Medical Committee
The University of Jordan

SLIDE [redacted] SHEET

Sheet #: 26

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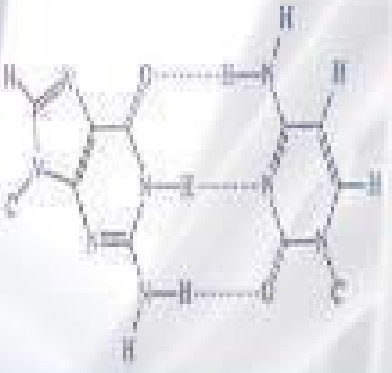
Biochemistry

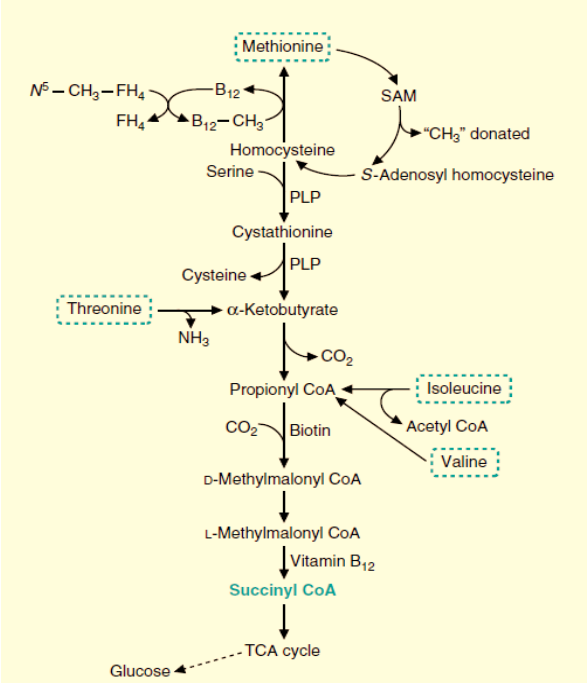


Majida Al-Foqaraa'

Amino acid carbon skeleton metabolism-cont

Amino acids that form succinyl-coA

- Methionine



at the beginning of methionine degradation pathway, a molecule of adenosine will be added to methionine forming **S-adenosyl methionine** (**SAM**), it is called S-adenosyl because the Adenosine is bound on the sulfur atom of methionine, then one carbon unit will be lost from SAM as CH3 converting SAM to SAH (S-adenosyl homocysteine), then the Adenosine molecule will be removed from SAH to form **Homocysteine**.

How Homocysteine is different from Methionine?
They are different by **One carbon unit** which is the carbon unit (CH3) that was lost from SAM to form SAH,so methionine can be regenerated from Homocysteine by the addition of one carbon unit to Homocysteine which requires both **tetrahydrofolate**and Vitamin B12 .

Homocysteine in this pathway is not converted back to Methionine, it joins with serine amino acid to synthesize Cysteine , we bring the carbon skeleton from serine and we bring the sulfur atom from methionine, join them together and form Cysteine, the rest of the carbon skeleton of methionine will form α-ketobutyrate which will then be converted to propionyl-coA this molecule will undergo carboxylation (requires biotin as a coenzyme) to finally form Succinyl-coA that's how methionine is related to succinyl-coA .

- Threonine

Threonine can be degraded by **Threonine dehydratase** to α-ketobutyrate releasing free ammonia ,α-ketobutyrate will then be converted (by default) to propionyl-CoA then to Succinyl-coA.

This similar to the reaction catalyzed by serine dehydratase in which serine gets converted to pyruvate releasing free ammonia

Whenever you see an amino acid undergoing a reaction catalyzed by dehydratase Enzyme, it means that it undergoes oxidative deamination process releasing free Ammonia

- Valine,Isoleucine ,Leucine

-These 3 amino acids are branched chain amino acids
-These amino acids make up about 25% of the content of average proteins which means that they are very important in protein metabolism in energy production
-they have high concentration in muscles and many of body builders take a supplementation of branched chain amino acids specifically to build up their muscles

What are the reactions that these amino acids undergo?

1- Transamination: There is an enzyme called branched chain α-amino acid aminotransferase .As the name implies, this enzyme transfer an amino group from branched chain amino acids and transform them to their corresponding Keto-acids.
2- Oxidative decarboxylation : catalyzed by branched chain α-keto acid dehydrogenase which converts the keto acids that result from transamination of branched chain amino acids to their corresponding CoA complexes and this reaction release CO2 and NADH.

