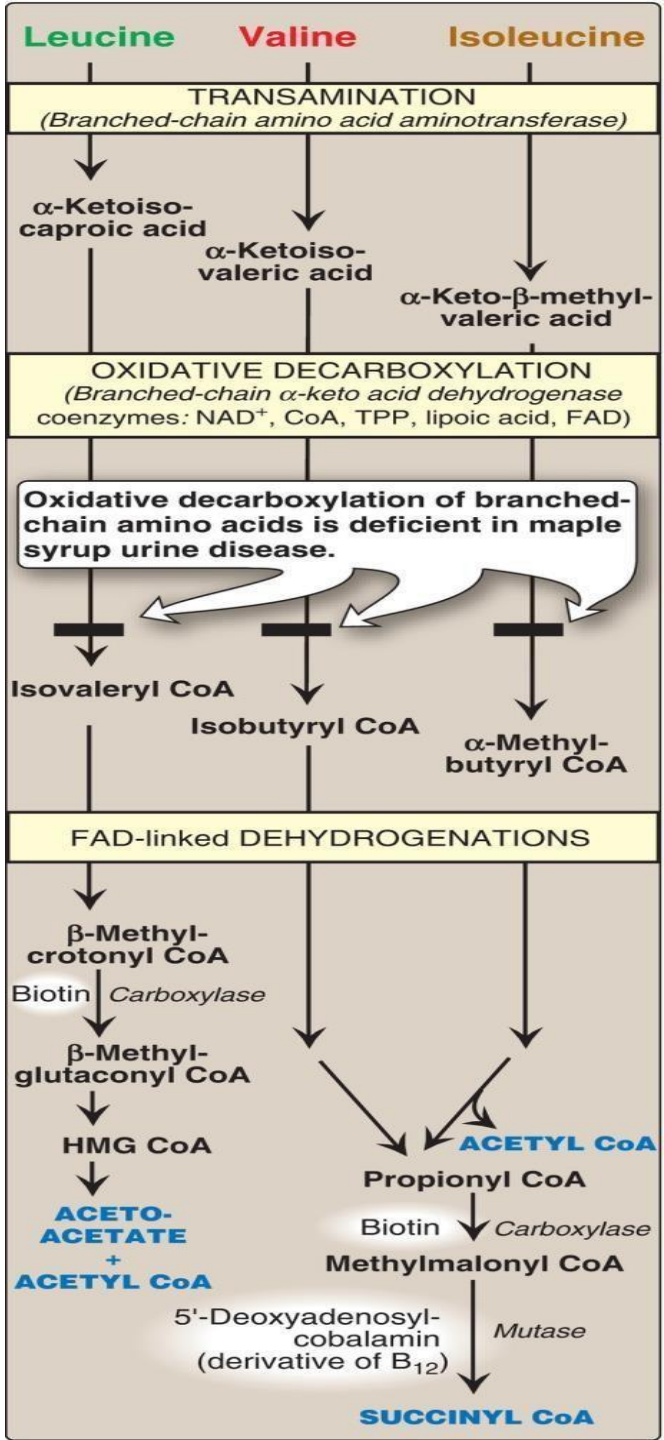
Ribose 5-phosphate



PRPP

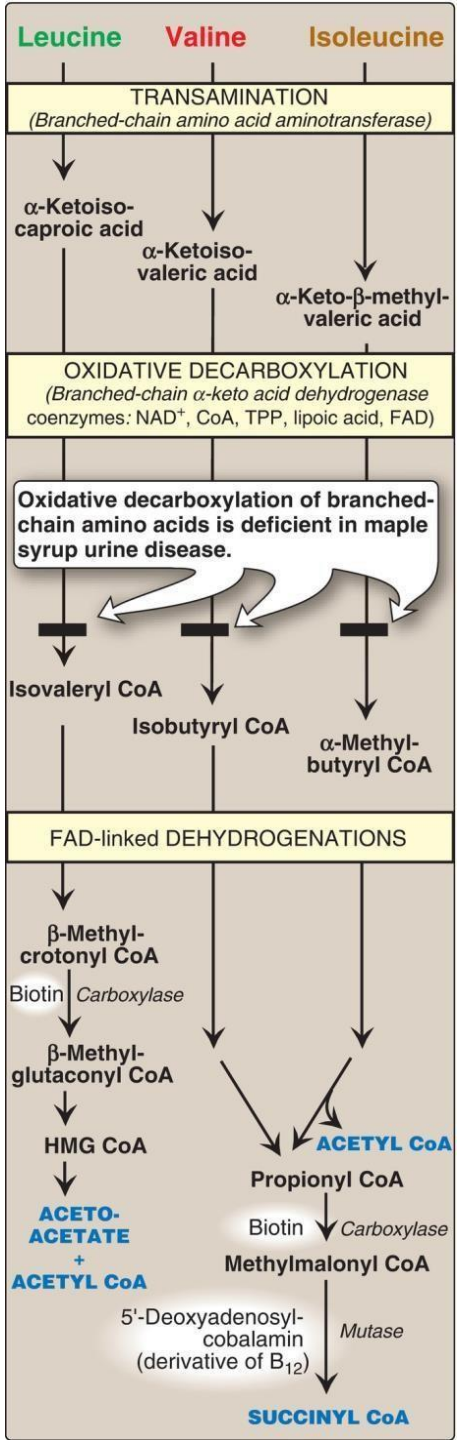
Catabolism to acetyl CoA or acetoacetyl CoA

