DOCTOR 2020 | JU

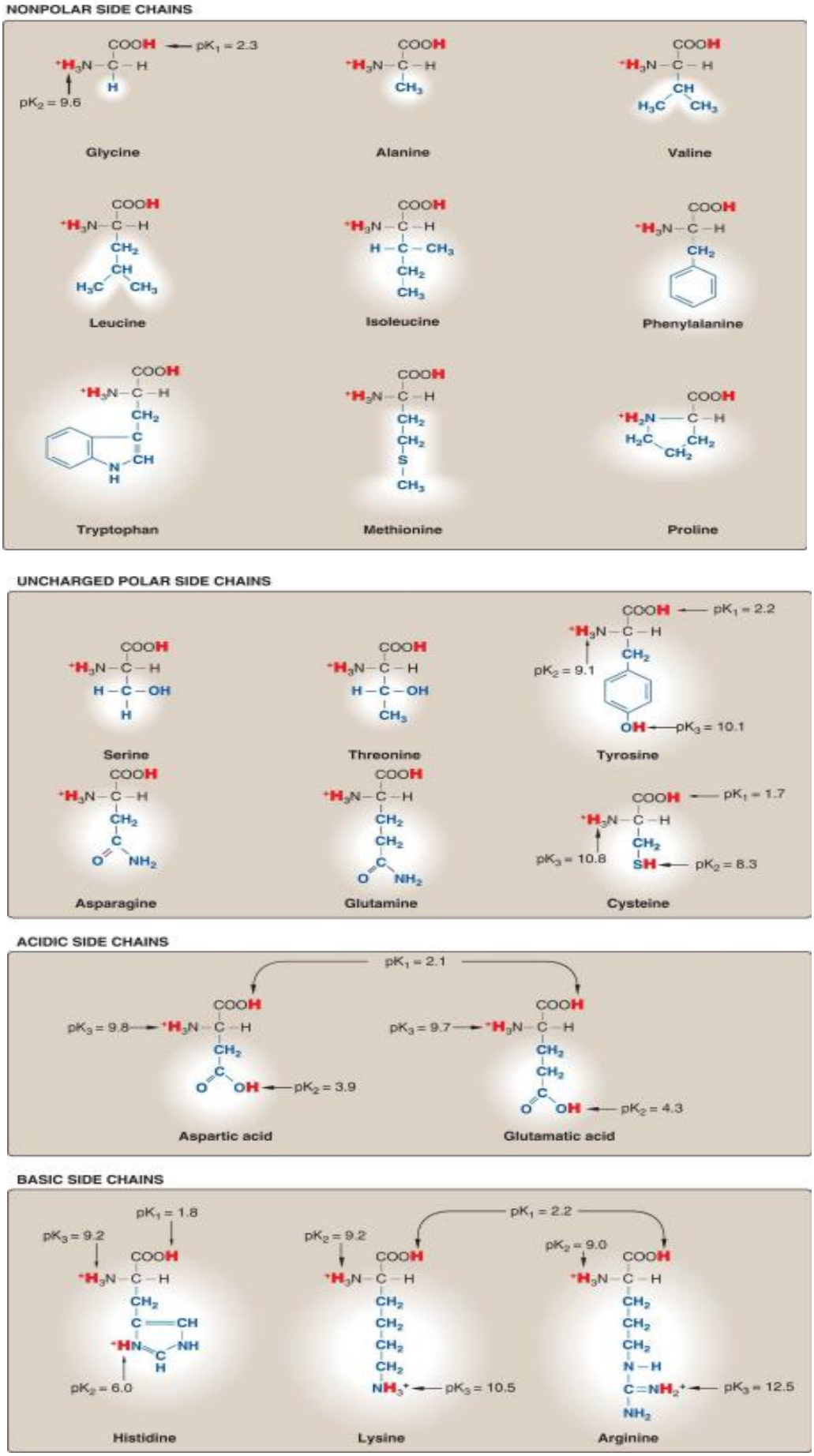
METABOLISM

WRITER : Mosaab Alhuniti

CORRECTOR : Ali Almahrook

DOCTOR: Diala Abu-Hassan

It is good for you to memorize the amino acids structures to make it easy for you in this lecture.



