Biochemistry
Team 434

Inborn Errors of Amino Acid Metabolism

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Biochemistry of:

- Phenylketonuria (PKU)
- Maple Syrup Urine Disease (MSUD)
- Albinism
- Homocyteinuria
- Alkaptonuria

abbreviations:

Phe-Phenylalanine
Tyr-Tyrosine
Trp- Tryptophan
Leu- Leucine
Ile- Isoleucine
Val- Valine
Met- Methionine

Inborn Errors of aa Metabolism:

Caused by enzyme loss or deficiency due to gene loss or gene mutation

Phenylketonuria (PKU)

Orientation to the figure

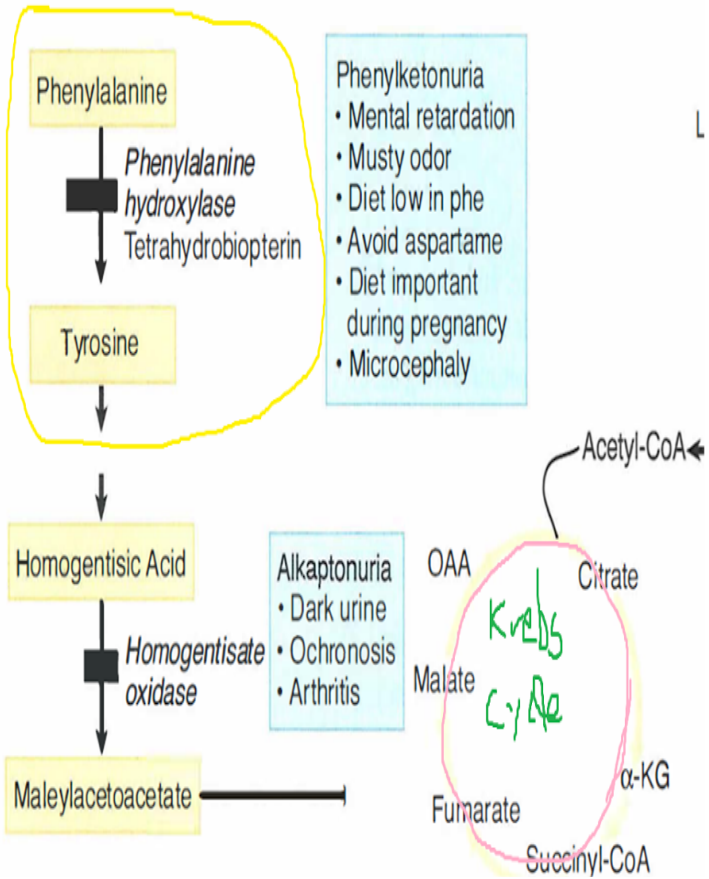
- The yellow circle points out the arrow we are interested in which gives rise to the pathology of PKU
- Notice that our body wants to use this phenylalanine amino acid for energy, & that is why it is eventually going to the Krebs cycle.
- Notice that the reaction Phenylalanine → Tyrosine requires the enzyme phenylalanine hydroxylase & the coenzyme tetrahydrobiopteren (BH4) (most important co-factor)

Pathology of PKU

- If there is a problem in the arrow that converts phenylalanine → tyrosine, this gives rise to phenylketonuria (PKU)
- Notice that to get PKU, there must be at least one of the following:

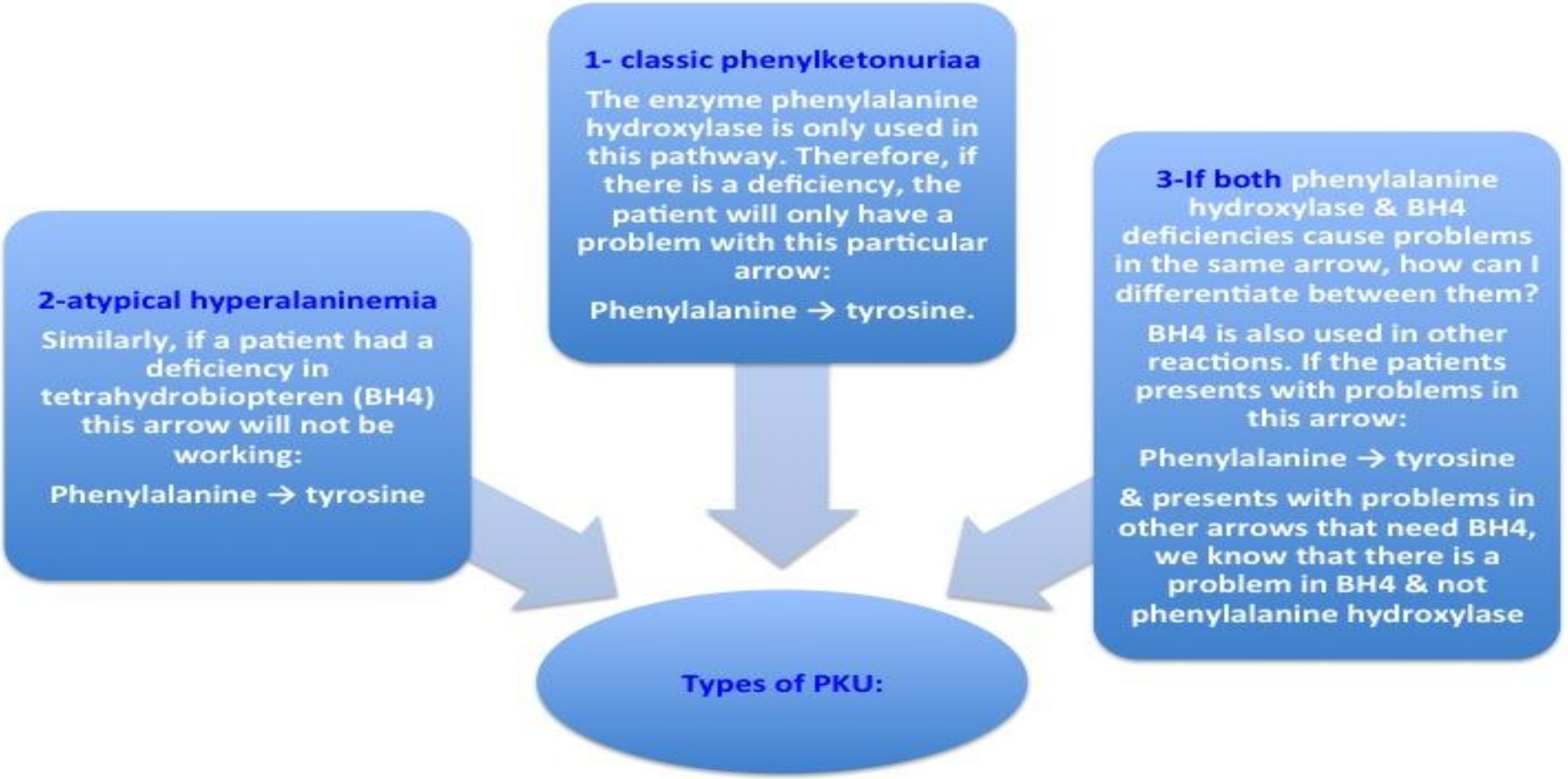
a) **classic PKU**: Deficiency in the enzyme phenylalanine hydroxylase (most common)

b) **atypical hyperphenylalaninemia** : Deficiency of the coenzyme tetrahydrobiopteren



Clinical Features of PKU

CNS symptoms	• seizures, inability of walking or talking, mental retardation
Deficiency of melanin	• because phenylalanine inhibits the enzyme tyrosinase which is used to synthesize melanin
Urine has mousy odor	• because phenylalanine is converted to other things that give this smell


1- classic phenylketonuriaa
The enzyme phenylalanine hydroxylase is only used in this pathway. Therefore, if there is a deficiency, the patient will only have a problem with this particular arrow:
Phenylalanine → tyrosine.
2-atypical hyperalaninemia
Similarly, if a patient had a deficiency in tetrahydrobiopteren (BH4) this arrow will not be working:
Phenylalanine → tyrosine
3-If both phenylalanine hydroxylase & BH4 deficiencies cause problems in the same arrow, how can I differentiate between them?
BH4 is also used in other reactions. If the patients presents with problems in this arrow:
Phenylalanine → tyrosine
& presents with problems in other arrows that need BH4, we know that there is a problem in BH4 & not phenylalanine hydroxylase
Types of PKU:

Where does BH4 come from?

- Before talking about the reactions BH4 takes part in, we should talk about where does it come from, & how could it become deficient.