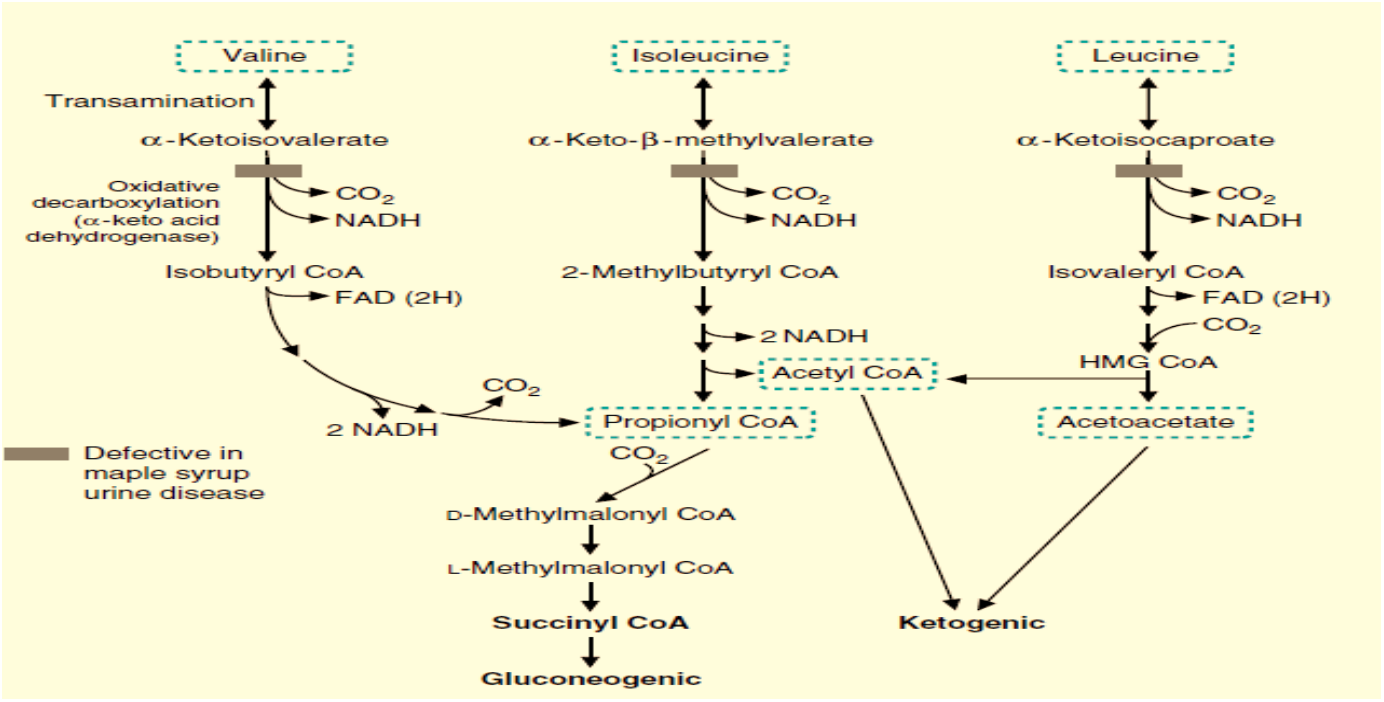
There are 2 other enzymes that are structurally and functionally similar to branched chain α-keto acid dehydrogenase which are:

- Pyruvate dehydrogenase : converts pyruvate (keto acid) to acetyl-CoA
- α-ketoglutarate dehydrogenase : converts α-ketoglutarate to succinyl-CoA

All of these dehydrogenases are multi-enzyme complexes that catalyze oxidative decarboxylation reaction which converts keto-acids to their corresponding CoA complex.

How many coenzymes are used by α-keto acid dehydrogenase complex?

5 coenzymes same as pyruvate dehydrogenase and α-ketoglutarate dehydrogenase .
(thiamine pyrophosphate, lipoic acid, FAD, NAD+, CoA).



-branched chain α-keto acid dehydrogenase it can be defective in function or can be mutated in certain people ,these mutations result in either complete loss of activity of the enzyme or partial loss of the activity .When the gene that codes this enzyme gets mutated this result in a disease called **Maple syrup urine disease** AKA branched-chain ketoaciduria , this disease results in elevation in the concentration of branched-chain keto acid and their corresponding branched-chain amino acid in the blood so they will be expressed in urine.

