SHEET NO.
22

METABOLISM

DOCTOR 2019 | MEDICINE | JU

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SCIENTIFIC CORRECTION :

GRAMMATICAL CORRECTION :

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بسم الله الرحمن الرحيم

In the previous lecture, we said that the amino acid degradation involves removal of the amino group through transamination and then oxidative deamination, the result was releasing of free ammonia , which is toxic and we deal with it through urea cycle. Now, we are talking about the second phase which include the catabolism of the carbon skeleton .

Simply, amino acid degradation starts with removal of the amino group followed by the catabolism of the rest carbon (carbon skeleton).

Glucogenic and ketogenic amino acids

Now, these pathways converge to form products directly enter the pathways of intermediary metabolism resulting either in the synthesis of glucose , ketone bodies, these products are : oxaloacetate, pyruvate, a-ketoglutarate, fumarate, succinyl coenzyme A (CoA), Acetyl CoA, and acetoacetate . Accordingly , amino acids can be classified into **glucogenic** or **ketogenic** or **both.**

Note: amino acid can be strictly glucogenic which means just produce glucose products like fumarate, or strictly ketogenic which means just produce ketone products like acetoacetate or mixed which means produce glucose products and ketone products.

This table show amino acids that contribute Either in synthesis of glucose products (glucogenic) or ketone products (ketogenic) or both, the table is also divided into essential and non-essential amino acid.

	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

Notes from this table:

1) Glucogenic and Ketogenic amino acids are called aromatic amino acids (tyrosine, phenyl-alanine, and Tryptophan). Isoleucine → it's not an aromatic, it's a branched one.

Doctor said we have to memorize this table

2) Branched amino acids like (valine, leucine, Isoleucine,) are essential because there is no enzyme to synthesis them in our body.

Remember : essential amino acids can not be produced from our body ,non-essential amino acid can be produced in our body

3) Although tyrosine is non-essential amino acid but it can be produced from phenyl-alanine which is essential amino acid, we must take it from food.

4) Tryptophan that has two major rings and thus, there is no precursor to build this amino acid. (essential amino acid)

5) Cysteine and methionine are sulfur containing amino acids and thus, one of these should be essential to give sulfur to another one . In this case methionine is essential and we use it in building cysteine.

Amino acid carbon skeleton catabolism

The pathways by which amino acids are catabolized are conveniently organized according to which one (or more) of the **seven intermediates** listed above is produced from a **particular amino acid** and thus we will discuss each product and the amino acids that can synthesize it.

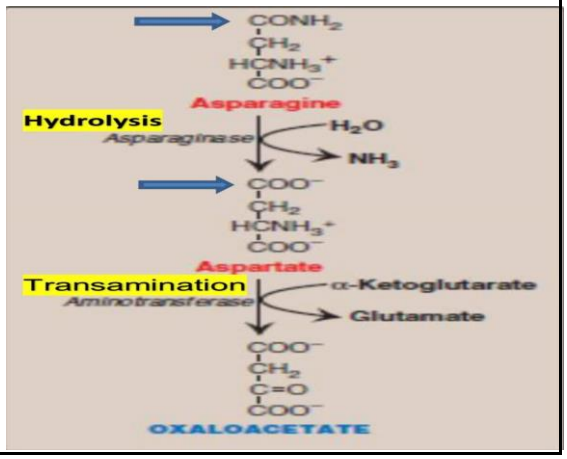
1) **Amino acids that form oxaloacetate**

There are two amino acids that can build up oxaloacetate aspartate and asparagine.

a) Aspartate

Reaction: Aspartate undergoes a transamination reaction to become oxaloacetate. The amino group is removed from aspartate and given to α-ketoglutarate to form glutamate and oxaloacetate. (we know this from previous lecture).

Enzyme: **Aspartate amino transferase (AST)**



Note : Asparagine is similar in structure to aspartate . The difference is that aspartate has a carboxyl group while asparagine has an amide group in its side chain (see blue arrows in picture).

b) Asparagine

Reactions: The conversion of asparagine into oxaloacetate in **two steps process**. The **first** is deamination of asparagine in a hydrolysis reaction to form aspartate. This is catalyzed by asparaginase. **The second step**, aspartate is converted into oxaloacetate. (the second step as the same above).
Enzymes: the first step is **asparaginase**, and the second step is **aspartate amino transferase (AST)**

Also, we can make Asparagine from Aspartate through process which is called amidation by asparagine synthetase enzyme, this process include removal of (O-) in side chain of aspartate and then addition amine group (NH3) and the bond which is formed between carbonyl group (CO) in aspartate and nitrogen atom in amine group (NH3) is amide bond .