- Leucine: exclusively ketogenic
- Isoleucine: both ketogenic and glucogenic
- Lysine:
  - Exclusively ketogenic
  - Neither of its amino groups undergoes transamination



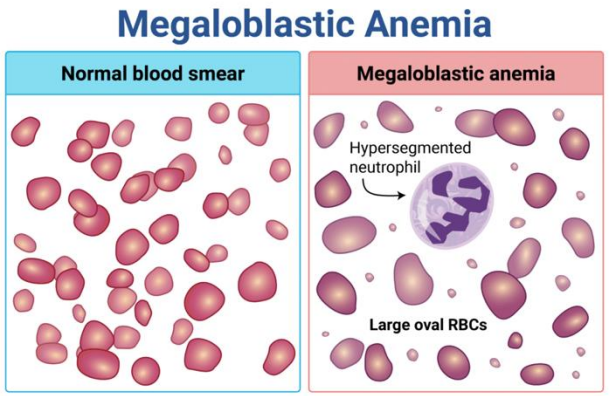
Branched-chain amino acid degradation

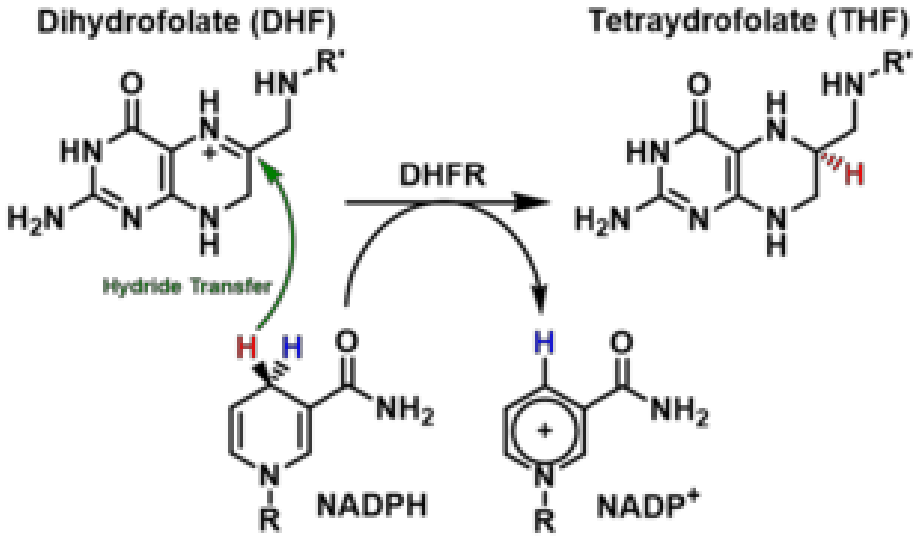
- BCAA are essential
- Particularly muscles
- Transamination (B6) branched-chain amino acid aminotransferase → Oxidative decarboxylation branched-chain α-keto acid dehydrogenase (BCKD) complex; E3 component is identical
- Produces unsaturated acyl CoA derivatives and $FADH_2$
- BCAA catabolism also results in glutamine and alanine being synthesized and sent out into the blood from muscle