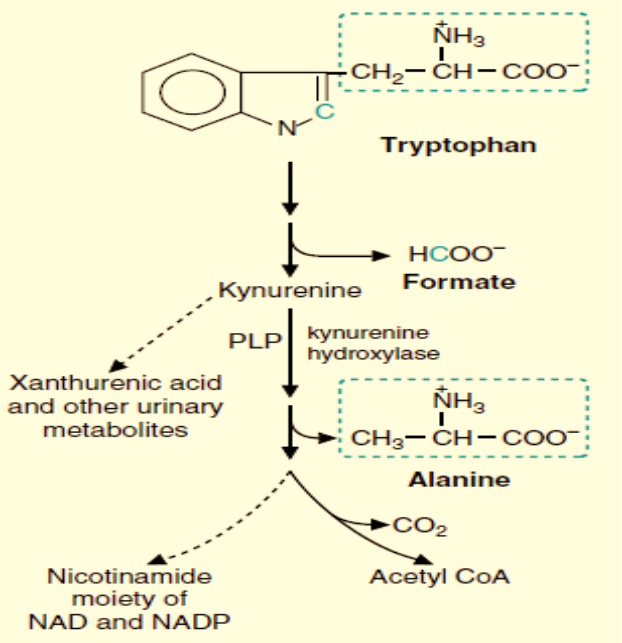
-Maple is known in Arabic as (قيقب) which is a tree that has a special smell which came from the branched chain amino acids and their keto-acids ,so when the amount of these keto-acids elevate in the urine it will have a smell similar to Maple tree (قيقب)and that's how they came up with this naming .

❖ <u>amino acids that form ketogenic compounds (acetoacetate +acetyl-coA)</u>

- They involve Leucine, Lysine (strictly ketogenic), Tryptophan ,Tyrosine, Phenylalanine, Isoleucine (Glucogenic +ketogenic)

Leucine and Isoleucine we have just explained them. Tyrosine and Phenylalanine, we have explained them in the previous lecture

❖ Tryptophane



-It's the biggest amino acid in size .It's side chain has 2 rings

-The back bone +the first carbon of the side chain without the 2 rings is exactly the same as **<u>alanine .</u>**In the degradation pathway of Tryptophan, this structure (The back bone +the first carbon of the side chain without the 2 rings) will leave the tryptophan as alanine. Alanine will be produced And the rest of the carbons (ring carbons) will be degraded to give Acetyl-CoA in a decarboxylation rxn which releases CO2. Alanine can be used to make glucose. That's why we consider tryptophan as both ketogenic(produce Acetyl CoA) and glucogenic (produce Alanine which glucose can be produced from).

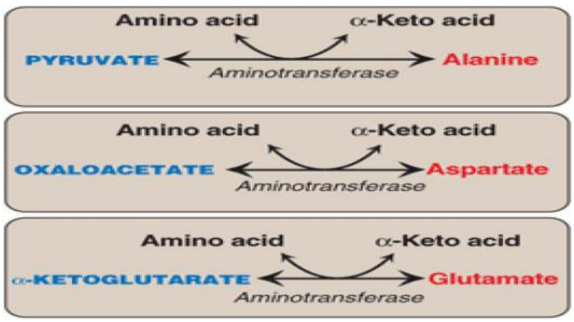
-The ring structure has Nitrogen atom and if we add another carbon to it, it will make a 6-ringed structure which will make the structure of **<u>Niacin</u>** (vitamin B3). Niacin is required to be obtained from diet ,and because the degradation of Tryptophan -which is an essential amino acid- gives a structure from which Niacin can be built, this help to decrease Niacin requirement from the diet ,"the more Tryptophan we eat, the less the requirement of Niacin from the diet".

-Niacin (nicotinic acid) can be used to build up NAD+ and NADP+

*the doctor will not talk about the degradation pathway of proline and lysine because he doesn't like them :D *

Biosynthesis of non-essential amino acids

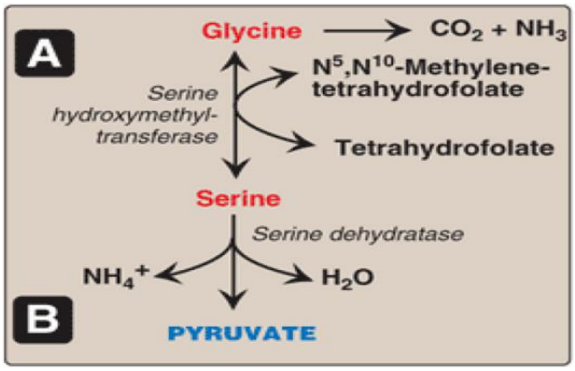
We are done with degradation now we will talk about synthesis ,Non-essential amino acids can be synthesized through different processes including:



- Synthesis from α-keto acids : **alanine** can be synthesized from *pyruvate* ,**glutamate** can be synthesized from *α-ketoglutarate* and **aspartate** can be synthesized from *oxaloacetate*.

