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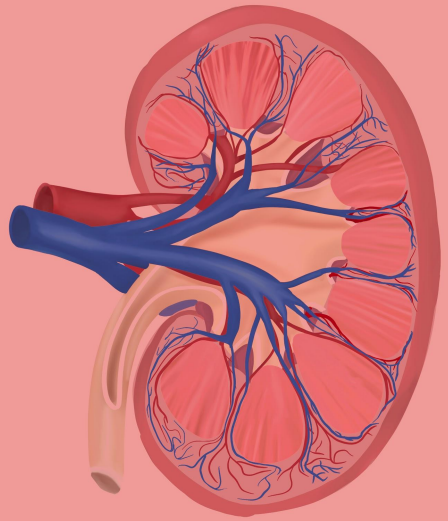
Inborn errors of amino acids metabolism



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Main text

IMPORTANT

Extra Info

Drs Notes

Revised & Approved by: Shayma Abdullah Alshaeran, Faisal Alotaibi

Renal Block - Biochemistry Team

MED439

Objectives:

- Identify the amino acid degradation and synthesis of non-essential amino acids
- Recognize the metabolic defects in amino acid metabolism that lead to genetic diseases

Inborn Errors of Amino Acid Metabolism

- Inborn Errors of Amino Acid Metabolism results from the **loss** or **deficiency** of a specific enzyme caused by gene loss or mutation.

- **As a result of the enzyme loss (or the cofactor):-**

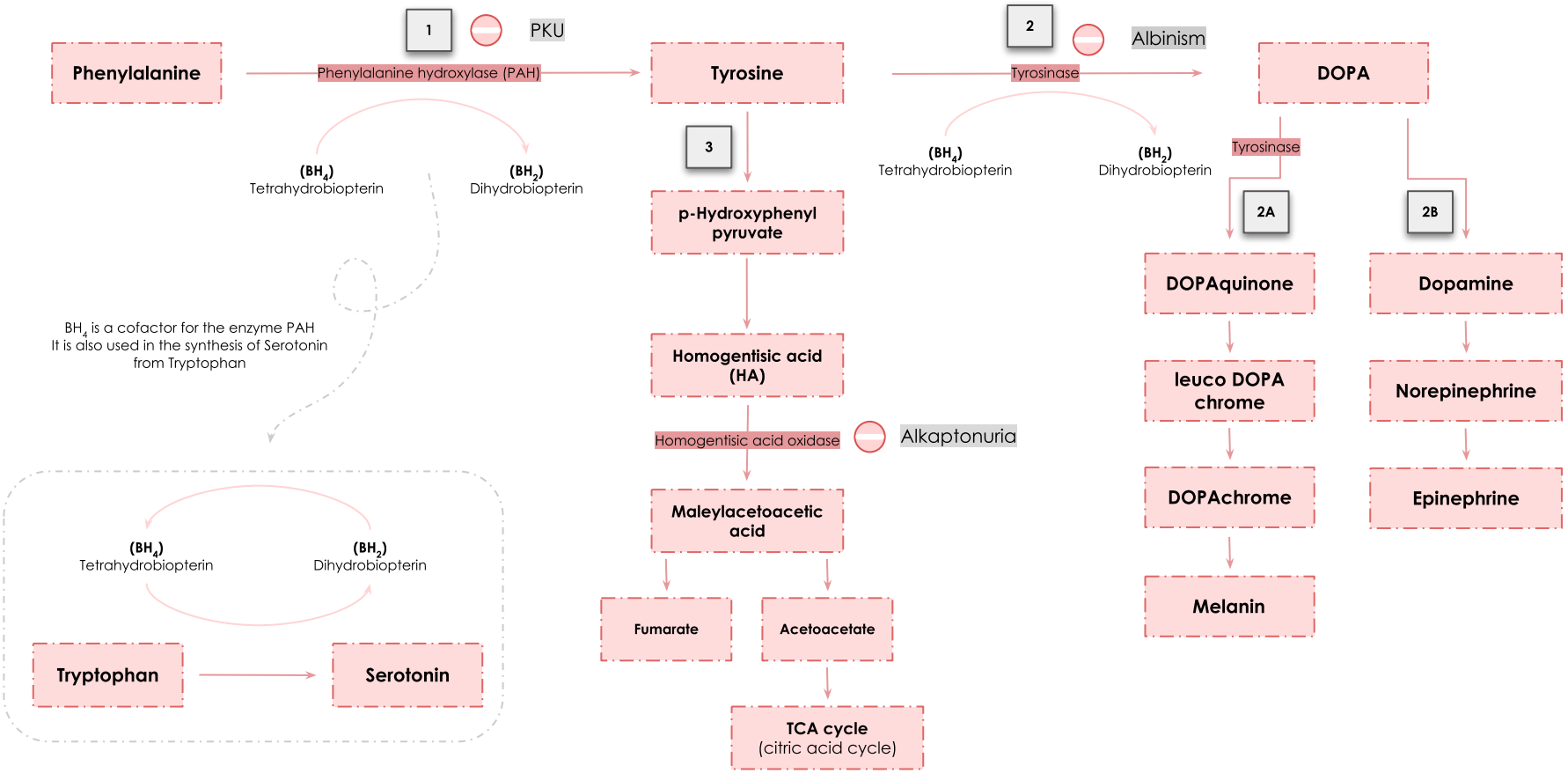
  - The substrate will **accumulate** in the body.
  - The body will face **deficiency** of the needed product.

