Medical Committee
The University of Jordan

SLIDE SHEET

LECTURE#: 25

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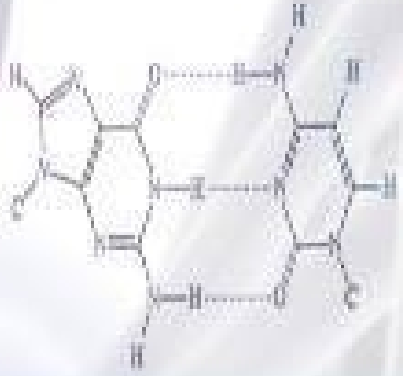
Biochemistry



Majida Al-Foqaraa'

Carbon Skeleton

Amino Acid Metabolism

Review:

In the previous two lectures we talked about:

- **How do we deal with proteins (how to degrade them, the enzymes, the site of action, then we reach the free amino acids and dipeptides & the tripeptides, from where we absorb them & what the signals are of for their degradation) & the products of proteins.**
- **Amino Acids; starting with the amino group.**
- **How do we deal with the amino group? → we have two general reactions (1- Transamination , 2-Oxidative Deamination)**
- **We talked about AST & ALT as major examples of transaminases with their medical applications.**
- **Glutamate dehydrogenase & D-amino acid oxidase as examples of oxidative deamination processes.**

**** Now, All of these reactions have made Ammonia (NH3) in the tissues, How to transport Ammonia by Alanine & Glutamine?**

By Two Mechanisms: → Glutamine synthetase
→Glucose-alanine cycle.

Now we reach the liver (we have a lot of ammonia in the liver): We made the Urea Cycle; 5 enzymes, 5 steps (2 mitochondrial & 3 cytosolic).

REMEMBER That: Arginase Enzyme is found ONLY in the Liver, which makes the Urea Cycle exclusively in The Liver.

From the Liver Urea will get out to the kidneys then to the Urine.
Urea: it isn't a problem in healthy adults while it circulates in the blood but it is a problem in Renal Failure Patients.

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About Questions in The Exam: each lecture will get 2 marks

→Urea cycle is very important (you must have a question about it)

→There must be a question about Reactions (Transamination + Deamination Reactions)

→There must be a question about Protein Degradation & Absorption processes.

→The doctor said that the average of the Mid-term exam was the best in his field among the 3 years he taught this subject☺, which means the questions were the best.

→The best exam (as he said): is the one which discriminate between students who are studying & who are not. Otherwise there is no benefit from it.

Let's Start , we talked about the amino group , now we will talk about the carbon skeleton of each amino group ; what happens in each carbon skeleton of each amino acid during degradation or syntheses ?
To Deal with carbon skeleton of amino acids, we should Deal with

- **Three Coenzymes :**

1. **Pyridoxal phosphate (PLP) : Vitamin B6 derivative (NOT Vitamin B6) , <u>Remember That : All Transaminases Reactions requires PLP</u> , Those reactions are Not Our Topic NOW (because they are dealing with amino group metabolism) but we are talking about the reactions that happen within the carbon skeleton " we will come to them " that require PLP .**

2. **Tetrahydrofolate (FH4):Folic Acid , Vitamin B9 derivative**

   <u>Whenever you have a Transfer of One Carbon unit (To OR From molecule) in amino acid metabolism Folic Acid is there .</u>You will notice this when there is one carbon loss or gain in structures.

So When You Have a Question between Two structures (hydrocarbons) and the difference is ONE Carbon Unit, then FOLIC ACID should be there.

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3. **Tetrahydribiopterin (BH4), important in Ring Hydroxylation (If you have a ring & you want to put a hydroxyl group in that ring, then you need BH4).**

➔ **THIS is important in the amino acid metabolism especially in Phenylalanine that will become Tyrosine upon hydroxylation.**

FH4 (Tetrahydrofolate) is the reduced form, how to convert it to its oxidized form?

By Removing TWO Hydrogens "becomes FH2 (Dihydrofolate)".This is done by Dihydrofolate Reductase; Reductase will add TWO hydrogens.