Amino Acid Carbon Skeleton Degradation

Last time we discussed urea cycle in which the amino groups that are released in the form of ammonia are converted to urea that is less toxic, so can be excreted by urine.

The common structure between AA that is going to be metabolised in common pathways is the amino group, the rest of the molecule (the carbon skeleton of amino acid) go to several pathways depending on the R group.

	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

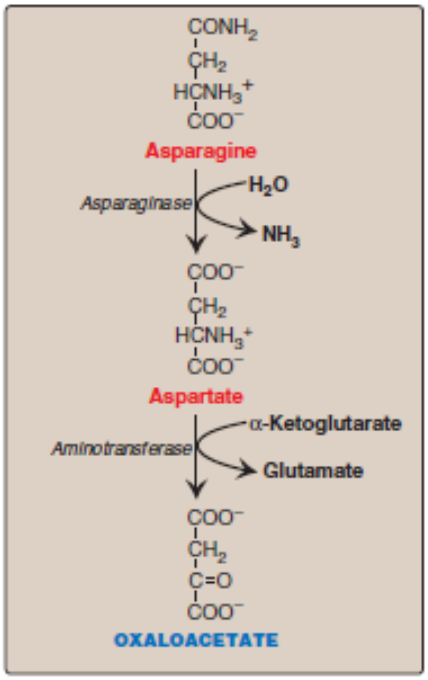
We divided the amino acids depending on the type of final product they produce. If they produce kerbs cycle intermediate (oxaloacetate, α-ketoglutarate, succinylcoA, pyruvate, etc…) these can be used as precursors of gluconeogenesis, that is why these amino acids considered **glucogenic** and amino acids produce acetylcoA, acetoacetylcoA, these can act as precursors of ketogenesis that's why they considered as **ketogenic.** Small number can be both meaning that they go multible pathways producing sevsral products.

1.Amino acids that form oxaloacetate

We already know that aspartate can be transaminated to produce oxaloacetate by the action of enzyme **AST**.

Asparagine is very close in structure to **aspartate**, having an extra amino group so it's an amide functional group in the R chain, but aspartate has carboxyl group. So if I remove the amino group by **asparaginase** enzyme through **hydrolysis** reaction (we add H_2O molecule to release ammonia from asparagen producing aspartate), then it can be **transaminated** to oxaloacetate.

So I consider asparagine and aspartate as amino acids that can produce oxaloacetate.



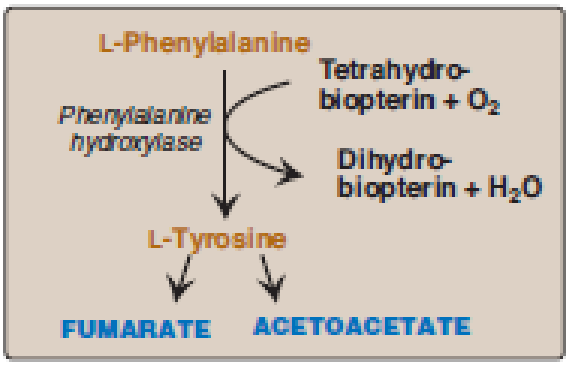
2. Amino acids that form α-ketoglutarate via glutamate

(Glutamine, Proline, Arginine, Histidine) these can be converted to glutamate then will be deaminated to produce α-ketoglutarate.

Glutamine structure is close to glutamate (same as asparagine and aspartate), hydrolysis of glutamine to glutamate then deamination to α-ketoglutarate.

Histidine has imidazole ring in the R chain, so it has to open the ring during this degredative pathway. Same thing in **proline**, which has a ring between R chain and amino group.

3. Amino acids that form fumarate



Tyrosine has a benzene ring and OH group in its R chain, so it goes multiple pathways, and because it considered ketogenic and glucogeinc, producing acetoacetate (form of ketone bodies) or producing fumarate in the other pathway.