- Amidation which is the formation of amide bond (nitrogen connected to carbon).The amino acids that can be formed through amidation (which is addition of an amino group/ free ammonia to structures) are: **Glutamine** (formed by adding amino group to *glutamate*) and **Asparagine** (from amidation rxn of *aspartate*).

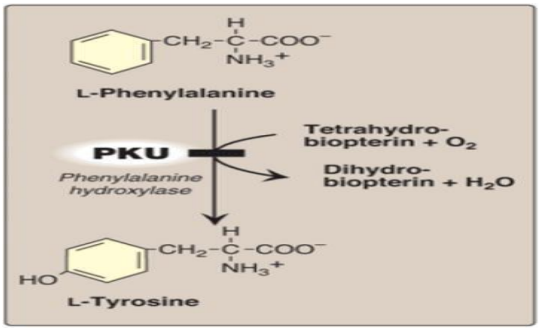
- **Proline** can be synthesized from *glutamate* through cyclization &reduction reactions (not important)



- **Serine** can be synthesized from *Glycine* by adding a methyl group with hydroxyl to glycine and this is catalyzed by the enzyme serine hydroxymethyl-transferase(requires tetrahydrofolate).

- **Glycine** can be synthesized from *serine* by the reverse direction of the previous reaction and by the same enzyme.

- **Cysteine**: carbon skeleton is obtained from *serine* and the sulfur group is obtained from *Homocysteine* which originally comes from *methionine*. The rest of the carbon skeleton of Homocysteine will be converted into α-ketobutyrate→propionyl CoA →succinyl CoA.



- **Tyrosine** can be synthesized by hydroxylating*Phenylalanine* which is catalyzed by the enzyme Phenylalanine hydroxylase and

this reaction requires tetrahydrobiopterin as a coenzyme .

Metabolic defects in amino acid metabolism

- they are commonly caused from mutation in genes, this defect may result in complete or partial loss in catalytic activity of the enzyme ,it's extremely rare to have a mutation which result in a complete loss of the catalytic activity of an enzyme responsible of amino acid metabolism

- Most amino acids diseases are rare, and to have a complete loss of the enzyme is very very rare; mutations in the enzymes responsible for amino acid metabolism most commonly result in a partial loss of the catalytic activity.

- When we have defect in amino acid metabolism the concentration of the enzyme substrate which is amino acid will be high in the blood and the urine and kidney this can result in kidney stones that you can get out through laser or surgical treatment but the most important problem in metabolic defects in amino acid metabolism is the accumulation of amino acids and their corresponding keto-acids in the brain ,they will accumulate and precipitate within the brain and they can't be degraded and if this starts early in a genetic disease resulting in mental retardation; most the amino acid metabolism defects if not treated will result in mental retardation.

Phenylketonuria (PKU)

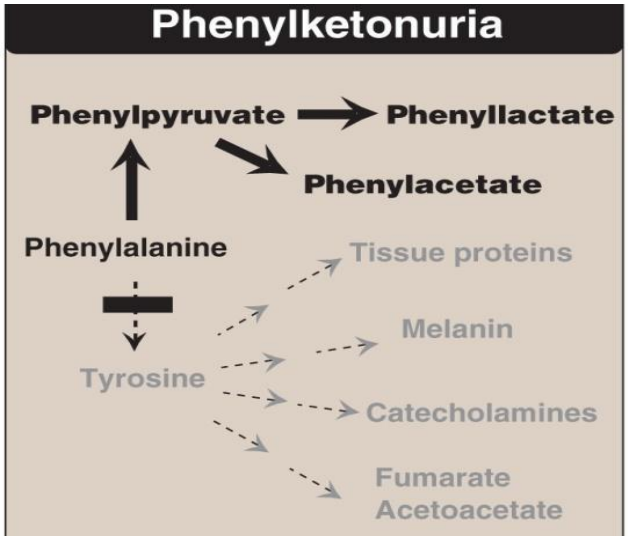
-It is the most common metabolic disorder in amino acid metabolism it's characterized by a deficiency in the enzyme Phenylalanine Hydroxylase (that converts Phenylalanine to Tyrosine) and this will cause accumulation of phenylalanine and deficiency in Tyrosine .