Amide bond as peptide bond and thus, adding water will breaking the bond and because the amine group is terminal (look to the structure of aspartate) addition of water will release free ammonia.

Aspartate is non-essential amino acid because we have in our body two sources to produce aspartate, asparagine and oxaloacetate that's why is non-essential amino acid, also asparagine is non-essential amino acid.

In some leukemia patients (blood cancer) scientists found that there is a very high dependence on asparagine (in another word cancer cells depend on asparagine to cause cancer), these patients are taking asparaginase enzymes (the route of entry is systemically in the blood) in their treatment plan and this enzyme will reduces the dependence of cancer cells on asparagine but why ???
Answer: this enzyme (asparaginase enzyme) will convert asparagine in cancer cells to aspartate and Aspartate may or may not be transformed to oxaloacetate and thus reduce the activity of this cancer cells.
(يعني كل القصة انه خلايا سرطان الدم بتعتمد بعملها على انها تستخدم الاسبراجين بكميات عالية وبالتالي من ضمن خطة العلاج بعطيهم هذا الانزيم الي بحول الاسبراجين للاسبارتيت وبقلل اعتماد هاي الخلايا على الاسبراجين وبالتالي بقلل نشاطها وبضعفها).

Important: CONVERT ASPARAGINE INTO ASPARTATE IS NOT REVERSIBLE IN THIS MANAR , HOWEVER IN OTHER CONDITIONS WE CAN MAKE ASPARAGINE FROM ASPARTATE.

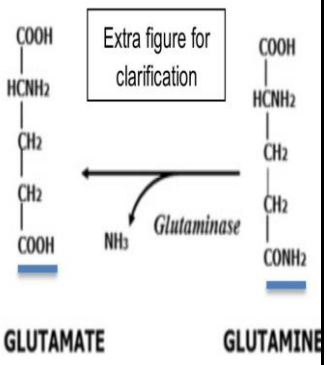
2) Amino acids that form a-ketoglutarate via glutamate (GHAP)

GHAP: just for good memorization
Each letter indicates to one amino acid

a) Glutamine

The idea here is the same as before with asparagine and aspartate. A similar **two steps reactions** occur.

1) Glutamine is converted to glutamate and ammonia by the enzyme **glutaminase.**



2) Glutamate is converted to a-ketoglutarate by transamination
Or through oxidative deamination by glutamate dehydrogenase

b) Proline

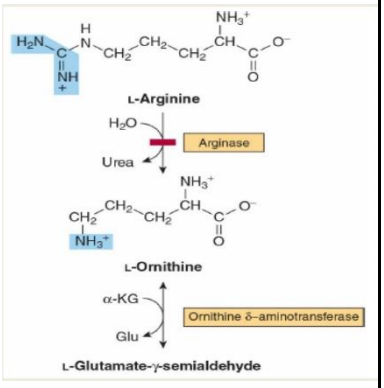
This amino acid is oxidized to glutamate. THEN, glutamate is transaminated or oxidatively deaminated to form a-ketoglutarate.

Doctor said there is no need to know the reactions in proline because it is very complex, we just have to know that proline is oxidized to glutamate.

Remember: proline contain three carbon, and the structure like cyclic (ring)

c) *Arginine*

Arginine is cleaved by arginase to produce Ornithine in the liver as a part of urea cycle.Then, Ornithine is converted into Glutamate which is converted into a-ketoglutarate.
Remember : Ornithine undergoes the transamination process. (always see the picture).



d) Histidine

- Structure-Histidine has an imidazole ring
- Reactions
  1) Histidase removes an amino group from the backbone of the amino acid (NOT the side chain as seen with asparagine and glutamine). This oxidative deamination forms urocanic acid.

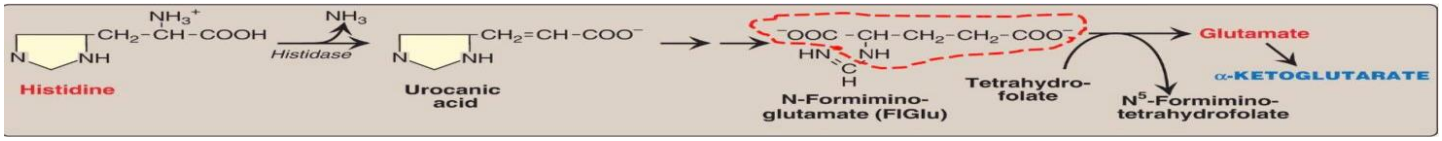
2) this urocanic acid which was produced from the first reaction, it undergoes a series of steps to produce compound which is called N-formimino-Glutamate (FlGlu), this structure is now glutamate with a group attached to the amino group this group (HC double bond NH) is known as formimino group . (see the picture below).

