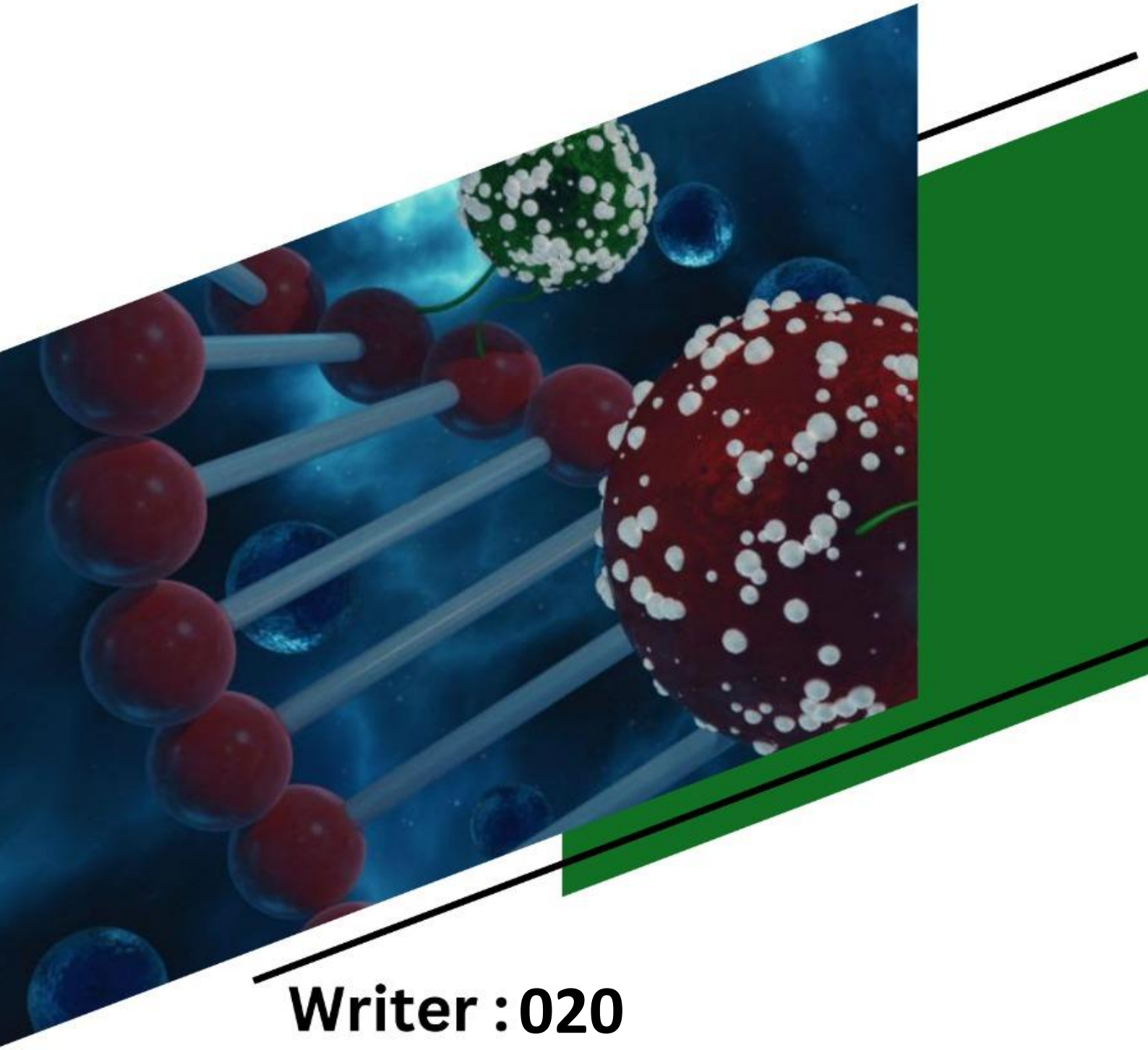
Doctor 021

METABOLISM

Sheet no. 29



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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 metabolized 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.