- **Enzyme or CoFactor deficiency → Product deficiency & Substrate accumulation.**

Diseases of inborn errors of amino acid metabolism:

- Phenylketonuria (PKU) (most common)
- Alkaptonuria
- Albinism
- Maple Syrup Urine Disease (MSUD)
- Homocystinuria

Normal Pathway of Phenylalanine / Tyrosine



Pathway of Phenylalanine

1 If you recall foundation block, Phenylalanine is an essential amino acid. **Normally**, it is converted to Tyrosine by an enzyme called **Phenylalanine hydroxylase (PAH)** along with its cofactor, which is called **Tetrahydrobiopterin (BH_4)**. Later on, this Tyrosine is catabolized or transformed to generate a wide variety of biologically important molecules just as in steps 2 & 3.
Also, tyrosine can be metabolized to produce hormones such as thyroxine.

A deficiency in the enzyme **Phenylalanine hydroxylase** OR its cofactor **(BH_4)** will lead to a disease called Phenylketonuria (PKU).

- **Note that:** BH_4 is also used in the synthesis of Serotonin from the amino acid Tryptophan.
- **Note that:** BH_4 is also used in the synthesis of DOPA from the Tyrosine.

2 Tyrosine is acted upon by an enzyme called **Tyrosinase** and it will be converted to DOPA, Then:

2A Tyrosine can serve as a precursor of the pigment **melanin**. The first step is the conversion of tyrosine to dopaquinone by the **SAME** enzyme known as **Tyrosinase**.

OR

2B It can be metabolized to produce catecholamines & neurotransmitters such as dopamine, adrenaline, or noradrenaline.

A deficiency in the enzyme **Tyrosinase** will lead to a disease called Albinism.

3 Tyrosine can also be catabolized all the way down into fumarate and acetoacetate. This particular pathway for tyrosine degradation starts with generation of p-hydroxyphenylpyruvate. Then, it will be converted to **homogentisic acid**. In order to proceed, a unique enzyme known as **Homogentisic acid oxidase** is required. Through this enzyme, maleylacetoacetate is created. then it will split into acetoacetate and fumarate. Acetoacetate is a ketone body, which is activated with succinyl-CoA, and therefore it can be converted into acetyl-CoA,

A deficiency in the enzyme **Homogentisic acid oxidase** will lead to a disease called Alkaptonuria.