3) now, the formimino group is removed to give glutamate. This is done with helping of tetrahydrofolate (THF)(folic acid), which carry single carbon units (such as formimino), after this molecule carry this carbon units (formimino group) his name becomes N5-Formimino-tetrahydrofolate and glutamate will produce.
Remember: after that glutamate is converted to **a-ketoglutarate (which is the goal of this process).**

Deficiency in some enzymes for this process.

1)Folic Acid Deficiency – If folic acid is deficient, then THF is deficient. Therefore, individuals deficient in folic acid excrete high amounts of FIGlu in the urine (as it can not be converted into glutamate). That's why an FIGlu excretion test can be used in diagnosing folic acid deficiency.

2)Histidase Deficiency-which is responsible of converting histidine to urocanic acid (as we discussed in the first step) and therefore accumulation high amount of histidine amino acid can lead to histidinemia (the concentration of histidine is high in blood).



3) Amino acids that form pyruvate (GSCAT2)

GSCAT2: just for good memorization each letter indicates to one amino acid that contributes in produce pyruvate.

a) Alanine

This amino acid (Alanine) loses its amino group by transamination to form pyruvate and pyruvate also can be convert to alanine depending on the concentration of these two substances (Alanine and pyruvate).

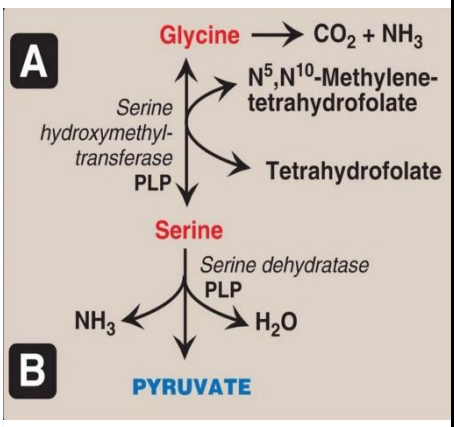
Enzyme: Alanine Aminotransferase (ALT)

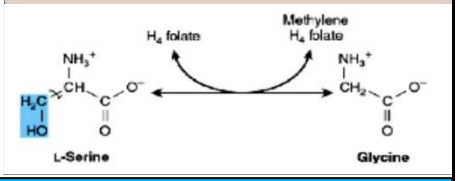
b) Tryptophan and Threonine

The doctor did not mention anything about this amino acids , he said just you should know that these amino acids can be used to produce pyruvate.

c) ***serine***

Serine has an OH group (side chain) and an amino group (backbone) ,serine have tow ways either to produce **pyruvate** or to convert Into **glycine.**





Note: the diiference between glycine and serine is methyl group and hydroxyl group

1) Serine can be converted into pyruvate by serine dehydratase enzyme which depends on (PLP), because of this we call this enzyme serine dehydratase (PLP) dependent enzyme.

Serine dehydratase catalyzes the reaction in which H2O (dehydration) and amine group (oxidation) are removed and pyruvate is formed

2) Serine can be converted into glycine by hydroxymethyl-transferase which transfer hydroxymethyl group from serine into tetrahydrofolate which will be converted to N5,N10-mehthyene-tetrahydrofolate. This reaction is reversible.

This reaction depends on the concentration of substrates (reactants) and folic acid (THF) it is present or not .

d) ***Glycine***

Firstly, glycine is a pyruvate related, because serine is also pyruvate related and both substrates we can transform them between each other.

Structure: glycine is very simple contain two carbon units and amine group , one of two carbons is carboxylic group and another one is (CH2). (see the picture above).

Conversion to pyruvate:

1) Glycine is firstly converted to Serine. To do so, it needs a carbon-OH group added. The enzyme that catalyzes this reaction is serine hydroxymethyl-transferase (the name indicates the group that is being added).This single carbon unit is brought by N5 ,N10 - Methylene-tetrahydrofolate.
2) Serine is converted to pyruvate.