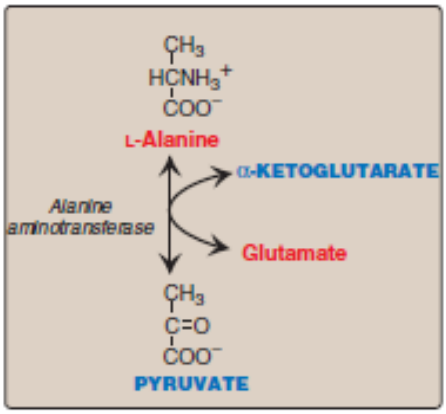
Phenylalanine can be hydroxylated to tyrosine (+OH) by the action of **phenylalanine hydroxylase** enzyme, so the degradation process of phenylalanine is the synthetic process of Tyrosine. So phenylalanine considered as amino acid that produces fumarate, in conclusion **Phenylalanine and Tyrosine are both glucogenic and ketogenic**.

Phenylalanine hydroxylase enzyme uses co-enzyme called **BH4 (tetrahydrobiopterin)** having 4 hydrogens that become during the reaction **BH2(dihydrobiopterin)** having two hydrogens.

The metabolism of tyrosine as well as phenylalanine is very important and connect to several diseases, the phenylalanine hydroxylase is mutated as an enzyme in a disease called **phenylketonuria PKU**, one of the most common genetic diseases that affect amino acids metabolism.

Tyrosine metabolism is also connected to other diseases like **albinism** and **alkaptonuria** (rare disease but it's found in Jordan, it was misdiagnosed for a long time and recently in few years was properly diagnosed and took a special care) we will talk about it later…

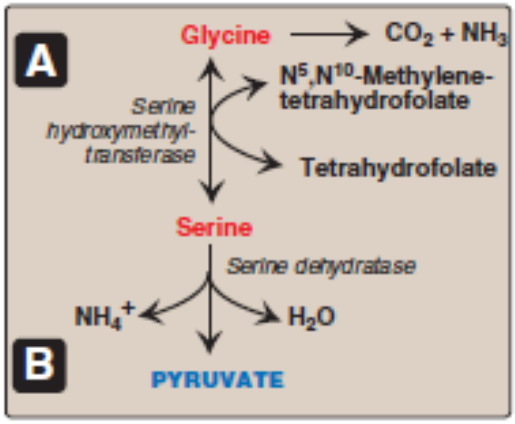
4. Amino acids that form pyruvate



1. Alanine: We know that alanine is transaminated to pyruvate by the action of the enzyme **alanine aminotransferase (ALT)**, and with the production of glutamate by the amination of α-ketoglutarate.

2. Serine (alanine +OH): and you can think that when I remove amino group and hydroxyl group I will have production of pyruvate, and this process done by the action of enzyme **serine dehydratase**.

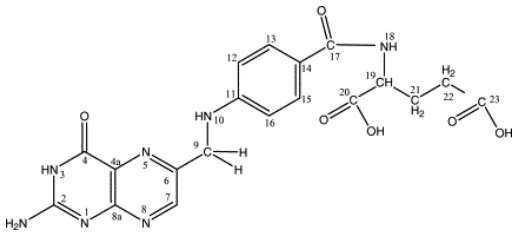
3. Glycine: the simplest amino acid has only H in its R chain, so it can go through degradative oxidation pathway converting it directly to CO_2 and NH_3.



It can also be converted to serine and then to pyruvate. So glycine will get methylated and hydroxylated to convert it to serine (addition of CH3 and OH), and the enzyme used is **serine hydroxymethyltransferase.**

But what is the source of the carbon atom?

We have different forms to transfer single carbon unit (methyl group, carboxyl group), and the main donor of carbon atoms in different reaction in the body is the methyltransferase called **SAM (S-adenosylmethionene)** mainly transfer the carbon in the form of methyl (CH3).