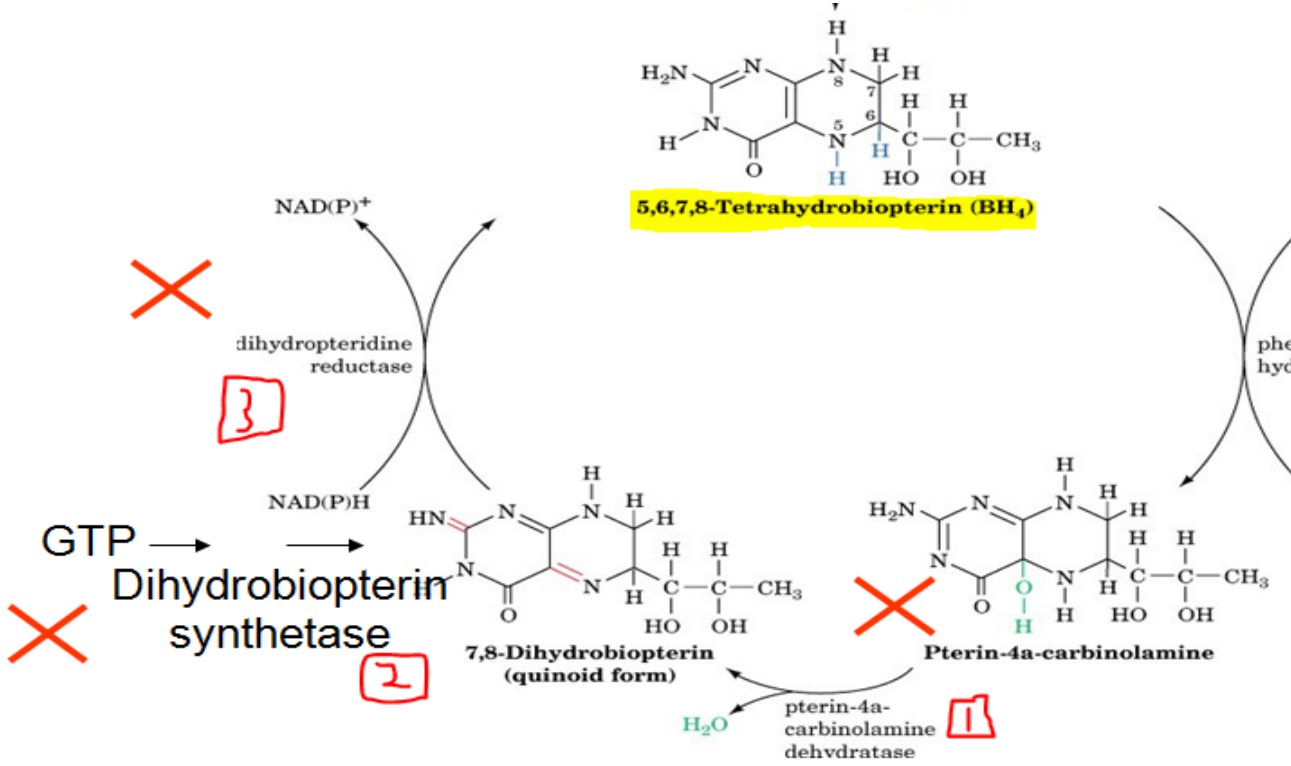
BH4 deficiency

BH4 may be deficient due to a problem with one of these enzymes:

1) Carbinolamine dehydratase

2) Dihydrobiopterin synthetase

3) Dihydropteridine reductase



These numbers are the same as the figure.

What pathways does BH4 participate in?

1) Phenylalanine → tyrosine
2) Synthesis of catecholamines such as dopamine, norepinephrine, & epinephrine
3) Synthesis of the neurotransmitter serotonin (5-HT)