Seven intermediates are produced during AA catabolism (oxaloacetate, pyruvate, α-ketoglutarate, fumarate, succinyl coenzyme A (CoA), acetyl CoA, and acetoacetate).

We divided the amino acids depending on the type of final product they produce:

1-Glucogenic amino acids catabolism yields pyruvate or one of the TCA cycle intermediates that can be used as substrates for gluconeogenesis in the liver and kidney.

If they produce Krebs cycle intermediate (oxaloacetate, α-ketoglutarate, succinylcoA, pyruvate, etc**…**) these can be used as precursors of gluconeogenesis(sometimes they undergo more than one pathway but the final products are a Krebs cycle intermediates or pyruvate therefore they still glucogenic amino acids), that is why these amino acids considered glucogenic .

2-Ketogenic amino acids catabolism yields either acetoacetate (a type of ketone bodies) or one of its precursors (acetyl CoA or acetoacetyl CoA).

amino acids produce acetylcoA, acetoacetylcoA, these can act as precursors of ketogenesis that's why they considered as ketogenic.

Other ketone bodies are 3-hydroxybutyrate and acetone

3- Small number can be both meaning that they go multible pathways producing several products.

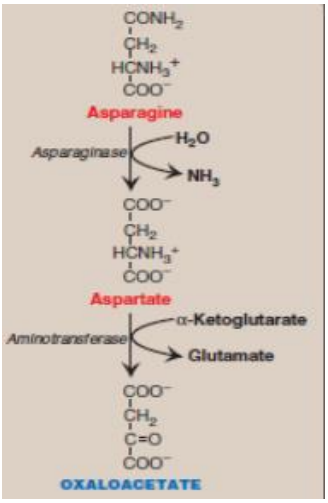
	Glucogenic	Glucogenic and Ketogenic	Ketogenic
Nonessential	Alanine Arginine Asparagine Aspartate Cysteine Glutamate Glutamine Glycine Proline Serine	Tyrosine	
Essential	Histidine Methionine Threonine Valine	Isoleucine Phenyl-alanine Tryptophan	Leucine Lysine

1. Amino acids that form oxaloacetate

We already know that aspartate can be transaminated to produce oxaloacetate by the action of enzyme AST(aspartate aminotransferase)

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 H2O 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 degradative 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 glucogenic, producing acetoacetate (form of ketone bodies) or producing fumarate in the other pathway.

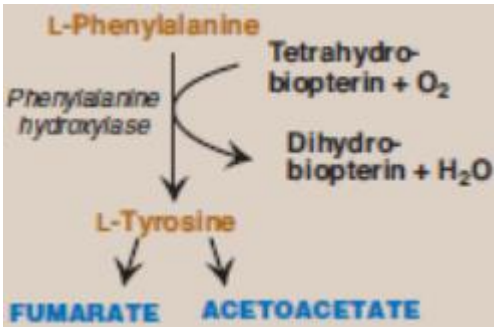
Phenylalanine can be hydroxylated to tyrosine (+OH) by the action of phenylalanine hydroxylase enzyme, so the degradation process of phenylalanine is the synthetic process of Tyrosine. So phenylalanine considered as amino acid that produces fumarate, in conclusion **Phenylalanine and Tyrosine are both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

Inherited deficiencies in the enzymes that metabolize Phe and Tyr lead to phenylketonuria, alkaptonuria and albinism.

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.