★ Red = very Important

Phenylketonuria (PKU)

- Most common disease of amino acid metabolism .
- Due to deficiency of **Phenylalanine hydroxylase enzyme (PAH)** .
- Results in hyperphenylalanin**emia** say that 5 times fast anyways let's continue (it results from elevated concentrations of the **amino acid phenylalanine** in the blood since it's not being hydroxylated) and **Tyrosine deficiency**.
- No hydroxylation of Phenylalanine = No Tyrosine = No catecholamines, no melanin, and no decomposition pathway (fumarate and acetoacetate).
- Phenylalanine hydroxylase enzyme (PAH) Cannot work without it is **CoFactor (BH_4)** .

Phenylketonuria (PKU) is divided into two types:

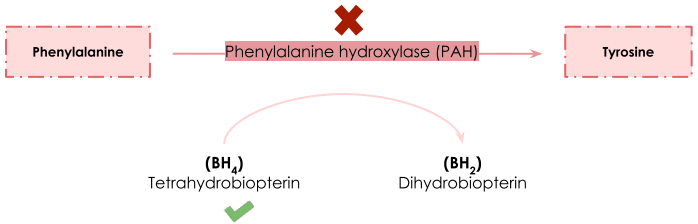
1. Typical PKU

Caused by:

Deficiency of the Enzyme

Phenylalanine hydroxylase (PAH)

CoFactor is there, but enzyme is defective / absent.



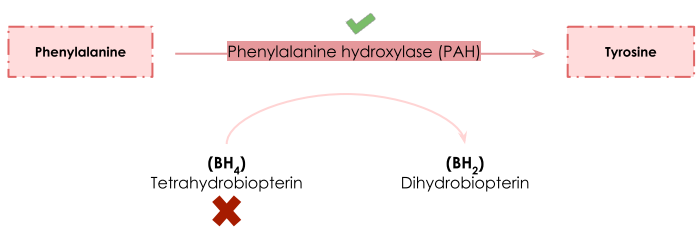
2. Atypical PKU

Caused by:

Deficiency of the CoFactor

Tetrahydrobiopterin (BH_4)

Enzyme is there, but cofactor is defective / absent.



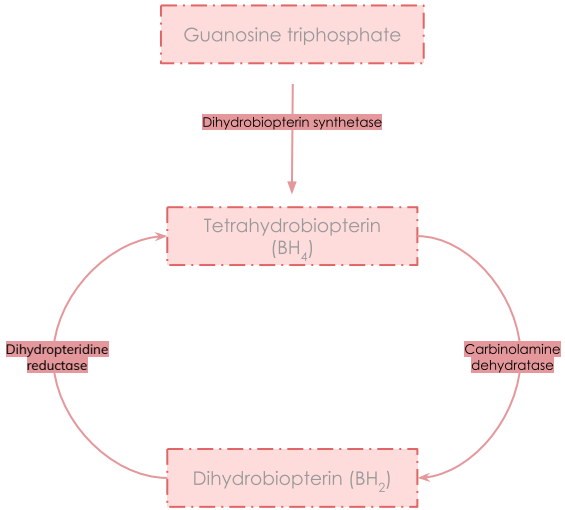
Atypical Phenylketonuria (PKU)

- We know that the conversion of Phenylalanine to Tyrosine cannot be done without the CoFactor (BH_4).
- We also know that the **deficiency BH_4** leads to Atypical PKU. Which means:
  - That even if phenylalanine hydroxylase level is normal, the enzyme will not function without BH_4,
  - That hence, Phenylalanine will be accumulated.

- Be aware that BH_4 is also used NOT only as a cofactor for the enzyme PAH, **it is also used in:**
  - **Melanin** biosynthesis from tyrosine.
  - Synthesis of catecholamines (requires BH_4 to **convert tyrosine into DOPA**).
  - Synthesis of serotonin (from the amino acid **tryptophan**).