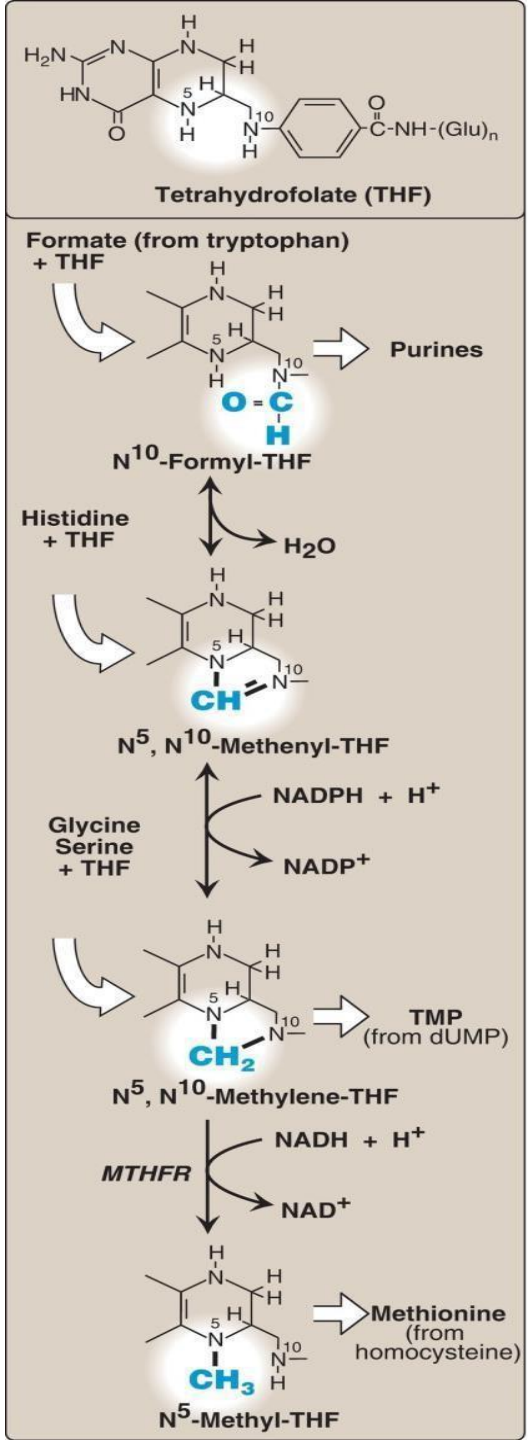


Folic acid and one-carbon metabolism

- Addition of single-carbon groups: formyl, methenyl, methylene, and methyl
- Carrier compounds such as THF and SAM
- THF, dihydrofolate reductase, (NADPH) (N5 or N10 or both)
- Folate deficiency presents as a megaloblastic anemia Bigger cells