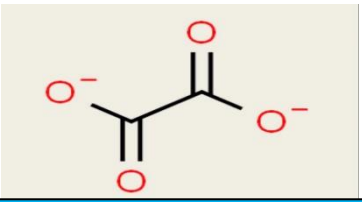
Another pathway for glycine

Glycine can be broken down to its derivatives by diaminoacid oxidase enzyme , this enzyme can break glycine and it results carboxyl group as (CO2) and amine group as (free ammonia) and the rest just one carbon(CH3).

Why we mention this mechanism ?????

Because through this process may produce molecule which is called glyoxylate, which is then oxidized to oxalate (dicarboxylic acid).

This Oxalate they can condense on top of each other and can Be produced **stones**.

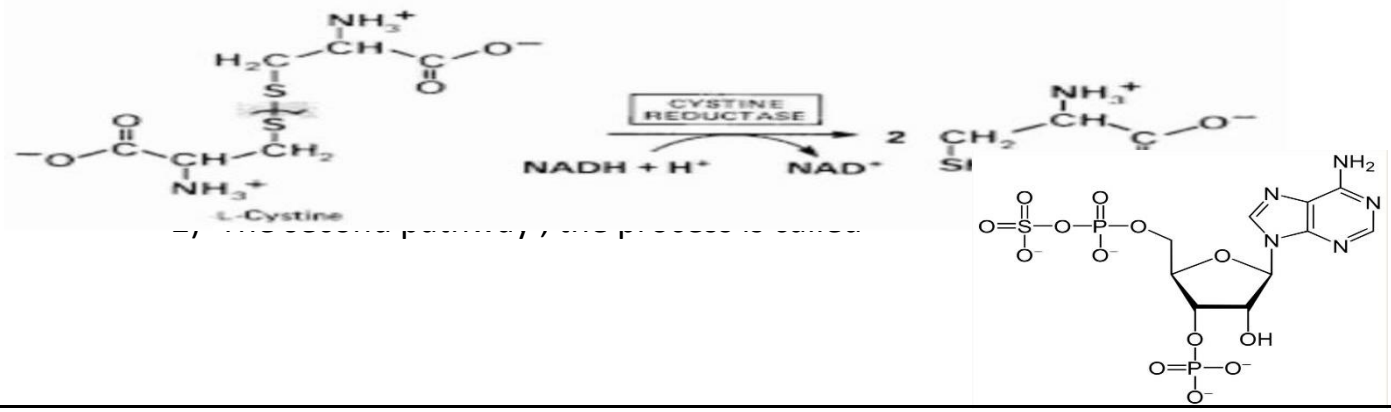


This is the structure of oxalate which is dicarboxylic acid (two carboxylic acid joined together)

E) Cysteine

Cysteine have many pathways but we will discuss two pathways :

1) Structure : Cysteine has a thiol group (SH). This is similar to serine, except serine has a hydroxyl group (OH). Consequently, the conversion to pyruvate will be similar. (sulfur containing amino acid).
   Reaction: Cysteine can be oxidized to its disulfide derivatives , cystine.
   Note: because Cysteine has a transporter in small intestine and kidney which is called **COAL** , it is considered a separate amino acid.



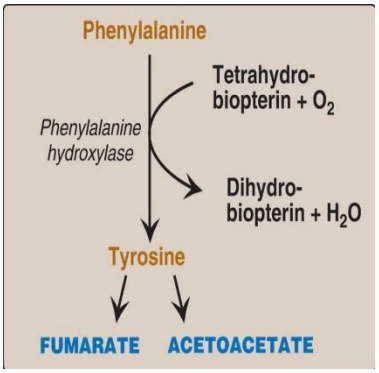
Desulfuration by the enzyme which is called desulfinase , works by removal of the sulfate group in Cysteine produces Alanine and then Alanine convert to pyruvate.

NOW, the sulfur group when it get out from Cysteine , it binds with molecule which is called 3'- phosphoadenosine-5'-phosphosulfate (PAPS), this (PAPS) molecule activated sulfate donor.(example to understand: ATP is a phosphate donor molecule).

The image above shows the structure of the (PAPS) molecule which contains adenosine and ribose with phosphate , also containing sulfate and therefore this molecules can accept or donates sulfate group. (exactly like ATP which release or donates phosphate).

4)Amino acids that form Fumarate (two amino acids)

Phenylalanine and tyrosine, both of them related to each other , both of them are related to produce fumarate , both of them are aromatic amino acid, both of them are related to glucogenic and ketogenic. (Mixed)



During the degradation of tyrosine there are two products Fumarate (glucogenic) and Acetoacetate (ketogenic) , because of that we call this amino acids mixed which means can produces glucose products and ketone bodies products.