So, What are the enzymes responsible for the deficiency of the CoFactor BH_4?

- **Dihydrobiopterin synthetase**.
- **Dihydropteridine reductase**.
- **Carbinolamine dehydratase**.



A very helpful explanation:
(no need to memorize function/mechanism, just know the names)

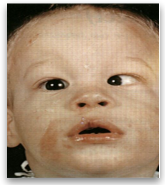
BH_4 is made from the molecule GTP (Guanosine triphosphate). GTP is converted into BH_4 in three stages, one of these stages is catalysed by the enzyme **(Dihydrobiopterin synthetase)**

And when BH_4 is used for chemical reactions (e.g. catalyzing the reaction of PAH), it is turned into another molecule, BH_2 in a reversible process with the help of the enzyme **(Carbinolamine dehydratase)**

BH_2 can then be **recycled** back into BH_4. " This recycling reaction is carried out by the QDPR enzyme **(Dihydropteridine reductase)** " .

So, in short, if one of these enzymes is mutated or defective, whole BH_4 thing is defected, and Atypical PKU will be seen.

Characteristics of Phenylketonuria (PKU)



- Deficiency in the enzyme (PAH) or CoFactor (BH_4) = **No Tyrosine + Accumulation of Phenylalanine .**
- **No Tyrosine** → **No Dopa** → **No neurotransmitters (catecholamines)** → CNS symptoms → Mental retardation, failure to walk or talk, seizures, etc..
- **No Tyrosine** → **No melanin** → Deficiency of melanin → **Hypopigmentation** → Pale/white/light skin in PKU . patients
- Remember that BH_4 is also necessary in other things. No BH_4 → No serotonin and No neurotransmitters and No Tyrosine.
- Accumulation of Phenylalanine → Inhibition of enzyme **Tyrosinase** (negative feedback) → No Hydroxylation of tyrosine . (Thus, no melanin and no neurotransmitters)
- Accumulation of Phenylalanine → Elevated phenylalanine in tissues, plasma, and **urine (Gives urine a mousy odor)**.
- High Phenylalanine in **urine** → Activation of degradation pathway → **Phe is degraded to:** Phenyllactate, Phenylacetate, and Phenylpyruvate.

Phenylketonuria (PKU)

Diagnosis of PKU:

- **Prenatal (before birth):** done by detecting gene mutation in fetus.
- **Neonatal (after birth, new born):** done by measuring blood Phe levels.

Treatment: A lifelong Phenylalanine Restricted diet.

Summary of PKU:

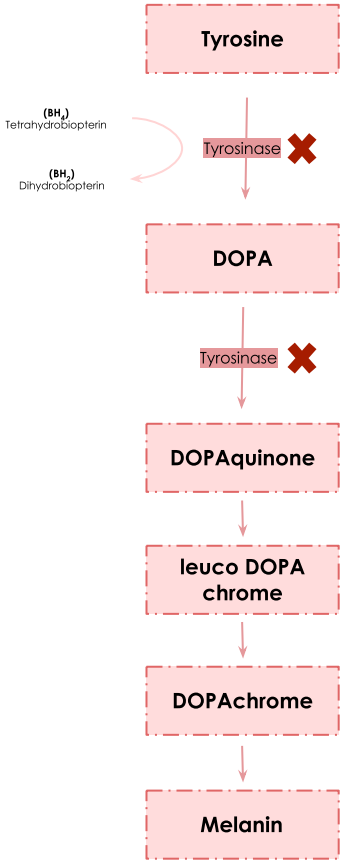
Typical PKU	Atypical PKU
Deficiency of enzyme Phenylalanine hydroxylase (PAH)	**Deficiency of CoFactor Tetrahydrobiopterin (BH_4)**
What caused the deficiency of PAH? Rare mutations	What caused the deficiency of BH_4? mutations in: Dihydrobiopterin synthetase, Dihydropteridine reductase, and Carbinolamine dehydratase
- **Note that:** Even if (PAH) levels were normal, the enzyme will not function WITHOUT its cofactor (BH_4). - **Note that:** BH_4 is also used in the synthesis of Serotonin AND DOPA.	
Characteristics of PKU: • Phenylalanine accumulation + Tyrosine deficiency. • CNS symptoms (e.g. mental retardation) • Hypopigmentation & melanin deficiency • Mousy odor of urine.	
Diagnosis: Prenatal (gene mutation in fetus) / Neonatal (measuring blood Phe levels). **Treatment:** A life long Phe-restricted diet.	