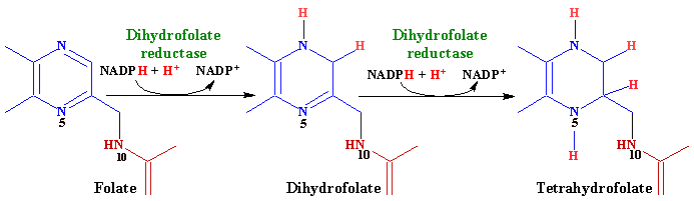
Another source is **folic acid (vitamin B9),** obtained mostly from vegetables and it's important for fertility of the women. And during pregnancy; if the mother has deficiency of folic acid, it results in severe formats of malformations and congenital abnormalities (like; spina bifida), and may lead to abortion. So its important to supply the pregnant with folic acid.

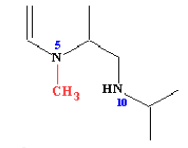
The important of folic acid that it is involved in the neuronal development and co-factor for many reactions, **it transfers single carbon units in different formats** (methyl, formyl C=O, methylene, methenyl).

Folic acid/folate needs to be **activated** by **reduction**, addition of 4H and become tetrahydrofolate(active) now it is ready to carry single carbon unit on two locations (5N, 10N) carrying the carbon units on any of them or both.

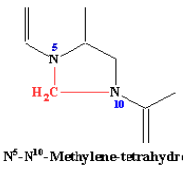
So, we get single carbon unit transtering it from **N^5, N^{10}tetrahydrofolate** and become **tetrahydrofolate,** donating it to glycine through the reaction mentioned above.

*These pictures are not included in our material, but I added it to clarify what doctor explained about folic acid activation.

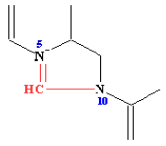




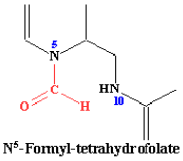
N^5-Methyl-tetrahydrofolate carries methyl groups



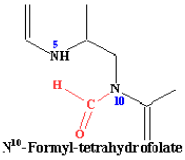
N^5-N^{10}-Methylene-tetrahydrofolate carries methylene groups



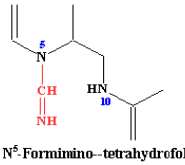
N^5-N^{10}-Methenyl-tetrahydrofolate carries methenyl groups



N^5-Formyl-tetrahydrofolate carries formyl groups

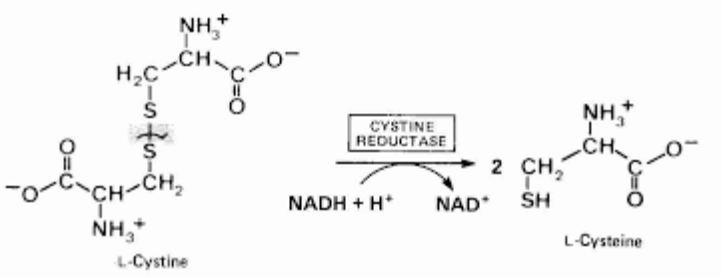


N^{10}-Formyl-tetrahydrofolate carries formyl groups



N^5-Formimino--tetrahydrofolate carries methenyl groups

4. Cysteine: in most cases makes disulfide bridges(oxidiesed) in the form of **cystine**, and we need to reduct it to cysteine, then **desulferation** of cysteine yields **pyruvate**.



Notice the NADH + H^+ act as a reductant.

5. Theronine: has an OH group so its metabolism is similar to serine metabolism, but the larger structure of the R group means more steps and allows it to go into different pathways producing different products.

So, first we can remove OH group and extra carbons and amine group to produce **pyruvate**, the other way is to convert it to α-ketobutyarate and then **succinyl CoA**.