Also, phenylalanine can be convert to tyrosine by adding hydroxyl group (OH) to phenylalanine by enzyme which is called **phenylalanine hydroxylase**.

We are adding this hydroxyl group from molecular oxygen (oxygenase) that it has two oxygen atom, but we are adding just one oxygen, because it is hydroxyl group, which we want to add, another oxygen it will backup hydrogen to form water molecule.

In addition to that , this reaction involves also convert coenzyme which is called Tetrahydro-biopterin into Dihydro-biopterin.
Genetics problem that may occur in this pathway are enormous, and most diseases related to nitrogen metabolism results from this pathway ,however

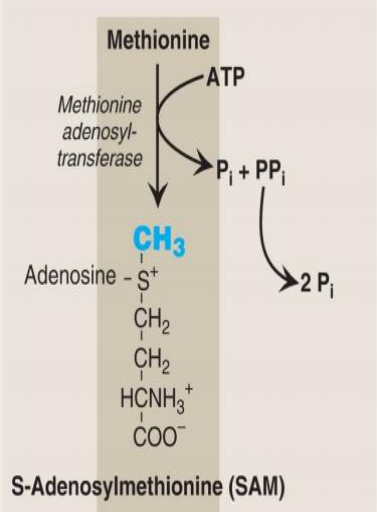
these diseases are rare like , phenylketonuria(PKU), tyrosinemia, alkaptonuria, as well as the condition of albinism.

5) amino acids that form succinyl CoA

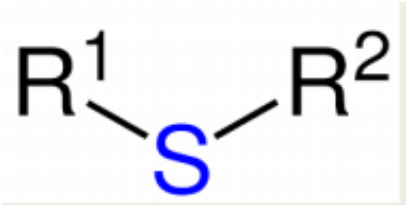
Methionine is one of four amino acids that form succinyl CoA

a) Methionine is converted to S-adenosylmethionine (SAM) by condensing ATP with methionine this reaction catalyzed by S-adenosyl-methionine synthetase

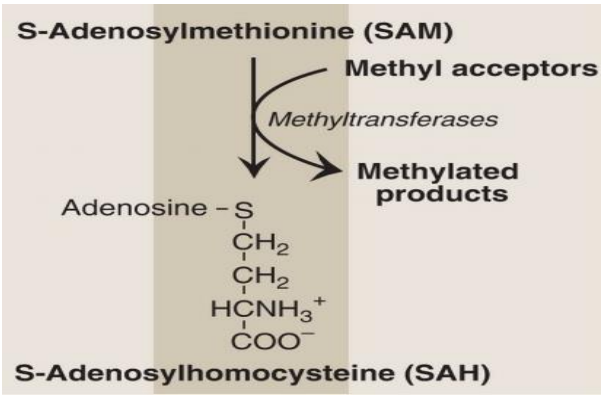
The weird thing happen here, that all phosphate group get out as three inorganic phosphate so high energy is consumed that's make this reaction irreversible the adenosine is attached to the sulfur atom this will make the (SAM) act as a universal methyl donor in carbon metabolism



b) The methyl group attached to the sulfur in SAM is activated and can be transferred by *methyltransferases* to a variety of acceptors such as norepinephrine in the synthesis of epinephrine. The reaction product, S-adenosylhomocysteine (SAH), is a simple thioether, analogous to methionine. The resulting loss of free energy makes methyl transfer essentially irreversible.



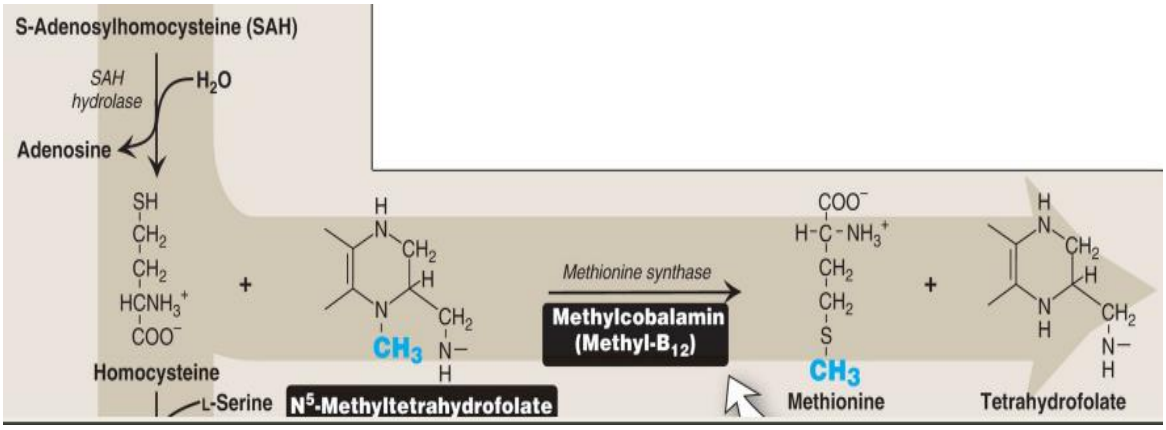
Thioether group :two R group attached to sulfur