Every time you read PKU be like: click here watch it till the end

Albinism

- A disease of **tyrosine** metabolism, and as we just said, Tyrosine is involved in **melanin** production.
- Deficiency of the enzyme **Tyrosinase** leads to albinism. (Tyrosinase is the enzyme catalyzing the 1st and 2nd steps in tyrosine degradation pathway)
- **Melanin** is a pigment of hair, skin, eyes, in albino patients, this pigment is absent.

The difference between melanin deficiency in albinism and in PKU is the causative defective agent, **to illustrate**: in PKU, the reason behind melanin deficiency was defective enzyme PAH or cofactor BH_4. However, here in albinism the problem and defect is in enzyme **Tyrosinase**.



Symptoms of Albinism:

Hair, skin, eyes appear **white.** (Due to the absence of melanin)
Albino people are more prone to skin cancer.

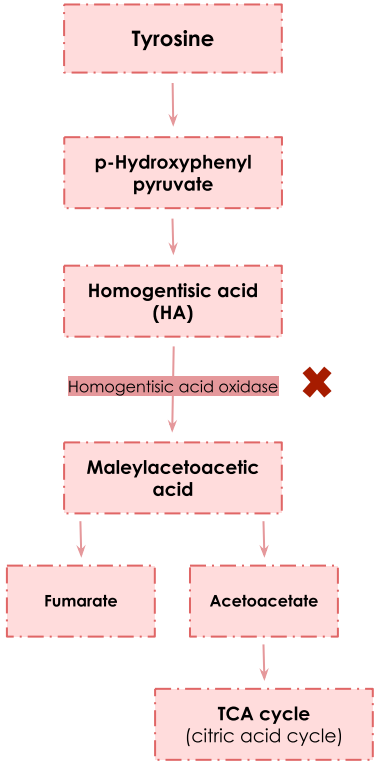
Vision defects, severely impaired sharpness of vision (visual acuity) and problems with combining vision from both eyes to perceive depth (stereoscopic vision).

Photophobia, an experience of discomfort or pain to the eyes due to **light exposure** or by presence of actual physical sensitivity of the eye.

★ **Dr:** Focus on the enzyme only

Alkaptonuria

- A rare disease of tyrosine degradation, usually asymptomatic until adulthood .
- Due to deficiency of the enzyme **homogentisic acid oxidase.**
- Homogentisic acid is accumulated in blood, **tissue,** and **cartilage.**
- Homogentisic aciduria: elevated homogentisic acid in urine (problem is that it'll get oxidised).
- This homogentisic acid will start the oxidative pathway and cause inflammation.



Characteristics of Alkaptonuria:

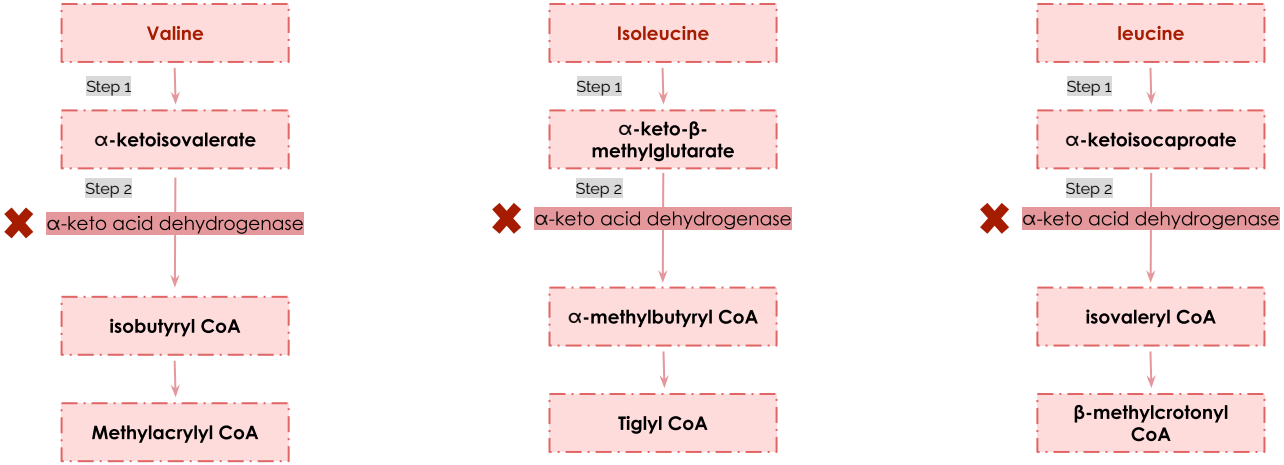
1. Early arthritis, Black pigmentation of cartilage and tissue .
2. Dark pigmented urine over time, due to **oxidation** of homogentisic acid .

Treatment of Alkaptonuria: Restricted intake of tyrosine and phenylalanine (because it will converts to tyrosine)
Will reduce homogentisic acid levels and reduce the dark pigmentation.

★ **Dr:** Focus on the 3 amino acid names + The deficient enzyme

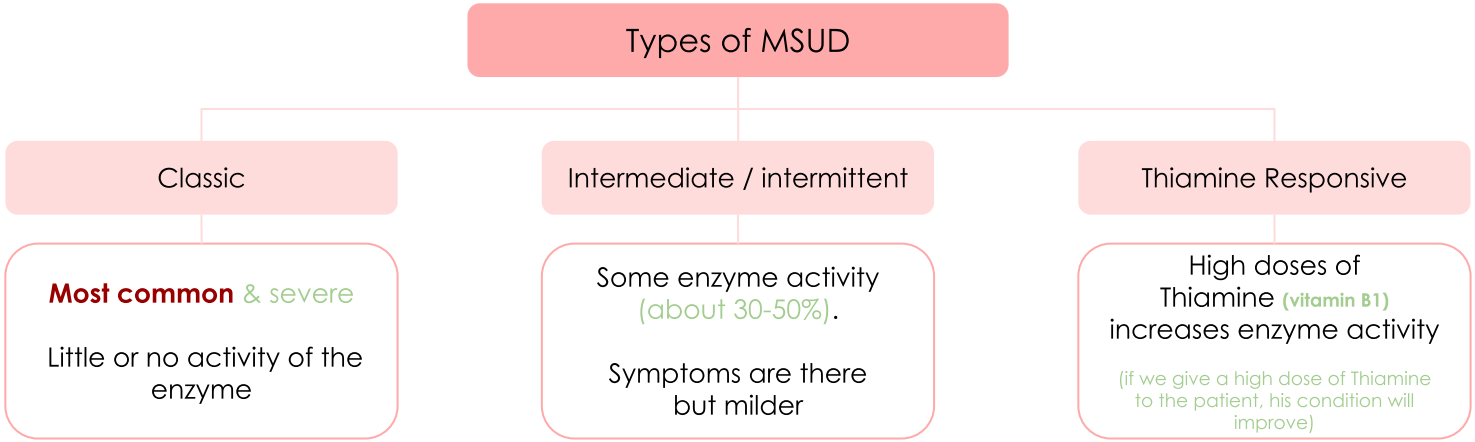
Maple Syrup Urine Disease (MSUD)