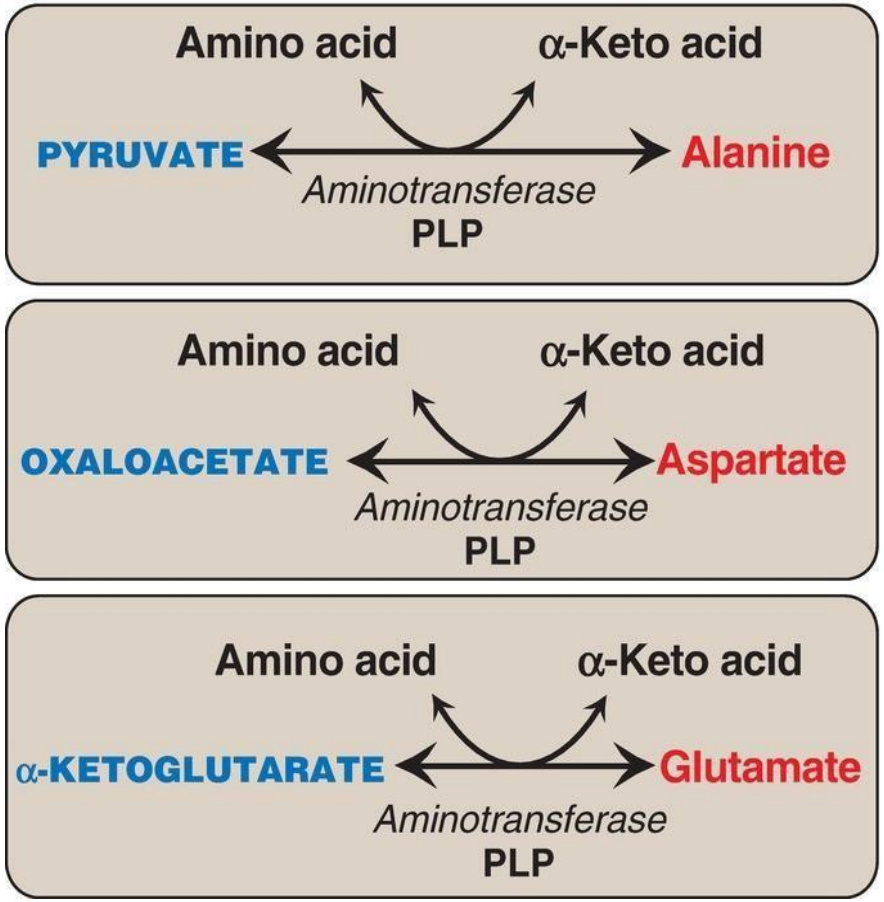


BIOSYNTHESIS OF NONESSENTIAL AMINO ACIDS

Can be synthesized inside our bodies

A. Synthesis from α-keto acids

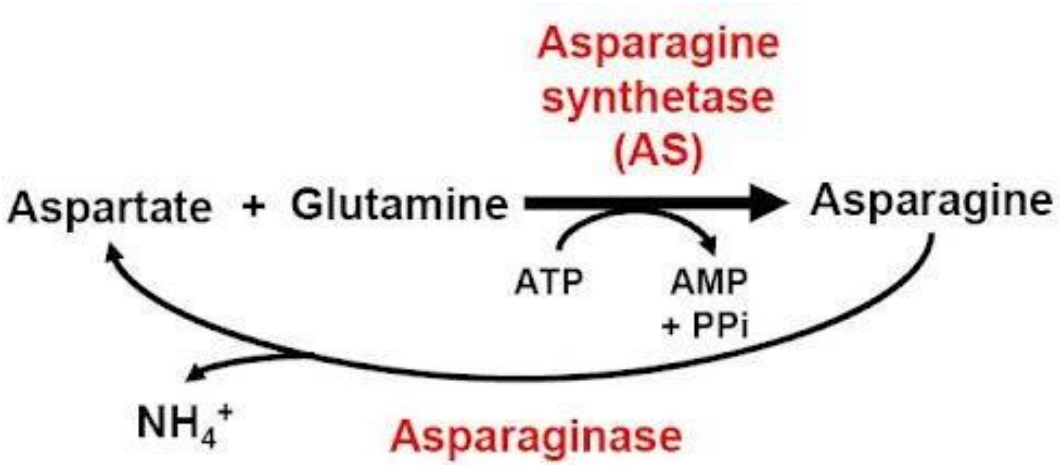
- Alanine, aspartate, and glutamate
- Transamination reactions
- Glutamate is unusual