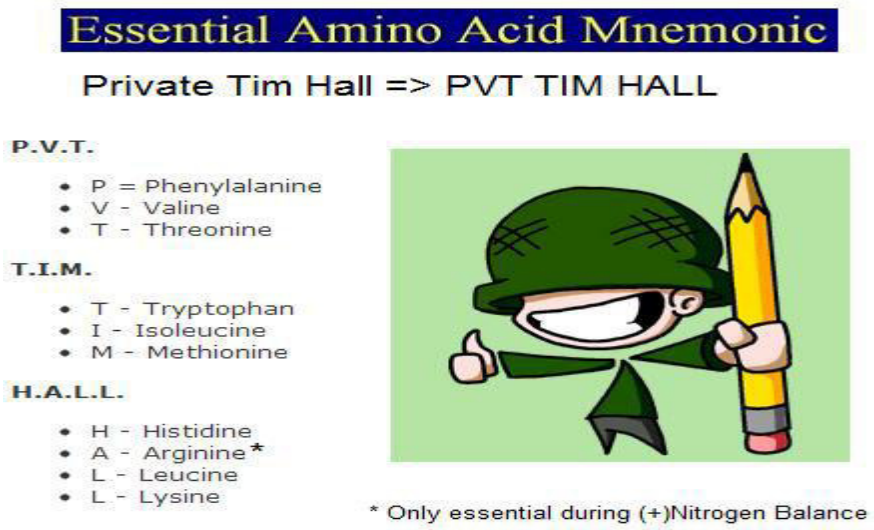
ALSO, BH4 (Tetrahydrobiopterin) is oxidized to BH2 (Dihydrobiopterin) BY Dihydrobiopterin Reductase.

::Remember That :: enzyme Deficiencies result in diseases.

"Amino Acids":

Some are Essential & some are Non-Essential.

✓ **The Essential ones (look at the picture below and Memorize them by the mnemonic "PVT TIM HALL")**



NOTIC that: the Essential amino acids are 9 but in case of Arginine it is considered as essential in the cases of positive nitrogen balance ONLY . Usually Arginine isn't found in this list.

- ✓ **The Non-Essential ones (11 Amino Acids) : All of them have a relation with GLUCOSE (THIS MEANS : They are Glucose Derived & Their Degradation will give Glucose) ,**
  EXCEPT: Cysteine, WHY? Because it has a THIOL Group "sulfur", Sulfur doesn't have any relation with Glucose.

→So Out OF the 11 Non-Essential amino acids; 10 are <u>Glucose Derived</u> (It Means: having relation with <u>Krebs cycle intermediates</u> OR <u>Glycolytic Process</u>).

→Two amino acids out of the 11 there should be a preceding amino acid for them so as to be there.

- ❖ **Which Are They?**

1- Tyrosine "not essential" needs phenylalanine "essential" to be there.
So you can't produce tyrosine without phenylalanine. Other amino acids can be generated by certain pathways.

2-Cysteine "Its carbon skeletal is Glucose derived but the sulfur is Not Glucose derived", so there should be Methionine "essential". <u>If Methionine is Deficient, Then Cysteine is Essential</u>

::Remember::The essentiality of Cysteine is governed By Methionine ; Methionine is there , then Cysteine isn't essential and vice versa .

Because we need the sulfur from Methionine to Generate Cysteine.

<u>::About the 10 amino acids that are Derived from Glucose ::</u>

→4 out of 10 amino acids are related to Glycolytic intermediates.
→6 out of them are related to citric acid cycle intermediates.
[4 of them are related to alpha-KetoGlutarate & 2 of them are related to oxaloacetate]

:: Degradation Of Amino Acids::

✓ Usually, the Synthetic pathway occur in a place & the Degradative pathway occur in other place. WHY? For better Regulation.

Almost every amino acid when it undergoes Degradation, we are talking about Oxidation Processes. [Degradation means Oxidation, Reduction means Building UP].

Every amino acid in the process of degradation "OXIDATION" involves the generation of NADH, for that reason we said that we have an amount of energy per gram of amino acids.

✍ Fate of the carbon units of each amino acid depends on the FED state of the individual " has low OR enough of energy " :

→If there is enough state of energy: it will make Glucose then Glycogen.

→If there isn't enough energy: it will be degraded to the Krebs Cycle Intermediates so produce energy.

IMPORTANT: Degradation of the amino acids occur in ALL Tissues of the body; however; The Liver is the ONLY tissue that has all the pathways of degradation & biosynthesis for all the carbon skeleton in the amino acids.