5. Amino acids that form succinyl CoA

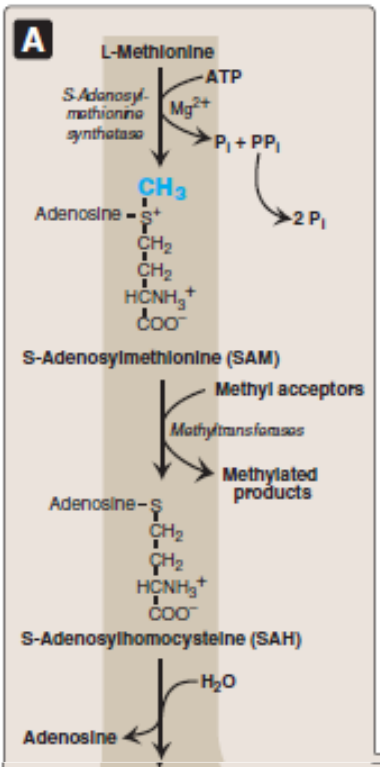
1. **Theronine** We talked about it above and it dehydrated to α-ketobutyrate, which is converted to propionyl CoA and then to succinyl CoA. It can also be converted to pyruvate.
2. **Valine and isoleucine** non-polar branched-chain amino acids, they generate propionyl CoA that is converted to succinyl CoA **by biotin- and vitamin B12–requiring reactions.**
3. **Methionine** it has sulfur atom between carbons so its non-polar amino acid, it is used as the first amino acid in translation whether it's part of protein structure or removed after that, and it is essential amino acid and must be sufficient.

Methionine is converted to SAM, the major methyl-group donor in one-carbon metabolism.

Methionine metabolism

1-Synthesis of SAM S-adenocylmethionine (a high-energy compound that has no phosphate) requires energy (ATP). Methionine should be connected with nucleoside adenosine from the sulfer atom by the action of **adonosyl methionine synthetase** (need ATP) enzyme.

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 in the methyl acceptor by **methyl transferase enzyme** (irreversible because of free energy loss), and SAM becomes homocysteine SAH (similar to cystiene).



***Homocysteine** is important molecule in the pathway makes a branching point in the process, and its accumulation in the blood is connected with several diseases especially cardiovascular diseases.

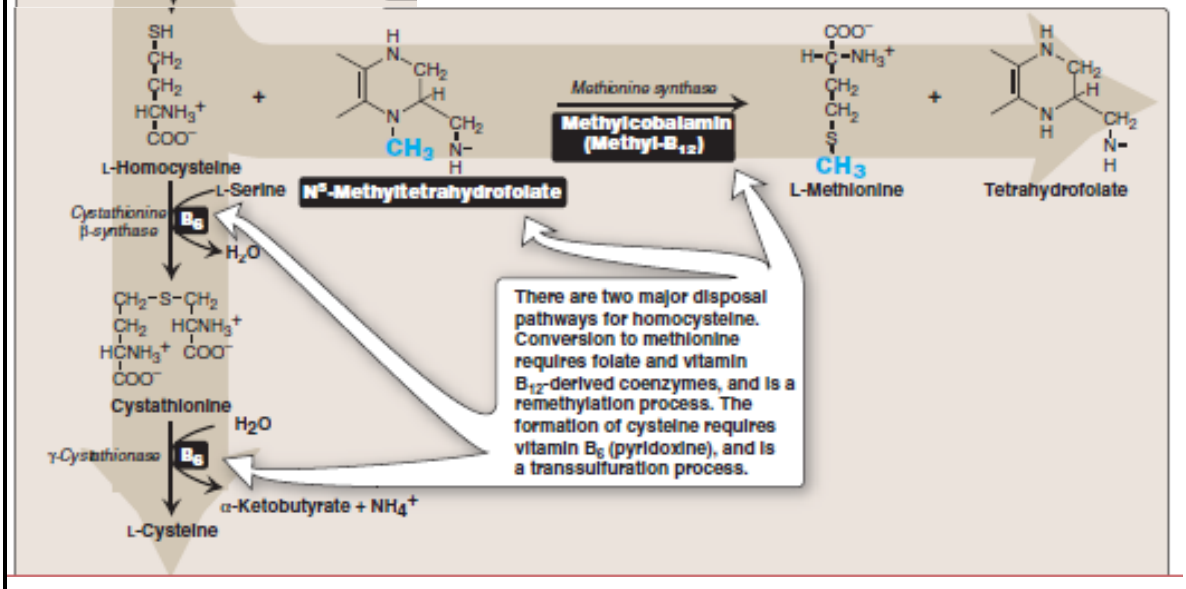
3-Hydrolysis of SAH to homocysteine and adenosine.