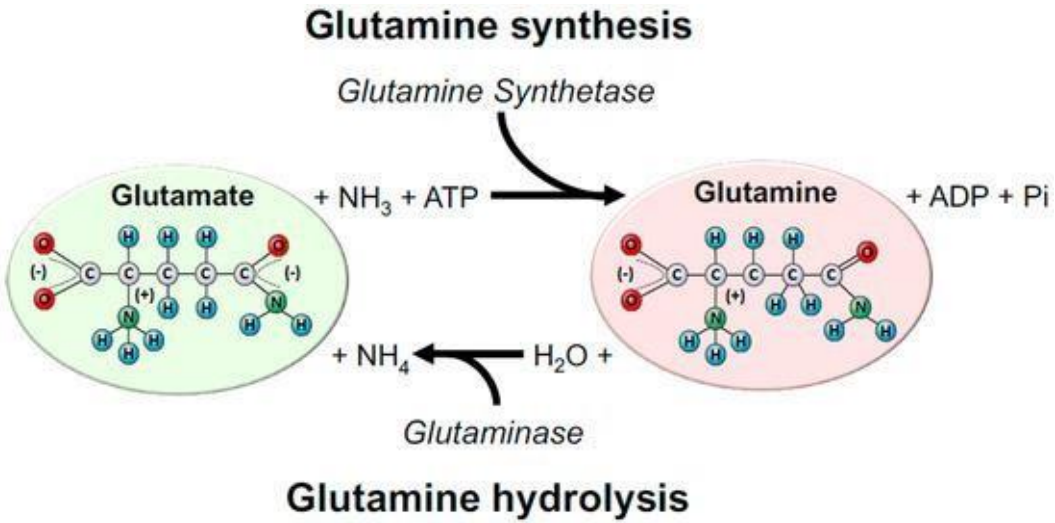


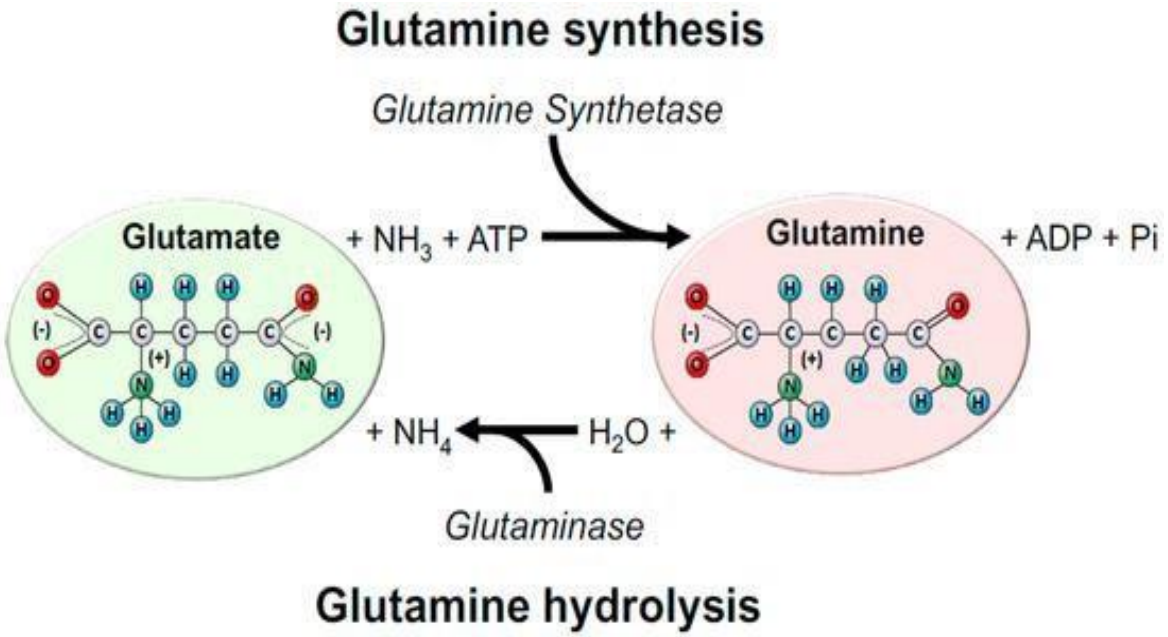
B. Synthesis by amidation

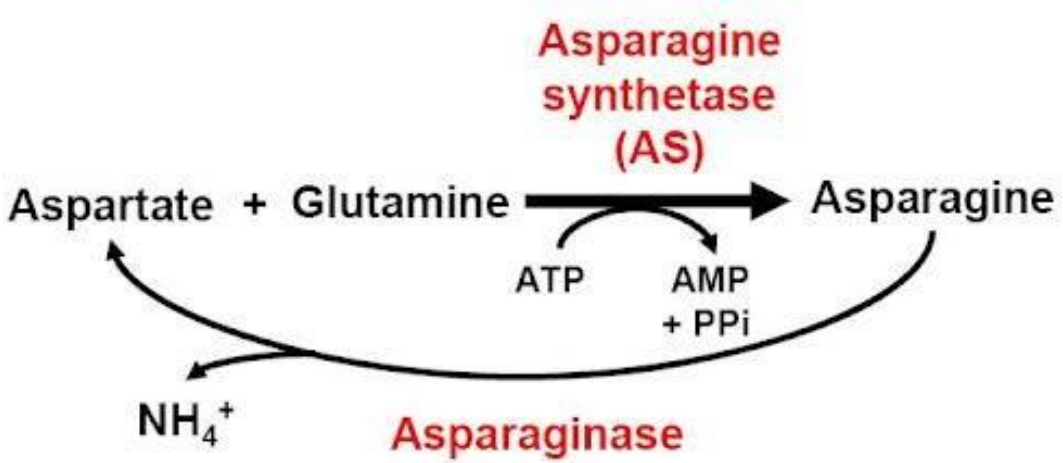
- Glutamine: glutamine synthetase; ATP, source?

- Asparagine: asparagine synthetase; glutamine; ATP, source?









Synthesis of glutamine is catalyzed by **glutamine synthetase** which requires ATP

It **can** fix free ammonia on glutamate

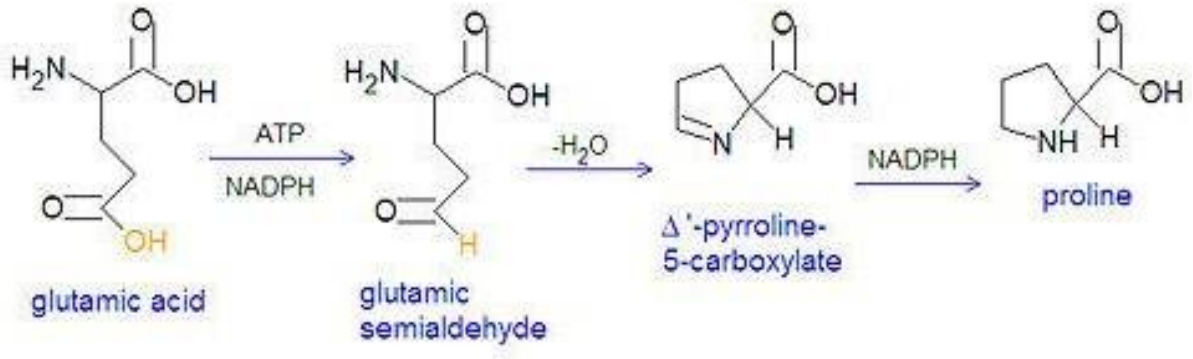
Synthesis of asparagine is catalyzed by **asparagine synthetase** which requires ATP