How to diagnose it ?

When the baby is born you start feeding proteins through milk to the newborn within 24 hours of his birth and after protein feeding you wait for 1-2 days for the diagnosis to take place and then you test the amount of amino acids , if the concentration of amino acids are normal then there is no defect but if a certain amino acid was high in concentration this means that it's not getting converted to its metabolite and the enzyme

is defected , if you find during this diagnosis that phenylalanine is higher than normal in the newborn and Tyrosine is low that means the babe has PKU .

How to limit the effect of the disease ?



1- restriction of Phenylalanine from the diet but this isn't enough , the real problem in the patients characterize by phenylketonuria is not just High amount of Phenylalanine in the blood but also the decrease in the amount of Tyrosine because Tyrosine in incorporated in tissue proteins and melanin, very essential in the synthesis of catecholamines (epinephrine, norepinephrine ,dopa; dopamine), and the product of carbon from its skeleton degradation are fumarate and acetoacetate; so if there is a defect in Tyrosine, you will have a problem in these compounds formation so you can't live without it.

2- So the restricting in diet will not correct the situation, you have to have a replacement therapy for tyrosine, so tyrosine will be converted to the other compounds. (replacement therapy).

Maternal Phenylketonuria : the mother has the disease and she is restricted from phenylalanine and taking supplements of Tyrosine , she should be very careful if she wants to have a babe, she should have a real restriction of phenylalanine in the diet; because it directly affects the child, she should starts to control it after knowing that she is pregnant because the intrauterine environment is rich in Phenylalanine which can cross the placenta accumulate in the babe causing mental retardation because the neural system is formed in the first few weeks of pregnancy; so the effect of high phenylalanine in the mother can be expressed in the child and affects his brain development.

As we said phenylketonuria results from deficiency in phenylalanine Hydroxylase enzyme, but is there any other way to develop the same symptoms as in PKU without phenylalanine hydroxylase defeciency ?

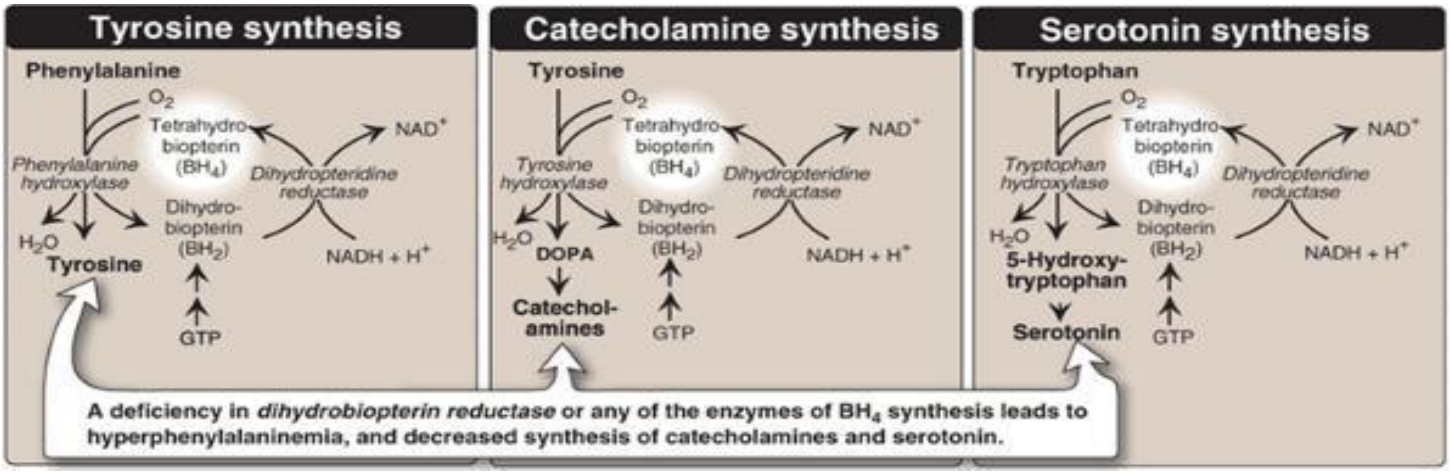
Yes in 2 cases :

1- If there was a deficiency in tetrahydrobiopterin (BH4) coenzyme which is the coenzyme responsible for ring hydroxylation (it's turned to its active oxidized state from BH4 to BH2 by the enzyme dihydrobiopteridin reductase)
2- If the coenzyme is there but there was a deficiency in dihydropteridin reductase enzyme which is responsible for converting the coenzyme from the reduced state (BH4) to the active oxidized state (BH2).