Homocysteine has two choices; either it gets the methyl group back to methionine, from N^5-methyltetrahydrofolate(vitamin B9), and this reaction catalyzed by **methionine synthase**. In addition, it needs another co-enzyme; vitamin B12. (It's regeneration pathway not synthetic pathway).

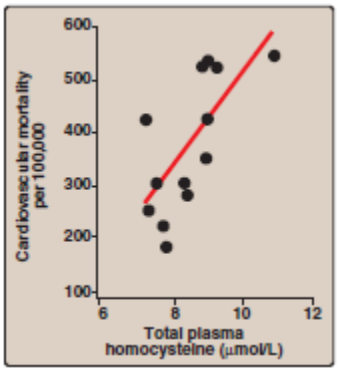
Another choice is to proceed cysteine amino acid; by interacting with serine (dehydroxylated), producing **cystothionine**, catalyzed by **cystotionine β synthase** with vitamin B6 as a co-enzyme.

Then serine releases from the molecule with the sulfur atom in the form of **cysteine**, and also producing α-ketobutyarate and ammonia.

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



Clinical hint: Homocysteine



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

Homocysteine accumulation is related to higher mortality in cardiovascular diseases, caused by either enzyme deficiency or vitamin deficiency (**Homocysteine levels are inversely related to levels of folate, B12, and B6**) and increases the incidence of neural tube defects (improper closure, as in spina bifida) in the fetus.

We can improve the situation by supplementation of vitamins B12, B6, B9(folate), and there are many diseases related with elevated homocystiene under studies.

6+7. Amino acids that form acetyl CoA or acetoacetyl CoA (ketogenic aa)

Phe and Tyr produce acetoacetate during their catabolism.

Leucine is exclusively ketogenic (acetoacetate and acetyl CoA).

Isoleucine is both ketogenic & glucogenic (acetyl CoA, acetoacetyl CoA and succinyl CoA).

Lysine is an exclusively ketogenic (acetyl CoA and acetoacetyl CoA).

Tryptophan has the largest R chain so, has multiple pathways and it is both glucogenic and ketogenic (acetyl CoA and acetoacetyl CoA).

Branched chain amino-acids (Leu, Val, Ile)

• Essential amino acids

• Important for the synthesis of neurotransmitter; excitatory glutamate and inhibitory gamma-aminobutyric acid (GABA) synthesized by glutamate.

• In contrast to other amino acids, they are metabolized primarily by the peripheral tissues (particularly muscle), rather than other amino acid that are mostly by the liver.

• Are metabolized by a similar route of metabolism; Transamination, and **their difference from other amino acids** that they undergo oxidative decarboxylation, dehydrogenation and then product formation.

Amino Acid Synthesis

We already discussed some synthetic processes during degradation pathways of amino acids. Note that we have only **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.

We know that phenylalanine is hydroxylated to tyrosine, and hydroxymethylation of glycine produces serine.