- The amino acids **leucine**, **isoleucine** and **valine** are broken down and decarboxylated by an enzyme.
- This enzyme is: branched chain **α-ketoacid dehydrogenase.**
- **Deficiency of this enzyme** will lead to: the accumulation of the branched-chain amino acids leucine, isoleucine and valine **in the blood** + Metabolic acidosis.
- This disease is characterized by **maple syrup odor** in the urine (unlike PKU which has a mousy odor)



Step 1 is the removal of the amino group. After this removal, we are left with KETO ACIDS (will cause metabolic acidosis).
Step 2 Then, it should be decarboxylated by the enzyme α-keto acid dehydrogenase. But it's deficient in this case.

Maple Syrup Urine Disease (MSUD)



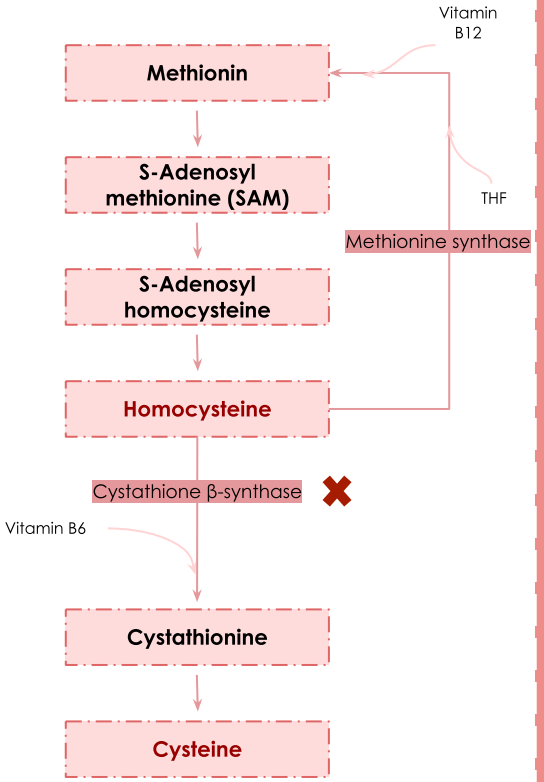
- **Symptoms are:** metabolic acidosis, mental retardation, and physical disability.
- **Treatment is:** limited intake of leucine, isoleucine, and valine.

Usually patients are given thiamine as a supplement to measure their responsiveness

★ Red = very Important

Homocystinuria

- A disease caused by defects in homocysteine metabolism.
- Homocysteine is a non-standard amino acid in our body, it is synthesized from another amino acid called methionine.
- So, we need to convert **homocysteine** to **cystathionine** by an enzyme called: **Cystathionine β-Synthase (CBS) + Its CoFactor (Vitamin B6)**
- Deficiency of **cystathionine β-synthase** will lead to high plasma and urine levels of homocysteine. (Homocystinuria)



Pathway explanation:

1. As you can see, methionine is converted to homocysteine in several steps.
2. Homocysteine in normal cases will be converted to Cystathionine by the enzyme: Cystathionine β-Synthase and Its CoFactor (Vit B6).
3. If there is a deficiency in the enzyme, **homocysteine will be converted back to methionine**, by the enzyme **Methionine synthase** and its cofactors **(Vit B12)** + **(Tetrahydrofolate, THF)**, and folic acid. And the cycle will keep going on and on..
4. So, as you can see, Methionine and its metabolites will be **accumulated** in case of deficiency of Cystathionine β-Synthase, and **cystine will be deficient**.

★ Red = very Important

Homocystinuria

High plasma homocysteine is associated with / risk factor for:

01

Vascular disease (Atherosclerosis) and heart disease. Recall CVS block

02

Skeletal abnormalities and osteoporosis. Recall MSK block

03

Mental retardation
Sad , can't say recall CNS block

04

Neural tube defect (spina bifida)

Not only caused by homocystinuria, but **also** by the Deficiency of: Methionine synthase, Tetrahydrofolate (THF), Vitamin B6, B12, and Folic acid.