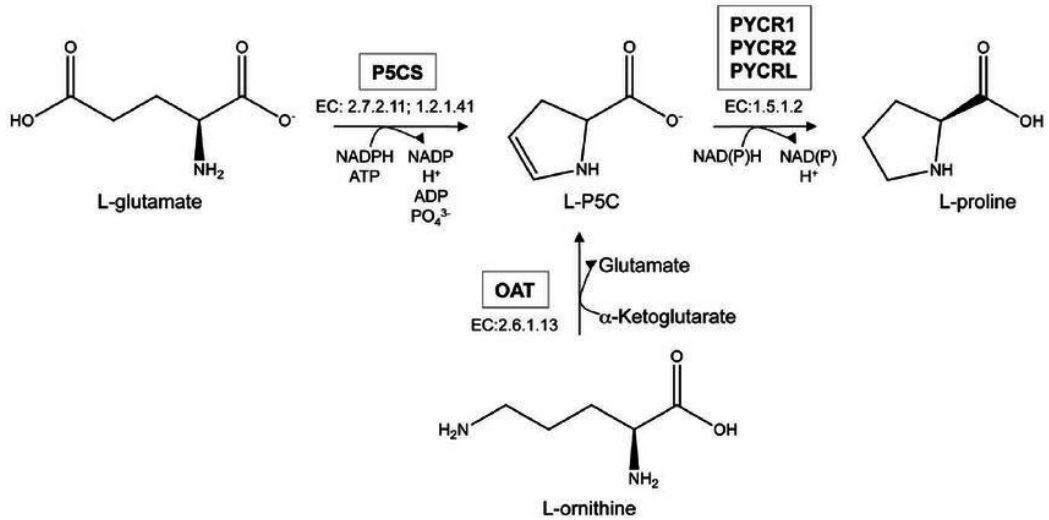
It **can't** fix free ammonia on glutamate from the solution, it gets the amino group from glutamine

C. Proline

- Glutamate via glutamate semialdehyde is converted to proline by cyclization and reduction reactions

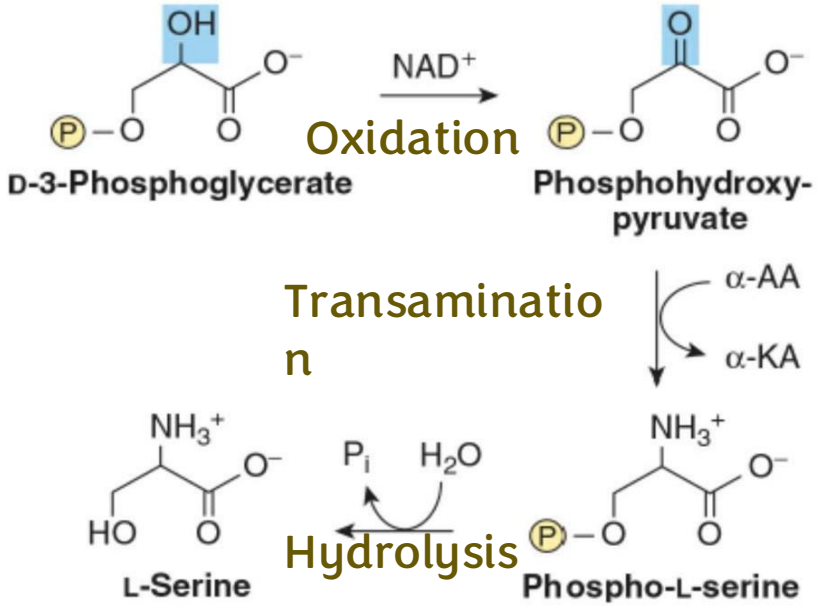
- The semialdehyde can also be transaminated to ornithine **which is related to glutamate**