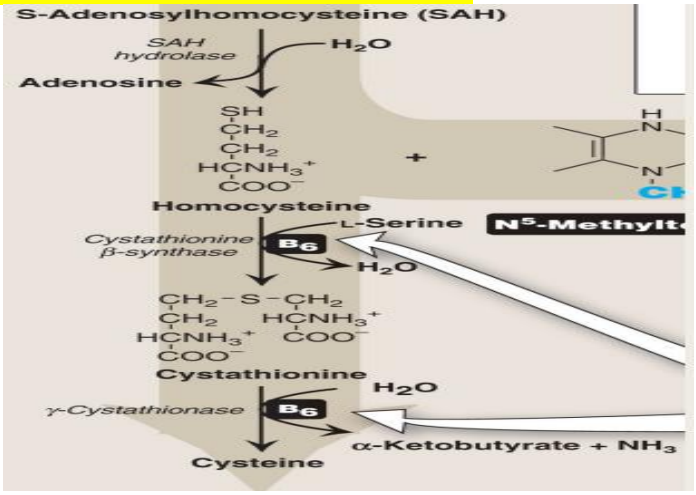
c) S.Adenosylhomocystelne hydrolysis: After donation of the methyl group, SAH is hydrolyzed to Hcy (homocystiene) and adenosine. Hcy has two fates. If there is a deficiency of methionine or the Hcy concentration is high in plasma, Hcy may be remethylated to methionine. If methionine stores are

adequate, Hcy may enter the transsulfuration pathway. where it is converted to cysteine.

1.first fate: Methionine resynthesis: Hcy accepts a methyl group from N5-Methyl-tetrahydrofolate (N5-methyl-THF) in a reaction requiring methylcobalamin, a coenzyme derived from vitamin B12 and the methyl group is transferred by methionine synthase



2. Second phase: Homocysteine condenses with serine, forming cystathionine and the enzyme called cystathionine synthase which require vit B6 . Cystathionine hydrolyzed by cystathionase (require vit-B6) to cysteine and α-ketobutyrate that will be oxidatively decarboxylated to form propionyl CoA and propionyl CoA converted to succinyl CoA .
**THE CARBON SKELETON OF CYSTEINE IS FROM SERINE AND JUST TAKE SULFUR FROM HOMOCYSTEINE
And the carbon skeleton of a-ketobutyrate from Hcy,because Hcy is synthesized from the essential amino acid methionine, cysteine is not an essential amino acid as long as sufficient methionine is available.



D) Relationship of homocysteine to vascular disease: Elevations in plasma Hcy levels promote oxidative damage, inflammation, and endothelial dysfunction and are an independent risk factor for occlusive vascular diseases such as cardiovascular disease (CVD) and stroke. Mild elevations (hyperhomocysteinemia) are seen in -7% of the population. Epidemiologic studies have shown that plasma Hcy levels are inversely related to plasma levels of folate, B12, and B6, the three vitamins involved in the conversion of Hcy to methionine and cysteine. Supplementation with these vitamins has been shown to reduce circulating levels of Hcy. However, in patients with established CVD, vitamin therapy does not decrease cardiovascular events or death. This raises the question as to whether Hcy is a cause of the vascular damage or merely a marker of such damage. [Note: Large elevations in plasma Hcy as a result of rare deficiencies in *cystathionine B-synthase* of the transsulfuration pathway are seen in patients with classic homocystinuria (resulting from severe hyperhomocysteinemia [>100 Jl.molll Deficiencies in the re-methylation reaction also result in a rise in Hcy

Elevated homocysteine and decreased folic acid levels in pregnant women are associated with increasing incidence of neural tube defects (improper closure, as in spina bifida) in the fetus. Periconceptual supplementation with folate reduces the risk of such defects.