05

Displacement of eye lens
Called Ectopia lentis

Treatment of Homocystinuria: Methionine-restricted diet **and** Oral administration of vitamins B6, B12 and folate.

Summary 

Disease	Substrate	★ Deficiency	Symptoms
PKU	Phenylalanine	Enzyme Phenylalanine hydroxylase CoFactor Tetrahydrobiopterin (BH_4)	Phenylalanine accumulation + Tyrosine deficiency, CNS symptoms, Hypopigmentation & melanin deficiency, Mousy odor of urine
Albinism	Tyrosine (or DOPA)	Tyrosinase	White hair, skin, eyes, Vision defects, Photophobia
Alkaptonuria	Homogentisic acid (HA)	Homogentisic acid oxidase	Pigmentation of urine, cartilage, and tissue.
MSUD	Leucine, isoleucine and valine	Branched chain α-ketoacid dehydrogenase	Maple syrup odor of urine, metabolic acidosis, mental retardation, and physical disability.
Homocystinuria	Homocysteine	Cystathionine β-Synthase (Its cofactor is Vit B6)	Vascular disease (atherosclerosis) and Heart disease Neural tube defect (spina bifida), Displacement of eye lens

Quiz

Q1 : Deficiency of the enzyme Tyrosinase leads to:			
A) PKU	B) Albinism	C) Alkaptonuria	D) Homocystinuria
Q2 : Branched chain α-ketoacid dehydrogenase acts on all the following except:			
A) Leucine	B) Lysine	C) Isoleucine	D) Valine
Q3 : Not a symptom of PKU ?			
A) Mental retardation	B) Hypopigmentation	C) Metabolic acidosis	D) Mousy odor of urine
Q4 : Defective in case of spina bifida ?			
A) Cystathionine β-synthase	B) Methionine synthase	C) Tetrahydrofolate	D) All of them
Q5 : CoFactor of Cystathionine β-Synthase ?			
A) Vitamin B12	B) Vitamin B6	C) Tetrahydrofolate	D) Folic acid.
Q6 : Have we finished all biochemistry lectures in the first year !!!!!!!!!!			
A) I'm shocked 🤯	B) So sad to say goodbye 😔	C) wait, what ! 	D) we're done? 

SAQs :

Q1: List some of the characteristics of PKU?

Q2: List the uses of BH4 beside being the cofactor of PAH

Q3: What are the amino-acids in MSUD? deficient enzyme? What is it characterized by?

Q4: List the types of MSUD and differentiate between them?

★ **MCQs Answer key:**

1) B 2) B 3) C 4) D 5) B 6) up to u 😝

★ **SAQs Answer key:**

1) No Tyrosine, Accumulation of Phenylalanine, No neurotransmitters (catecholamines), Deficiency of melanin, Elevated phenylalanine in tissues, plasma, and urine.

2) Melanin biosynthesis from tyrosine, Synthesis of catecholamines (convert tyrosine into DOPA), Synthesis of serotonin (from the amino acid tryptophan).

3) Amino acids: leucine, isoleucine and valine. Enzyme is: branched chain a-ketoacid dehydrogenase. Characterized by maple syrup odor in urine.

4) Check **slide 13**

Girls team:

- Manal Altwaim
- Duaa Alhumoudi
- Norah Almasaad
- Rania Almutiri
- Alia Zawawi
- Noura Alshathri
- Renad Alhomaidi
- Fatimah Alhelal

Boys team:

- Omar Alsuliman
- Abdullaziz Alomar
- Hamad Almousa
- Abdullah Alanzan
- Abdullah Almazro
- Abdullaziz Alrabiah

Revised by

Shatha Aldhohair

Made by

Abdulaziz Alsalem

Biochemistry439@gmail.com

@Biochemistry439