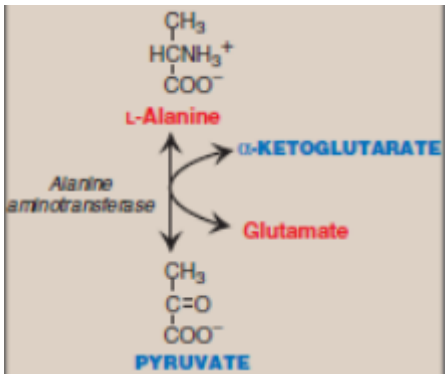
Tyrosine metabolism is also connected to other diseases like **albinism** and **alkaptonuria** (rare disease but it's found in Jordan, it was misdiagnosed for a long time and recently in few years was properly diagnosed and took a special care) we will talk about it later…



3. Amino acids that form pyruvate

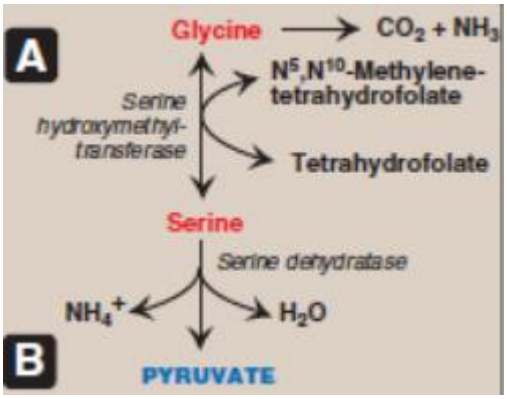
1. Alanine: We know that alanine is transaminated to pyruvate by the action of the enzyme alanine aminotransferase (ALT), and with the production of glutamate by the amination of α-ketoglutarate.

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 CO2 and NH3(simple molecules, not degraded). 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).

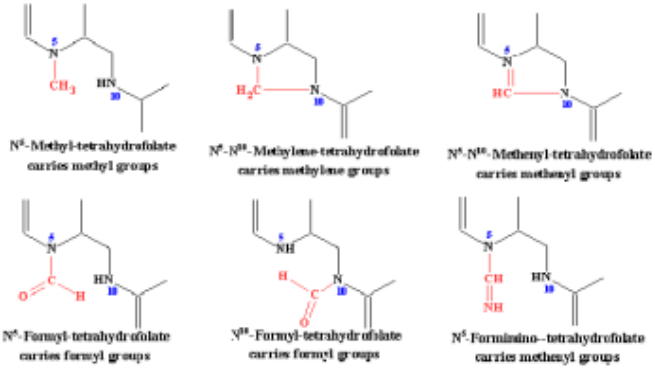
Another source is **folic acid (vitamin B9),** obtained mostly from leaf vegetables(leafy greens) and it's important for fertility of the women. And during pregnancy; if the mother has deficiency of folic acid, it results in severe formats of malformations and congenital abnormalities (like; spina bifida), 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).

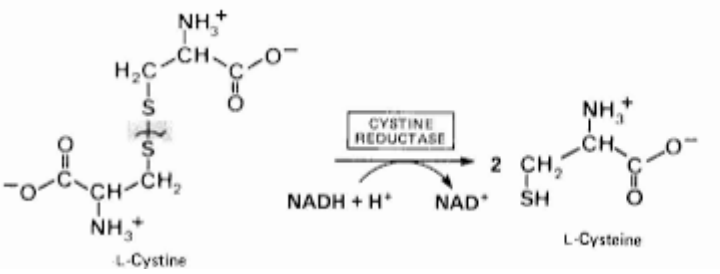
Folic acid/folate needs to be **activated** by **reduction**, addition of 4H and become tetrahydrofolate(active) now it is ready to carry single carbon unit (Carbon pieces have one carbon can be transferred during reaction)on two locations (5N, 10N) carrying the carbon units on any of them or both.

So, we get single carbon unit transferring it from **N5 , N10tetrahydrofolate** (in the form of methylene)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.



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



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

4. **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 (a TCA cycle intermediate and glucogenic compound)

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, we have to focus on methionine because :

1- it is used as the first amino acid in translation whether it's part of protein structure or removed after that.

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

it is essential amino acid and must be sufficient.

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 (nitrogenous base with a five-carbon sugar) from the sulfur atom by the action of adenosyl methionine synthetase (need ATP) enzyme, so now is used in methylation reactions.