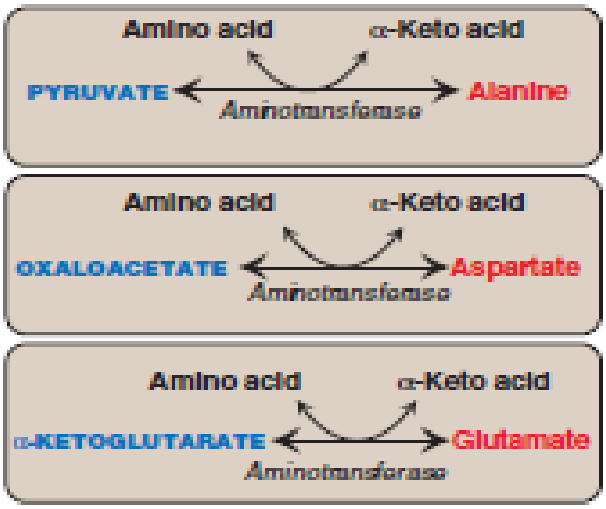
Nonessential amino acids are synthesized from:

1. Metabolic intermediates (mostly).

2. from the essential amino acids.

Synthesis from α-keto acids

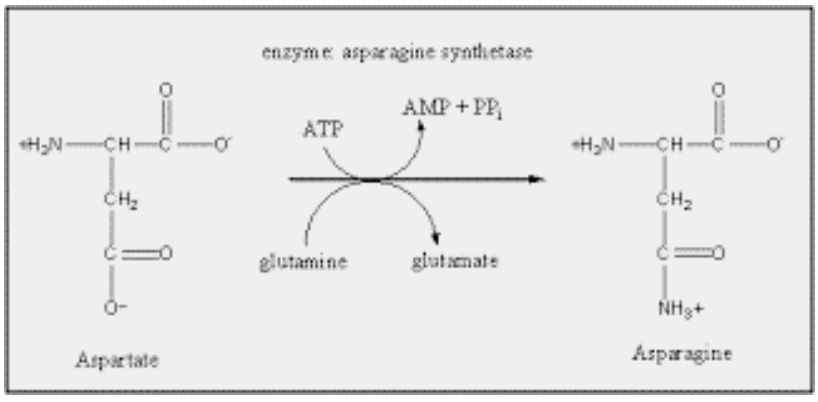
We can synthesize amino acids from their α-keto acids by reversing transamination reactions, (AST,ALT, glutamate dehydrogenase).

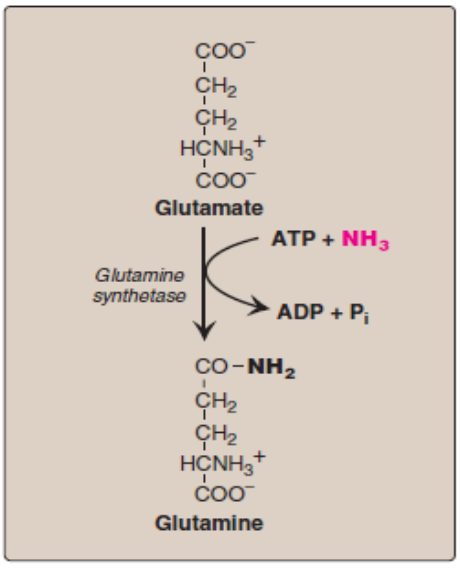


Synthesis by amidation

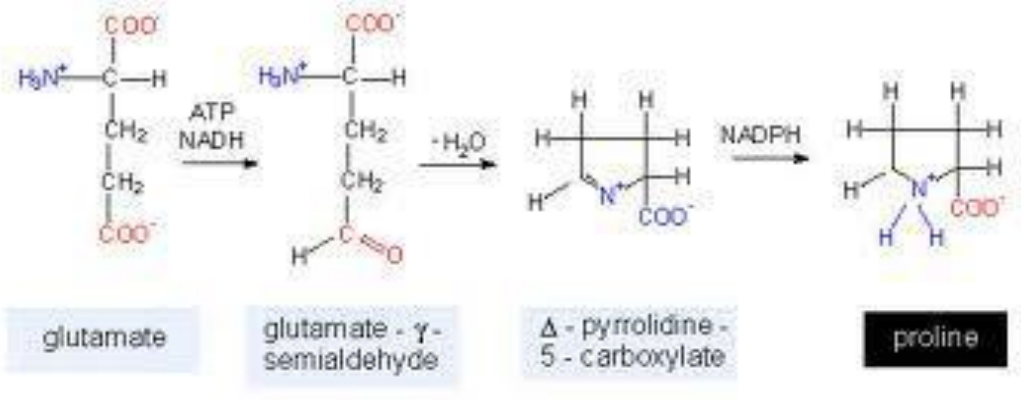
1. **Gln** formed from Glu by **glutamine synthetase.**