The coenzyme is also involved in converting Tyrosine to catecholamines (dopa, dopamine, norepinephrine, epinephrine, melanin) through Tyrosine hydroxylase enzyme so if you have coenzyme deficiency there will be a decrease in the amount of these catecholamines and if you have Phenylalanine Hydroxylase deficiency, Phenylalanine is not converted to Tyrosine and Tyrosine is not converted to the other molecules because it's not there so there should be another way to differentiate between the two causes of PKU.

How to differentiate if the symptoms of PKU are caused from a deficiency in Phenylalanine Hydroxylase enzyme or deficiency in the coenzyme ?

Through a reaction that converts Tryptophan to serotonin and this reaction requires BH4 as a coenzyme (ring hydroxylation), if you have phenylalanine Hydroxylase deficiency as a disease you will have low Tyrosine high phenylalanine and normal levels of Tryptophan and serotonin but if you have a deficiency in BH4 coenzyme or dihydropteridin reductase enzyme you will have low Tyrosine high phenylalanine ,LOW SEROTONIN AND HIGH TRYPTOPHAN .



Symptoms of phenylketonuria

1- People who have phenylketonuria usually have a mousey odor (رائحة فيران) this odor is caused by high concentration of Phenylalanine and it's metabolites :phenyllactate ,phenylacetate, phenylpyruvate (these metabolites smell like mice because they are found in high concentrations in them) when phenylalanine is not converted to Tyrosine, it will start to be converted to this metabolites.

2- CNS symptoms like mental retardation, failure to walk or talk,seizures, …., and failure to grow; any problem of the CNS will affect those patients depending on the aggregation of amino acids and where it happens and what function the amino acids disrupts. Untreated PKU typically shows symptoms of mental retardation by year one .

3- Hypopigmenation because Tyrosine is needed to be converted to melanin so if the amount of Tyrosine is low , melanin will be low resulting in hypopigmenation (fair hair , light skin color ,blue eyes)

Maple syrup urine disease

We already mentioned it so we will revise it , branched chain amino acids are converted to their corresponding keto acids by branched chain α-amino acid aminotransferase then these keto acids will get converted to their coA complex by branched chain α-keto acid dehydrogenase which also produces CO_2 and NADH .

-If there is any mutation in branched chain α-keto acid dehydrogenase then Maple syrup urine disease will occur which is characterized by high concentrations of branched chain amino acids and their keto acids in the blood and urine .As other amino acids metabolites, they are toxic to the CNS and interfere with the brain function so if not treated, it will result in mental retardation .

Treatment : there is no treatment for genetic diseases but I can limit the disease by dietary restriction of in the amounts of the branched chain amino acids: leucine , isoleucine and valine and there are specific formulas which can be sold for those patients with low branched chain amino acids concentrations.

Homocystenuria

As the name implies it means high amount of homocysteine in urine and also we have homocystenemia (high amounts of homocysteine in the blood)

How can I get Homocysteine ?

Methionine joins adenosine forming SAM then one carbon unit will be lost forming SAH then adenosine will be lost forming Homocysteine.

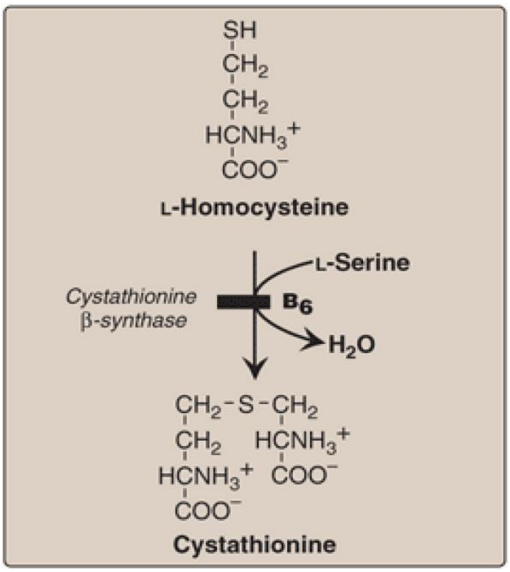
How can the amount of Homocysteine get high in the blood ?

If its building up is high or if there are defects in the pathways responsible for its degradation which are two pathways , one pathway converts homocysteine back to methionine and the other pathway in which homocysteine joins with serine to eventually form cysteine and α-ketobutryate which results in Succinyl CoA.