❖ Degradation of the amino acids *may* GIVE things related to glucose [related to CARBS], ketone bodies [related to LIPIDS].

Those products of degradation SEPARATE " or classify" the amino acids into : 1-Glucogenic (produce glucose related materials) , 2- Ketogenic (produce ketone bodies related materials) , 3-

Glucogenic & ketogenic "called : Combined" (produce glucose & ketone bodies related materials) .

<u>You Must Memorise Them All (look at the picture below)</u>

	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

<u>Notice</u>: →The strictly ketogenic amino acids are only two & start with "L": [Lysine and leucine].

→The mixed 'combined' ones are the Aromatic Amino Acids: [Phenylalanine, Tryptophan and Tyrosine] + Isoleucine "Not Aromatic ".

→The rest are Glucogenic.

→You might be asked about them in the exam.

** Degradation of amino acids can produce many intermediates:

- Krebs cycle related (Oxaloacetate , alpha-Ketoglutarate , Succinyl CoA , Fumarate)
- Glycolysis related (Pyruvate)
- Ketone bodies related (acetyl CoA & Acetoacetate)

:: Amino Acids That are Related To Oxaloacetate::

1. Aspartate: The first one must come to your mind, it is the corresponding amino acid for oxaloacetate, by transamination reaction (Involving Vitamin B6 Derivative "PLP").

✓ If Aspartate has a relation, then Asparagine has a relation TO Oxaloacetate.
{The Difference between the two structures only an amino group, so the carbon skeleton is the SAME.}

2. Asparagine: HOW to convert it to Aspartate?
* remember the difference is an amino group *

Hint: We talked "previous lecture" about how to transfer an amino group from the tissues to the liver => by transfer of the FREE amino group to the Glutamate and so become Glutamine by the enzyme "Glutamine synthetase"

→Glutamine synthetase can Fix "add" Free Ammonia to the structures , Few Enzymes IN The Body Can Do That , Asparagine synthetase isn't one of them .

Now, How to add the free amino group to the Aspartate to be Asparagine? * remember that Asparagine synthetase has NO capability to do this * Then, we will get the amino group from Glutamine so we convert it to Glutamate.

Asparagine synthetase convert the Aspartate to Asparagine .And Asparagine will be broken down to Aspartate by Asparaginase, Just Similar to Glutaminase "Convert Glutamine to Glutamate".

We have <u>ONLY Three Human Enzymes</u> that can Fix Free Ammonia on structures:

- **Glutamine Synthetase.**
- **CPS1 "Carbamoyl Phosphate Synthetase 1" →First step in Urea Cycle ((CO2 + NH3 = Carbamoyl Phosphate)).**
- **Glutamate DH.**

For certain leukemias "سرطانات الدم " ; by researches & observational studies they found that certain leukemic cells utilize Asparagine a lot to divide well , How to Deal with those cancer cell ?

TO give systemically in the blood Asparaginase Enzyme "to degrade Asparagine ", to slow the Growth of these cancer cells.

:: Amino Acids Related To alpha-Ketoglutarate::

1- **Glutamate: The first one should come to your mind, it is the corresponding amino acid to alpha-Ketoglutarate.**

→How to get alpha-Ketoglutarate out of Glutamate?
BY : #1- <u>Oxidative Deamination</u> "Glutamate DH extracts the amino group out of the Glutamate to make alpha-Ketoglutarate & Free ammonia come out ; and it can put the amino group on alpha-Ketoglutarate to make Glutamate"

***Remember: Glutamate DH is one of The Three enzymes that can fix Free Ammonia on structures ***

#2-Transamination (MOST Transaminases Use alpha-Ketoglutarate as the ACCEPTOR of the amino group) => so most amino acids make Glutamate.

2-Glutamine: produced by Glutamine synthetase "that fix free ammonia on Glutamate, and its degradation gives Glutamate + Free ammonia "By Glutaminase".

3-Arginine: we talked about it in the Urea Cycle, the last step in it was the breakage down of Arginine by Arginase "Remember: Found ONLY in the liver"

☒ **The products of Arginine break down are: Urea "Goes out" + Ornithine, which goes back to the cycle, can be converted by the Transamination reactions to Glutamate, which can be converted to alpha-Ketoglutarate.**

Proline is also an amino acid that is related to alpha-Ketoglutarate but the doctor doesn't want to talk about it because of its long processes.