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

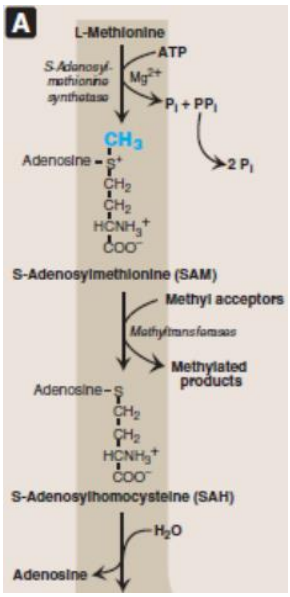
methionine synthase. In addition, it needs another co-enzyme; vitamin B12. (It's regeneration pathway not synthetic pathway).

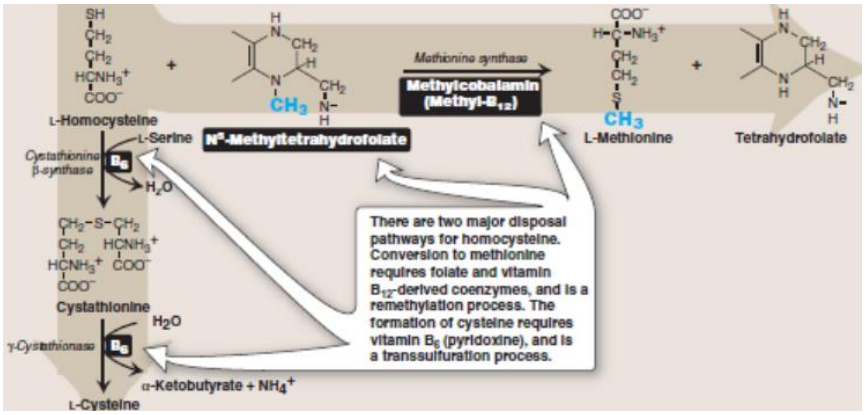
Another choice is to proceed cysteine amino acid; by interacting with serine (dehydroxylated), catalyzed by cystotionine β synthase with vitamin B6 as a co-enzyme, producing cystothionine,

NOTE: the degradation of methionine is associated with the synthesis of cysteine, in other words the degradative pathway of methionine is also synthetic pathway for cysteine .

Then serine releases by hydrolysis reaction(+H2O) from the molecule with the sulfur atom in the form of cysteine, and also producing α-ketobutyarate and ammonium.

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





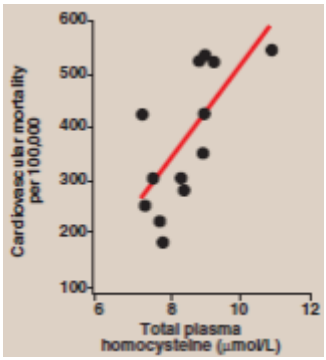
Clinical hint: Homocysteine and vascular disease

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)**

Elevated homocysteine or decreased folic acid levels during pregnancy 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

1-Phe and Tyr produce acetoacetate during their catabolism.

2-Leucine is exclusively ketogenic (acetoacetate and acetyl CoA).

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

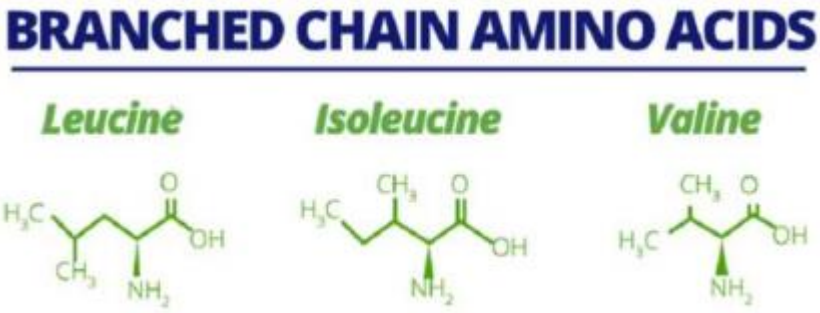
4-Lysine is an exclusively ketogenic (acetyl CoA and acetoacetyl CoA).

5-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 gammaaminobutyric 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.