Other amino acids that form succinyl CoA

1. Valine and Isoleucine: These amino acids are branched-chain amino acids (BCAA) that generate propionyl CoA, which is converted to methylmalonyl CoA by biotin and then converting of methylmalonyl CoA to succinyl CoA required vitamin B12.

Threonine: This amino acid is dehydrated to a-ketobutyrate, which is converted to propionyl CoA and then to succinyl CoA.
Propionyl CoA, then, is generated by the catabolism of the amino acids methionine, valine, isoleucine, and threonine. [Note: Propionyl CoA also is generated by the oxidation of odd-numbered fatty acid

6)Amino acids that form acetyl CoA or aceto-acetyl CoA

Tryptophan, leucine, isoleucine, and lysine form acetyl CoA or aceto-acetyl CoA directly, without pyruvate serving as an intermediate. As noted earlier, phenylalanine and tyrosine also give rise to acetoacetate during their catabolism Therefore, there are a total of six partly or wholly ketogenic amino acids

*Tryptophan: This amino acid is both glucogenic and ketogenic, because its catabolism yields alanine and aceto-acetyl CoA , Quinolinate from tryptophan catabolism is used in the synthesis of nicotinamide adenine dinucleotide (NAD) But how ever we can synthesize it in our body it still essential because it is derived from tryptophan

7)Branched-chain amino acid degradation

The BCAA isoleucine, leucine, and valine are essential amino acids.
In contrast to other amino acids, they are catabolized primarily by the peripheral tissues {particularly muscle), rather than by the liver. Because these three amino acids have a similar route of degradation, it is convenient to describe them as a group

a.Transamination: Transfer of the amino groups of all three BCAA to a-ketoglutarate is catalyzed by a single, vitamin Be-requiring enzyme, *branched-chain amino acid aminotransferase,* that is expressed primarily in skeletal muscle.

b. Oxidative decarboxylation: Removal of the carboxyl group of the a-keto acids derived from leucine, valine, and isoleucine is catalyzed by a single multienzyme complex, *branched-chain a-keto acid dehydrogenase (BCKD) complex.* This complex uses thiamine pyrophosphate, lipoic acid, oxidized flavin adenine dinucleotide (FAD}, NAD+, and CoA as its coenzymes and produces NADH.
[Note: This reaction is similar to the conversion of pyruvate to acetyl CoA by the *pyruvate dehydrogenase (PDH) complex* {see p. 1 09) and a-ketoglutarate to succinyl CoA by the *a-ketoglutamtedehydrogenase complex*. The *dihydrolipoyl dehydrogenase (Enzyme 3,* or *E3)* component is identical in all three complexes.]

c. Dehydrogenations: Oxidation of the products formed in the *BCKD* reaction produces a-B-unsaturated acyl CoA derivatives and FADH2. These reactions are analogous to the FAD-linked dehydrogenation in the B-oxidation of fatty acids . [Note: Deficiency in the *dehydrogenase* specific for isovaleryl CoA causes neurologic problems and is associated with a "sweaty feet" odor in body fluids.]

FOLIC ACID AND AMINO ACID METABOLISM

Folic acid used in addition of single-carbon groups: formyl, methenyl, methylene, and methyl to molecules by carrier compounds such as THF and SAM

CO_2, coming from bicarbonate (HCO_3^-) is carried by the vitamin biotin, is not considered a member of the one-carbon pool, which is a prosthetic group for most carboxylation reactions
Defects in the ability to add or remove biotin from *carboxylases* result in multiple *carboxylase* deficiency. Treatment is supplementation with biotin.

*Folic acid and one-carbon metabolism

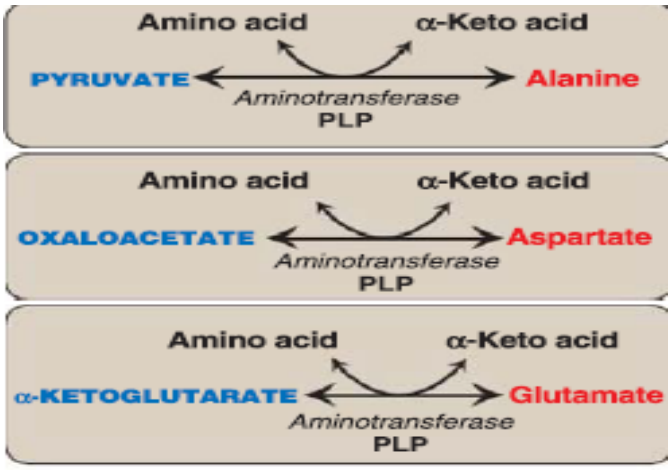
The active form of folic acid, THF, is produced from folate by *dihydrofolate reductase* in a two-steps reaction requiring two nicotinamide adenine dinucleotide phosphate (NADPH). The one-carbon unit carried by THF is bound to N5 or N10 or to both N5 and N10.
Folate deficiency presents as a megaloblastic anemia because of decreased availability of the purines and of the thymidine monophosphate needed for DNA synthesis