4- Histidine: Its Structure (Side chain: has Five membered Ring With another Carbon, Alpha Carbon, Amino Group, Carboxylic Group) is SIMILAR to Glutamate.

**** The difference "between Histidine & Glutamate" is:**

- Histidine has One Carbon Unit Extra and that Carbon has Nitrogen.

-Histidine has five membered ring but Glutamate is Aliphatic.

→The First reaction will remove the amino group from the Histidine By the Histidase Enzyme , Now we have a carbon skeleton that Undergoes two subsequent reactions Forming : N-Formiminoglutamate " FIGLU" [From The Name you can notice that it contains : Glutamate , Amino Group or Nitrogen " Imino" , & Extra one carbon unit " Form" .

**** Form- means in Chemistry: Formyl Group = One Carbon Unit**

→Now by removing This Extra <u>ONE</u> Carbon with the Nitrogen, We will form Glutamate. This Reaction "Removal of ONE carbon Unit "should involve Tetrahydrofolate Coenzyme (FH4).

How was the diagnosis of Folic Acid Deficiency in the past?

They were measuring the blood concentration of Formiminoglutamate; if it was high this indicates that there is Folic Acid Deficiency, WHY? Because there is NO (FH4) to take the carbon unit with its nitrogen from (FIGLU) and form Glutamate.

→So High Conc. Of (FIGLU) within your blood means Folic Acid deficiency.

The Other Reaction of Histidine:

Conversion of Histidine to Histamine (the allergic material) By <u>Histidine Decarboxylase</u>, which take out the carboxylic group from the back bone of Histidine. This Reaction requires <u>Vitamin B6.</u>

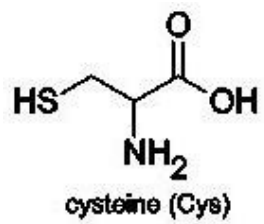
:: Amino Acids Related To Pyruvate::

1-Alanine: The First one should come to your mind, it is the corresponding amino acid for the Ketoacid Pyruvate,

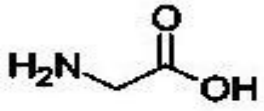
This is by Transaminase reaction which is called Alanine Transaminase "ALT".

2-Glycine. 3- Serine.

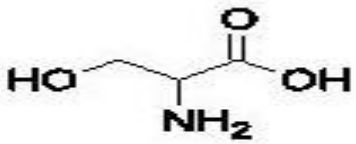
By looking at the structures of the three amino acids "Cysteine, Glycine & Serine"



cysteine (Cys)



glycine (Gly)



serine (Ser)

→Glycine: is the smallest amino acid that has "Alpha carbon, carboxylic group & amino group"

→The Difference between Glycine & serine is JUST one Methyl Group with Hydroxyl Group. So to convert Glycine to Serine we need an Enzyme which is called "Serine HydroxyMethyl Transferase" which Transfer One Carbon Unit so Tetrahydrofolate is involved as Coenzyme.

→IN Structure wise: What is the difference between Serine & Cysteine?

Serine has Hydroxyl Group but Cysteine has Thiol Group .The carbon skeleton is exact between them. So in order to make Cysteine we will fetch two amino acids " Serine & Methionine " ; then we put the sulfur atom " from Methionine" on Serine .

→Serine can be converted to Pyruvate by Serine Hydratase "which takes the amino group out ". Because serine and glycine have a relation with Pyruvate and Cysteine has a relation with Serine, Then Cysteine is related to Pyruvate.

4-Cysteine: To make it we need two amino acids "Serine [Take the carbon skeleton] & Methionine [Take the Sulfur]"

We will talk about Methionine & its Degradation, it will be converted to what is called "HomoCysteine ", we will talk about SAM "S-Adenosyl Methionine" & SAH "S-Adenosyl HomoCysteine"

→You need to be familiar with HomoCysteine: NOW, they are measuring the HomoCysteine level for the patient, it might be related to the Autism .HomoCysteine is established with CVDs "Cardiovascular Diseases ". So it is good to be familiar with this metabolite of Methionine which is HomoCysteine.