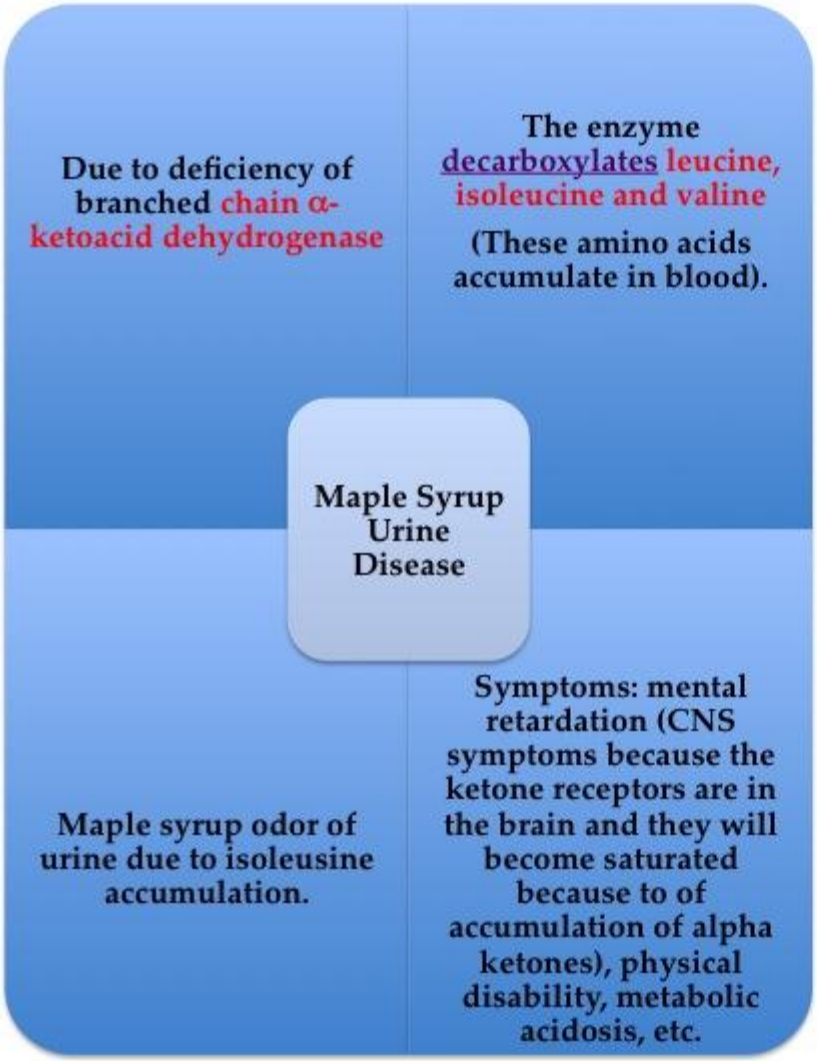
- Phenylalanine hydroxylase (classic PKU) has nothing to do with these pathways

Management of patients

- Prenatal diagnosis is available by gene studies
- Neonates may be diagnosed by measuring phenylalanine levels in blood
- Treatment: life long restricted phenylalanine diet

Extra information

- Why isn't the disease called phenylalanineuria?
- What happens is that in case phenylalanine accumulates, this amino acid will undergo a deamination reaction: the NH3 group will be removed; & this NH3 group is what gives rise to the CNS symptoms.
- The rest of the amino acid skeleton will get associated with ketones & will form phenylketones. These phenylketones will be dumped in the urine leading to phenylketoneuria



Classic type:

- Most common, due to little or no activity of α-ketoacid dehydrogenase.

Intermediate and intermittent forms:

- Some enzyme activity, symptoms are milder.