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





Proline



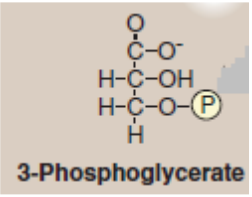
The proilne AA is metabolized to produce α-ketoglutarate via glutamate, so I can use glutamate to synthesize proline (reverse reaction).

Proline have a ring structure connected to amino group in the backbone.

So, we start of removing carboxyl group by reduction to aldehyde to become glutamate semialdehyde, then by dehydration we remove the oxygen atom, and connect the R group with the aminogroup in the backbone, and finally reduced to proline**. (so the reaction is cyclation and reduction).**

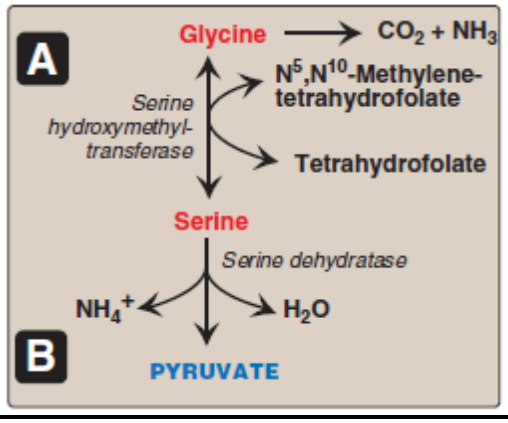
Serine and glycine

Serine arises **from 3-phosphoglycerate** (glycolytic intermediate) that is oxidized to 3-phosphopyruvate, and then transaminated to 3-phosphoserine. Serine is formed by hydrolysis of the phosphate ester.

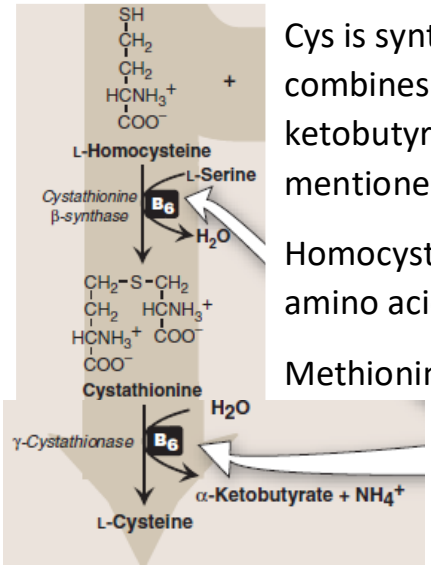


Serine can also be formed from glycine through transfer of a hydroxymethyl group by **serine hydroxymethyl transferase** (N5, N10-methylene- THF is the one carbon donor).

Glycine is synthesized from serine by removal of a hydroxymethyl group, also by **serine hydroxymethyl transferase** (THF is the one carbon acceptor removed from serine).



Cysteine



Cys is synthesized by two consecutive reactions in which homo cysteine combines with serine, forming cystathionine that is hydrolyzed to α-ketobutyrate and Cys (vitamin B is needed) remember enzymes that are mentioned in methionine metabolism.

Homocysteine is derived from Methionine, Because Met is an essential amino acid, Cys can be synthesized the Met dietary intake is adequate.

Methionine is essential but Cys in non-essential (we can produce it).

Tyrosine

Tyr (non essential AA) is formed from Phe (essential AA) by phenylalanine hydroxylase. The reaction requires molecular oxygen and the coenzyme **tetrahydrobiopterin (BH4)**.

BH4 is oxidized to dihydrobiopterin (BH2).

BH4 is regenerated from BH2 by the enzyme **<u>NADH-requiring dihydropteridine reductase</u>**.