**** According to the Reactions {making Cysteine out of HomoCysteine} ****

HomoCysteine is joined with Serine to Form Cystathionine [Structure wise: serine is joined with the sulfur atom of HomoCysteine] by the enzyme: Cystathionine synthase, this RXN is Vitamin B6 Required. Then Cysteine is Formed , the rest of the Carbon skeleton of homocysteine " which comes from Methionine " will form alpha-Ketobutryate .

Alpha-Ketobutryate has 4 carbon units ; and whenever we see it (in any metabolic pathway) , it will give Propionyl CoA and through series of reactions it will give Succinyl CoA .

So because Methionine gives Homocysteine & Succinyl CoA → IT Is Succinyl CoA Related.

But Cysteine isn't related to Succinyl CoA, because all the structure (carbon skeleton) of Cysteine IS come From Serine.

REMEMBER:: that the essentiality of Cysteine is Governed by the level of Methionine. Though Cysteine isn't an essential amino acid. If there is Methionine Deficiency then Cysteine is essential. And it "Cysteine" must be obtained from Diet.

High level of Cysteine in our diet spares Methionine .

Till Now, What makes the level of HomoCysteine HIGH?

By: Cystathionine Synthase Deficiency OR Vitamin B6 "PLP" Deficiency.

::Amino Acid Related To Fumarate ::

1-Aspartate: We talked about it in the Urea Cycle. It differs from Fumarate By having an Extra Amino Group. When the amino group enters the cycle to make Urea , the rest of the carbon skeleton of aspartate left the cycle as Fumarate, which is one of The Net Products of the Urea Cycle.

→So the carbon skeleton of Fumarate came from Aspartate.

2-PhenylAlanine & Tyrosine: They are connected to each Other (Remember the structure).

→How to make Tyrosine out of Phenylalanine?

By Hydroxylation; by Phenylalanine hydroxylase (so we are hydroxylating the Phenylalanine to Tyrosine). If this enzyme is genetically deficient, then Phenylketonuria "a disease" will occur.

During the degredative pathway of Phenylalanine & Tyrosine there is something formed called "Homogentisic Acid ". Then it will Undergo Oxidation by Homogentisic Acid Oxidase. If this enzyme is deficient, then Alkaptonuria "a disease" will occur.

The end products of Phenylalanine & Tyrosine metabolism are: Fumarate "which means it is Glucogenic" + Acetoacetate "which means it is Ketogenic"

:: Remember:: Phenylalanine & Tyrosine are aromatic amino acids , which means they are BOTH (Glucogenic & Ketogenic)

:: Methionine as Succinyl CoA Related ::

→Methionine is converted to SAM molecule, what is SAM?

It is S-Adenosyl Methionine as the name implies there is Adenosine connected to Methionine via Sulfur atom.

→When One Carbon Unit is leaving out of SAM, Then SAH is generated .What is SAH?

It is S-Adenosyl HomoCysteine, How is "SAH" different from Homocysteine? By the Adenosine ONLY.

If Adenosine leaves then we generate Homocysteine, this is How we make Homocysteine out of Methionine.

Then Homocysteine is joined with Serine to make Cysteine & Alpha-Ketobutryate, then Alpha-Ketobutryate will be converted to Propionyl CoA then To Succinyl CoA. This is how Methionine is related to Succinyl CoA.

**In The process of conversion of Homocysteine to Succinyl CoA, the Vitamin B6 "PLP" is involved. So deficiency in Vitamin B6 can lead to High level of Homocysteine.

→How The structures of Homocysteine & Methionine are different ? it is just One Carbonyl Extra on Methionine .so this conversion (Homocysteine back to Methionine) requires also Vitamin B9 "Folic Acid" , and usually when Vitamin B9 is required ,Vitamin B12 is also required .

:: As Conclusion::

→ High levels of HomoCysteine is Caused by:

1-Vitamin B6 Deficiency.

2-Vitamin B9 Deficiency.

3-Vitamin B12 Deficiency.

4-Enzyme Cystathionine Synthase Deficiency.

BEST OF LUCK :)

يَسعَى الفَتَى لِأمورٍ لَيسَ يُدرِكُها فَالنَفسُ واحَدةٌ والهَمّ مُنتَشِر.

والمَرء مَا عَاشَ مَمْدودٌ لَهُ أمَلٌ لَا تَنتَهي العَينُ حَتّى يَنتَهي الأثَرُ.