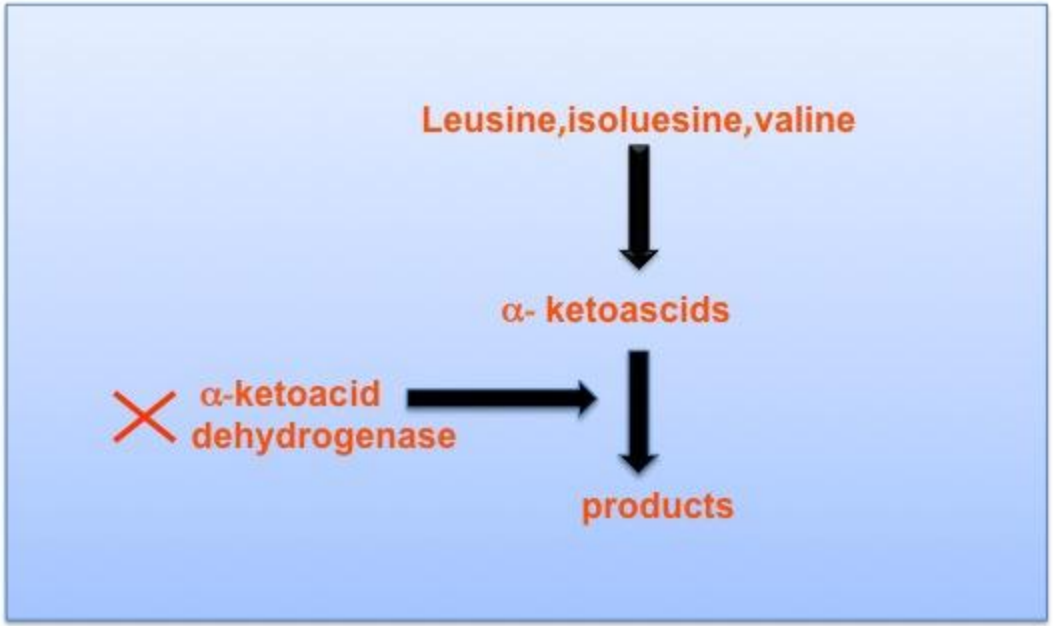
(in this case 15% of the enzyme is working but the remaining are inactive due to mutation somewhere in the enzyme but not the active site)

Thiamin-responsive form:

- High doses of thiamin increases α-ketoacid dehydrogenase activity, so they respond positively to treatment with thiamine (rare type).

Treatment of Maple Syrup Urine Disease:

Limited intake of leucine, isoleucine and valine.



Albinism

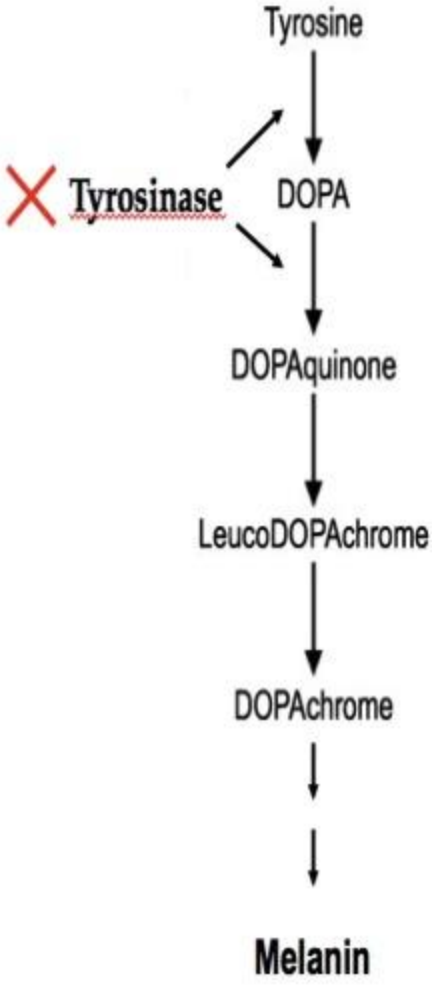
A disease of tyrosine metabolism Due to tyrosinase deficiency

Tyrosine is involved in melanin production, so Melanin is absent in albino patients

Melanin is a pigment of hair, skin, eyes

Hair and skin appear white

Vision defects, photophobia (an experience of discomfort or pain to the eyes due to light exposure or by presence of actual physical sensitivity of the eyes)