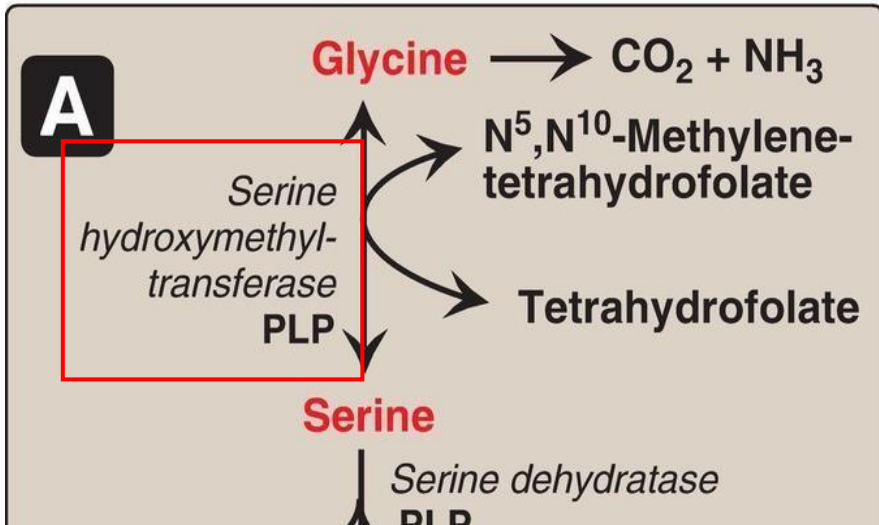
D. Ser, Gly, and Cys: The pathways of synthesis are interconnected

- Serine - 1: Glycolytic intermediate
  - 3-phosphoglycerate → 3-phosphopyruvate → 3-phosphoserine → Serine
  - Oxidation; transamination; hydrolysis



- Serine – 2:
  - From Gly; serine **hydroxymethyltransferase** using THF as the one-carbon donor