-The conversion of Homocysteine to methionine requires vitamin B9 and B12 if any of them was deficient then Homocysteine will be high.

- The conversion of Homocysteine to succinyl-coA requires PLP if it was deficient then homocysteine will be high

-The conversion of Homocysteine to cysteine by joining Serine involves cystathionineβ-synthase if it was deficient then homocysteine will be high



So there are multiple causes of Homocystenuria :

1- Deficiency in Vitamin B9
2- Deficiency in Vitamin B12
3- Deficiency in Vitamin B6
4- Deficiency in cystathionie β-synthase enzyme

-However the most common cause of Homocysternuria is a defect in cystathionie β-synthase enzyme .

How can we treat this disease ?

1- supplementation of the coenzyme that is deficient or a combination therapy of all that vitamins (B9 .B12,B6) so the enzyme will work better and the amount of homocysteine will be decreased.
2- Restriction in the amount of methionine to decrease the building up of homocysteine.

Albinism

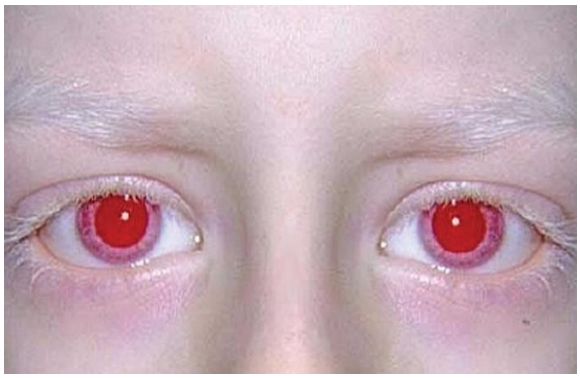
You all know Albenos people; they are so white , their eyelashes are white…

-Albinism Refers to a group of conditions in which a defect anywhere in converting tyrosine to melanin; at any step if there is a problem there will be albinism (defect in tyrosine metabolism results in a partial or full deficiency in the production of melanin .

-Tyrosinase enzyme catalyzes the addition of –OH on tyrosine and it catalyze the rate limiting step of melanin production .Complete albinism which extremely rare is result from a complete deficiency in Tyrosinase activity .

Characteristics of complete Albinism :

1- Extreme whiteness to the extent that veins can be seen in their hand soles.
2- No pigmentation in the eye and the pupil of their eyes appear red because they are very clear so they show the blood behind them.



- Most commonly in albinism is the partial loss more common than the complete loss.

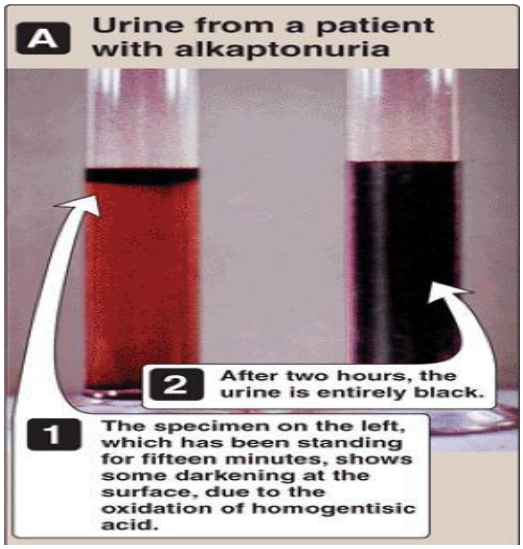
Complications associated with loss of melanin production in albinism in general :

1- Vision defects because the melanin in the pupil helps to protect the retina preventing UV light from entering to the retina so the retinal cells will not be affected and can work efficiently ,so when melanin is not there the retinal cells will be affected resulting in vision defects
2- Higher risk of skin cancer because melanin normally protect the cells of the skin from UV.

Alkaptonuria

-This disease is characterize by a deficiency in homogentisic acid oxidase enzyme which will cause the accumulation of homogentisic acid (known by its black color) in urine and blood.

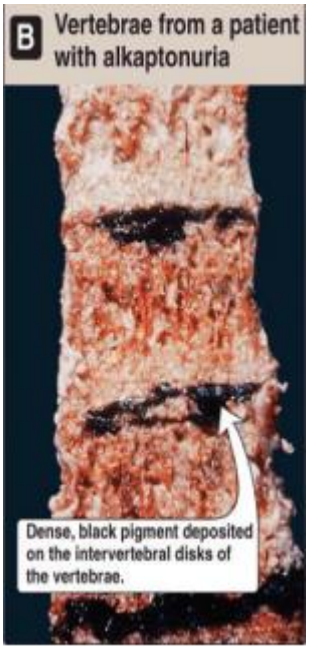
-homogentisic acid is an intermediate produced in the pathway of degradation of Phenylalanine and Tyrosine ,it will be oxidized by Homogentisic acid oxidase to eventually give fumarate and acetoacetate .