BIOSYNTHESIS OF NONESSENTIAL AMINO ACIDS

Nonessential amino acids are synthesized from intermediates of metabolism or, as in the case of tyrosine and cysteine, from the essential amino acids phenylalanine *and* methionine.
Some amino acids found in proteins, such as trydroxyproline and hydroxylysine, are produced by posttranslational modification (after incorporation into a protein) of their precursor (parent) amino acids

A. Synthesis from α-keto acids

Alanine, aspartate and glutamate are synthesized by Transamination reactions, Glutamate is unusual in that it can also be synthesized by reversal of oxidative deamination, catalyzed by *glutamate dehydrogenase* when ammonia levels are high.

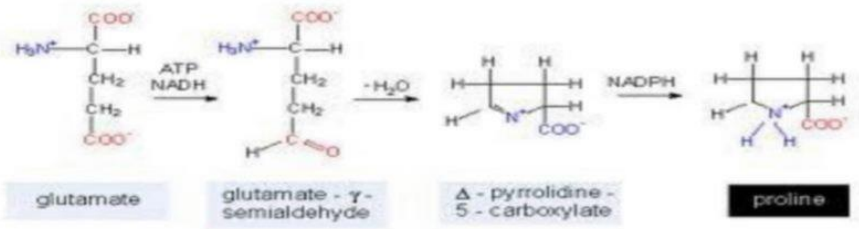


B.Synthesis by amidation

Glutamine and asparagines are synthesized by amidation of glutamate and aspartate withtwo enzymes *glutamine* Synthetase *and asparagine* Synthetase

C.Synthysis from proline

Glutamate via glutamate semialdehyde is converted to proline by cyclization and reduction reactions. The semialdehyde can also be transmitted to ornithine.



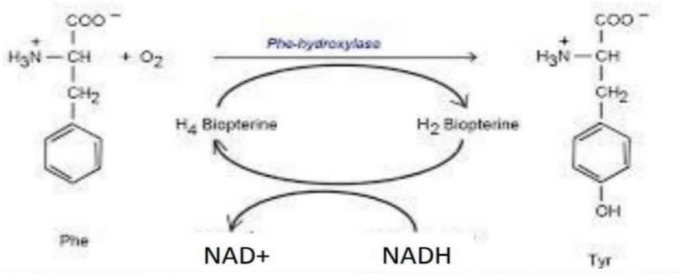
D. Serine, glycine, and cysteine

The pathways of synthesis for these amino acids are interconnected

1. **Serine**: This amino acid arises from 3-phosphoglycerate, a glycolytic intermediate, which is first 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 hydroxymethyltransferase* using N5, N10-MTHF as the one-carbon donor
2.**Glycine**: This amino acid is synthesized from serine by removal of a hydroxymethyl group, also by *serine hydroxymsthyltranstsrase* THF is the one-carbon acceptor.
3. **Cysteine**: This amino acid is synthesized by two consecutive reactions in which Hcy combines with serine, forming cystathionine, which, in turn, is hydrolyzed to a-ketobutyrate and cysteine

E. Tyrosine is formed from phenylalanine by *PAH* (see p. 263). The reaction requires molecular oxygen and the coenzyme tetrahydrobiopterin (BH4), which is synthesized from guanosine triphosphate. One atom of molecular oxygen becomes the hydroxyl group of tyrosine, and the other atom is reduced to water. During the reaction, BH4 is oxidized to dihydrobiopterin (BH2). BH4 is regenerated from BH2 by NADH-requiring *dihydropteridine reductase.*



Note : Tyrosine, like cysteine, is formed from an essential amino acid and is, therefore, nonessential only in the presence of adequate . dietary phenylalanine.

This is the end of the sheet the remain concepts doctor said that you just need to read them from slides

وَاصْبِرْ فَإِنَّ اللَّهَ لَا يُضِيعُ أَجْرَ الْمُحْسِنِينَ

Wish you all the best