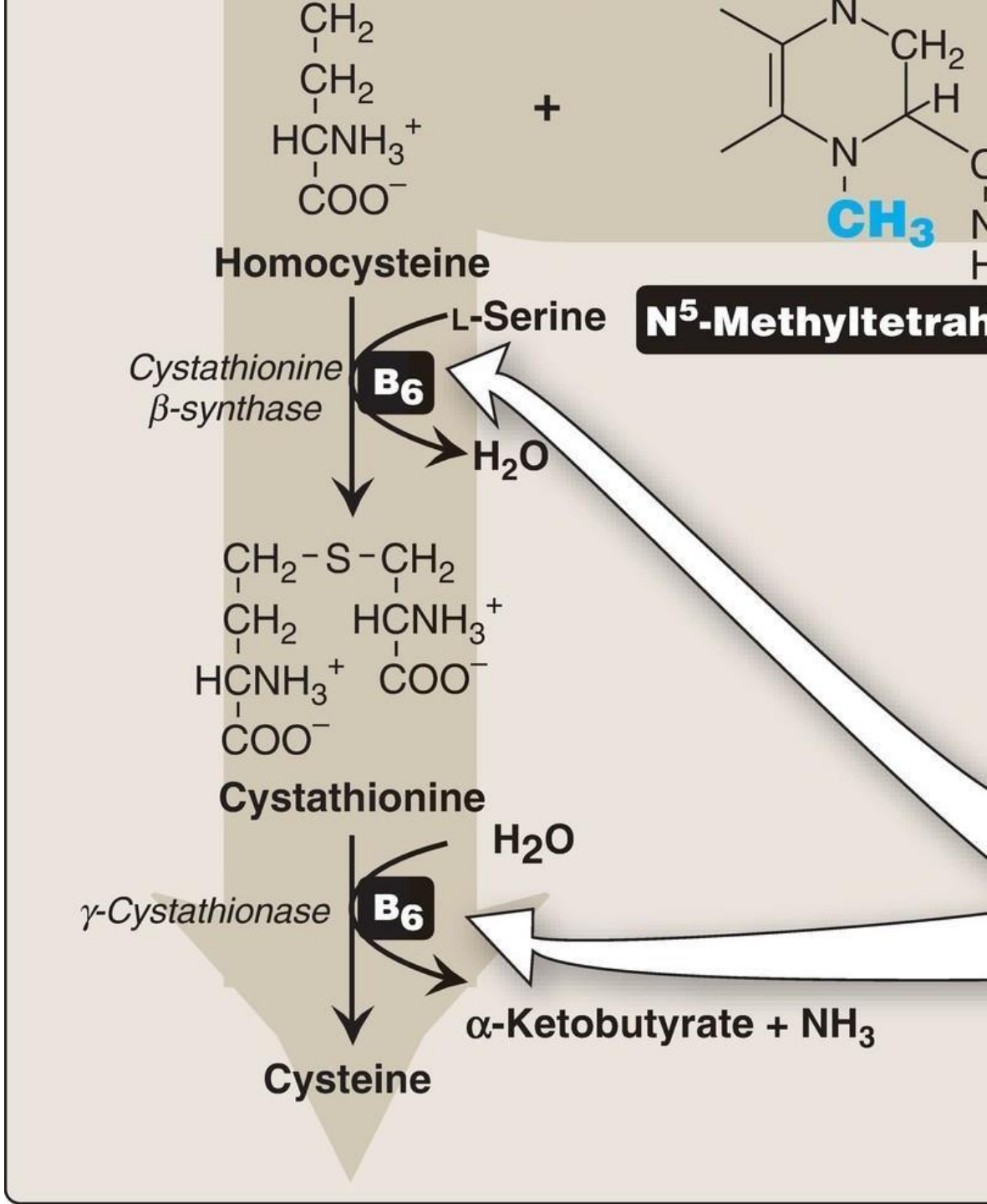
  Vitamin B9 dependent



D. Ser, Gly, and Cys: The pathways of synthesis are interconnected

- Glycine:
  - From serine by removal of a hydroxymethyl group, also by serine hydroxymethyltransferase
  - THF is the one-carbon acceptor

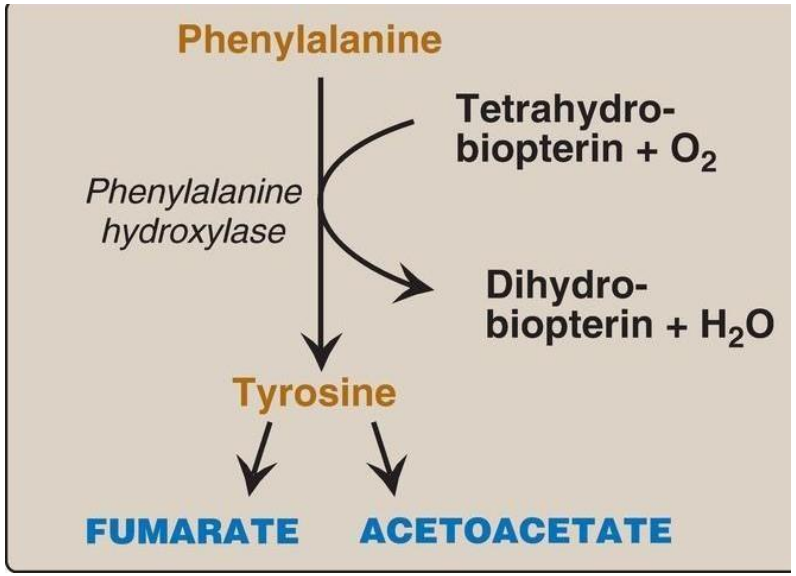
- Cysteine:
  - Hcy combines with serine, forming cystathionine
  - Hydrolysis to α-ketobutyrate and cysteine



E. Tyrosine

- Tyrosine is formed from <u>phenylalanine</u> by PAH
- Requires molecular oxygen and the coenzyme **tetrahydrobiopterin (BH_4)**, which is synthesized from guanosine **triphosphate** (GTP)
- One atom of molecular oxygen becomes the hydroxyl group of tyrosine, and the other atom is reduced to water
- BH_4 is oxidized to dihydrobiopterin (BH_2). BH_4 is regenerated from BH_2 by NADH-requiring **dihydropteridine reductase**
- Tyrosine, like cysteine, is conditionally essential

Phenylalanine
is Essential AA



Low level in tyrosine indicates a deficiency in one of these three:
Phenylalanine hydroxylase
Dihydropteridine reductase
In the coenzyme

Or it can be a deficiency from diet

Additional Resources:

رسالة من الفريق العلمي:

﴿ لَا يُكَلِّفُ اللَّهُ نَفْسًا إِلَّا وُسْعَهَا ﴾

Allah does not burden a soul beyond that it can bear

لا يَحدُث للإنسان شَيء إلا وقَد منحهُ الله القُدرة عَلى تَحمُله والصَبر عليه، فَهوَ يَعلَمُ كُلَ نَفسٍ وطاقتُها عَلى التَحمُل فَلا يُكَلِفُها فَوقَ طاقَتها، وهذهِ نِعمَةٌ ورَحمَةٌ رَبانية كَبيرَة أَن كُل ما في حَياتنا نَحنُ قادرينَ عَليه سِواءً كانَ مَرضًا أو هَمًا أو ظَرفًا صَعب.

Nothing happens to a person except that Allah has already granted them the strength to bear it and be patient with it. He knows every soul and its capacity for endurance, and He does not burden it beyond its ability. This is a great divine blessing and mercy — that everything in our lives, whether it be illness, sorrow, or hardship, we are capable of enduring

For any feedback, scan the code or click on i

- Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			