Diagnosis : it's done by taking a urine sample it will be yellowish, put it in the open air and within few minutes it will turn red then it will turn completely black because the Homogentisic acid which is accumulated in that urine sample will be oxidized by the air and it will give this black color

Complications of Alkaptonuria :

Because it is high in the blood, it will enter the tissues; it will accumulate on the joints and intervertebral disks resulting in black pigmentation and because this material is accumulating on the joints the movement will become very hard and painful.



-Alkaptonuria is not life threatening (not fatal), however it's associated with Arthritis that could be severely crippling; so you won't be able after w hile to move your joints at all .

Review test (solve these questions when you finish all 4 lectures)

1-Which of the following compounds is shared in both TCA and urea cycle

A- α-ketoglutarate
B- Pyruvate
C- Succinyl-coA
D- Fumarate

2-in a 55-year old man ,who has been diagnosed with cirrhosis of the liver ,Ammonia is not getting detoxified and can damage the brain , all the following enzymes can covalently bind ammonia to structures to decrease it's amounts except :

A- Carbamoyl phosphate synthase 1
B- Asparagine synthase
C- Glutamin synthase
D- Glutamate dehydrogenase

3-in a new born presenting with refusal to feeds and irritability , a deficiency is cystathionineβ-synthase has been detected which one of the following compounds will elevate in the blood ?

A- Serine
B- Glutamate
C- Homocysteine
D- Valine

4- 3 month year old child evaluated with vomiting and an episode of convulsions .Laboratory results show hyperammonemia which of the following enzyme defects is most likely to be here ?

A- Glutaminase
B- Arginase
C- Argininosuccinate synthase
D- Carbamoyl phosphate synthetase 1

5-Which of the following amino acids is NOT converted to succinyl-coA ?

A- Histidine
B- Valine

C- Isoleucine
D- Methionine

6-The synthesis of all the following compounds except one is deficient in a patient suffering from PKU which one ?

A- Melanin
B- Serotonin
C- Catecholamine
D- Thyroid hormones

7-All the following amino acids are donors of one carbon compounds except :

A- Histidine
B- Tryptophane
C- Serine
D- Tyrosine

8- The first line of defense in the brain against Hyperammonemiais :

A- Urea formation
B- Glutamine synthase
C- Asparagine synthase
D- Glutaminase

9-A patient diagnosed with homocystenuria should be supplied by all the following except :

A- Folic acid
B- PLP
C- Tetrahydrobiopterine
D- Vitamin B12

10 –In a patient suffering from Cystenuria which of the following amino acids will not be seen in the patients Urine :

A- Methionine
B- Arginine
C- Lysine
D- Ornithine

11- Regarding Glutamate dehydrogenase which of the following statements is correct:

A- Required in transamination reaction
B- Universally presented in all the cells of the body
C- Can utilize either NAD+ or NADP+
D- Catalyze conversion of glutamate to glutamine

12-In mammalian tissues Serine can be the biosynthetic precursor of which amino acid ?

A- Methionine
B- Glycine
C- Aspartate
D- Alanine

13- A child was brought to the pediatric with a complaint of black colored urine .A disorder in phenylalanine metabolism was detected .A low phenylalanine diet and supplements of vitamin C were recommended which enzyme is defected in that child ?

A- Homogentisic acid oxidase
B- Phenylalanine Hydroxylase
C- Tyrosinase
D- Cystathionineβ-synthase

14- A person with PKU will convert :

A- Phenylalanine to phenylpyruvate
B- Phenylalanine to Tyrosine
C- Phenylpyruvate to phenylalanine
D- Tyrosine to phenylalanine

15-Tryptophane degradation pathway can give all the following except :

A- Niacin
B- Acetyl-coA
C- Glycine
D- Alanine

16- Autocatalytic activity is found in which of the following enzymes :

A- Pepsine
B- Trypsine
C- All of the above
D- Elastase

1-D	2-B	3-C	4-D	5-A	6-B	7-D	8-B	9-C	10-A
11-C	12-B	13-A	14-A	15-C	16-C				

Best of luck for everyone in the finals :D

Dedication to MuhannadHaddadin and hasan hammo for their continuous support