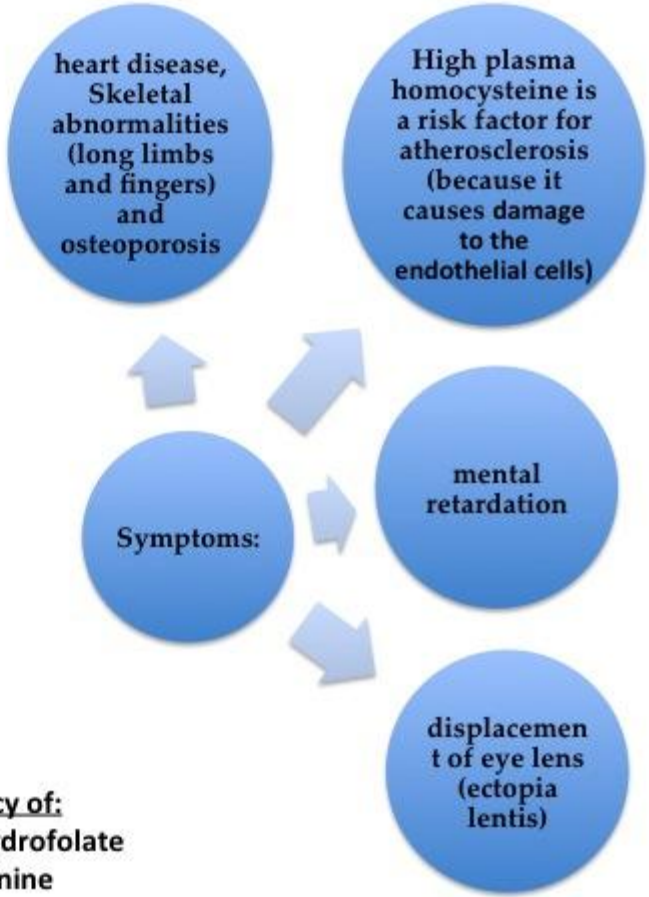


Homocystinuria

Due to defects in homocysteine metabolism because of deficiency of β-synthase that Converts homocysteine to cystathione which causes High plasma and urine levels of homocysteine.

Hyperhomocysteinemia is also associated with:

-Neural tube defect* (spina bifida:A birth defect in which a developing baby's spinal cord fails to develop properly.)
-Vascular disease (atherosclerosis).



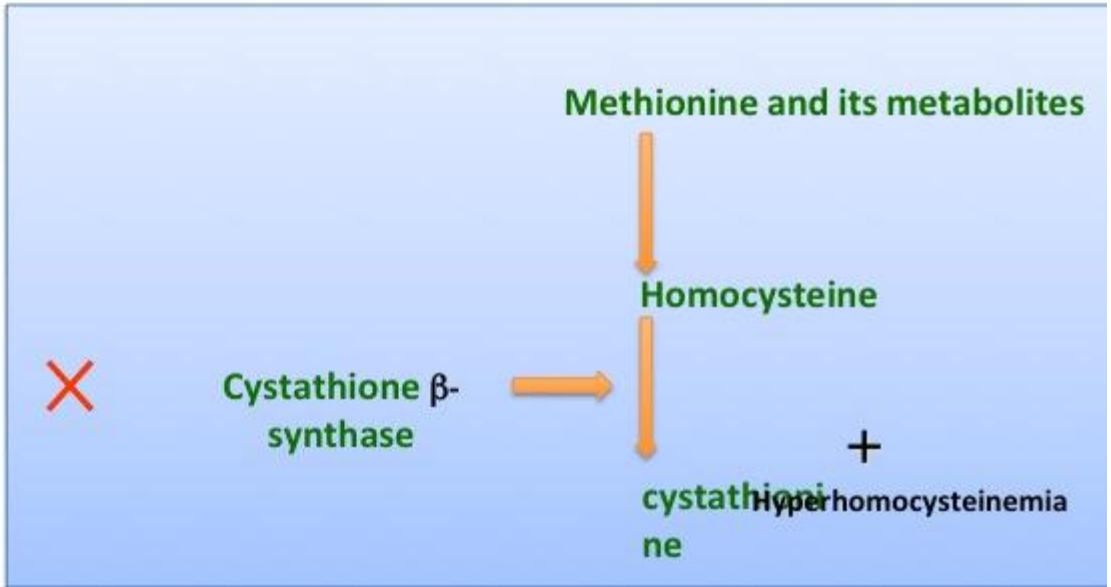
Neural tube Defect*

Deficiency of:
- Tetrahydrofolate
- Methionine synthase
- Vitamin B_6, B_{12}
- Folic acid

Treatment:

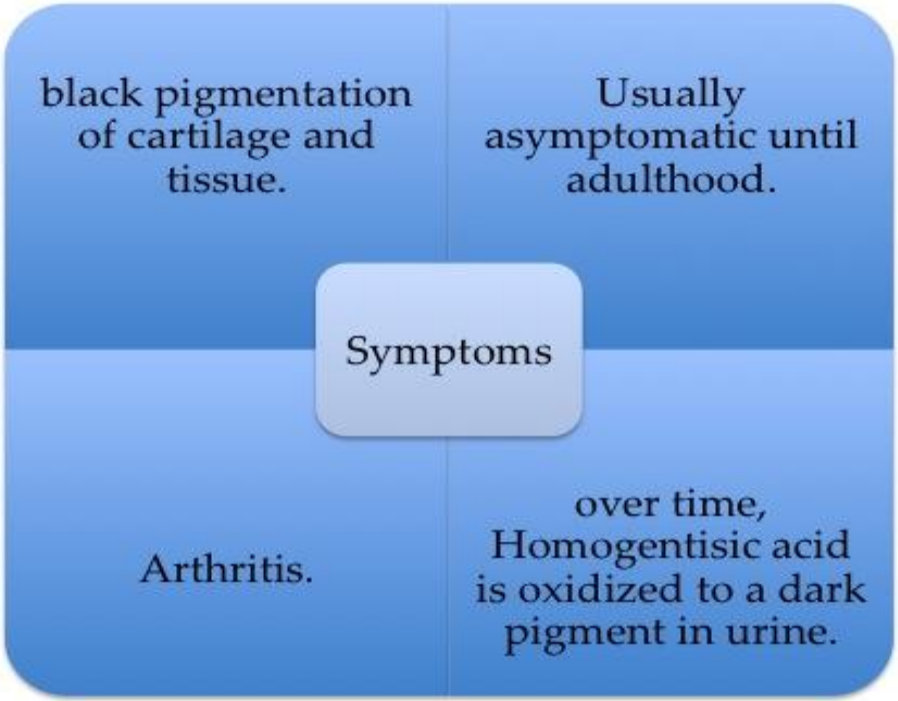
-Oral administration of **vitamins B_6, B_{12} and folate** (Vitamin B_6 is a cofactor for cystathionine β-synthase).

-Methionine-restricted diet because **Methionine and its metabolites are accumulated.**



Alkaptonuria

-A rare disease of tyrosine degradation Due to deficiency of homogentisic acid oxidase.
-Homogentisic acid is accumulated in tissue and cartilage.
-Homogentisic aciduria: elevated homogentisic acid in urine.



Treatment: Restricted intake of tyrosine and phenylalanine reduces homogentisic acid and dark pigmentation.

summary:

	Disease	Enzyme	Aminoacids involved
1	Phenylketonuria	Phenylalanine hydroxylase	Phenylalanine
2	Maple syrup urine disease	Branched chain α-ketoacid dehydrogenase	Isoleucine, leucine and valine
3	Albinism	Tyrosinase	Tyrosine
4	Homocystinuria	Cystathionine β-synthase	Methionine
5	Alkaptonuria	Homogentisic acid oxidase	Tyrosine and phenylalanine

MCQs:

1-which one of the following is the Most common disease of amino acids metabolism?

A- Homocyteinuria
B- Albinism
C- Phenylketonuria
D- Maple Syrup Urine Disease

2- Atypical hyperphenylalaninemia due to deficiency of?

A- phenylalanine hydroxylase
B- Dihydropteridine synthase
C- Carbinolamine dehydratase
D- a-ketoacid dehydrogenase

3- a-ketoacid dehydrogenase normaly …… leucine, isoleucine and valine?

A- hydroxylate
B- decarboxylate
C- dehydrate
D- oxidate

4- which of the following conditions is a risk factor for atherosclerosis and heart disease?

A- Homocysteinemia
B- Alkaptonuria
C- Albinism
D-Maple Syrup Urine Disease

5-which of the following is a cofactor for cystathionine b-synthase

A- BH4
B- Vitamin B6
C- vitamin c
D- zinc

6-Methionine-restricted diet is used to treat patients with?

A- PKU
B- AKU
C- Homocystinuria
D- MSUD

SAQs:

1-name two enzymes by which their deficiency may cause hyperphenylalaninemia?

-phenylalanine hydroxylase
-Carbinolamine dehydratase

2-name three sites where you can find Melanin pigment?

hair, skin, eyes

3- Prenatal diagnosis in PKU patients is done by?

detecting gene mutation in fetus

4-how to treat a patient with Maple Syrup Urine Disease?

Limited intake of leucine, isoleucine and valine

5-name sign for Alkaptonuria?

black pigmentation of cartilage and tissue

6-name the three types of MSUD?

- classic type
- Intermediate and intermittent type
- Thiamin-responsive type

YouTube

PKU:
https://www.youtube.com/watch?v=hpaki7F4HR0

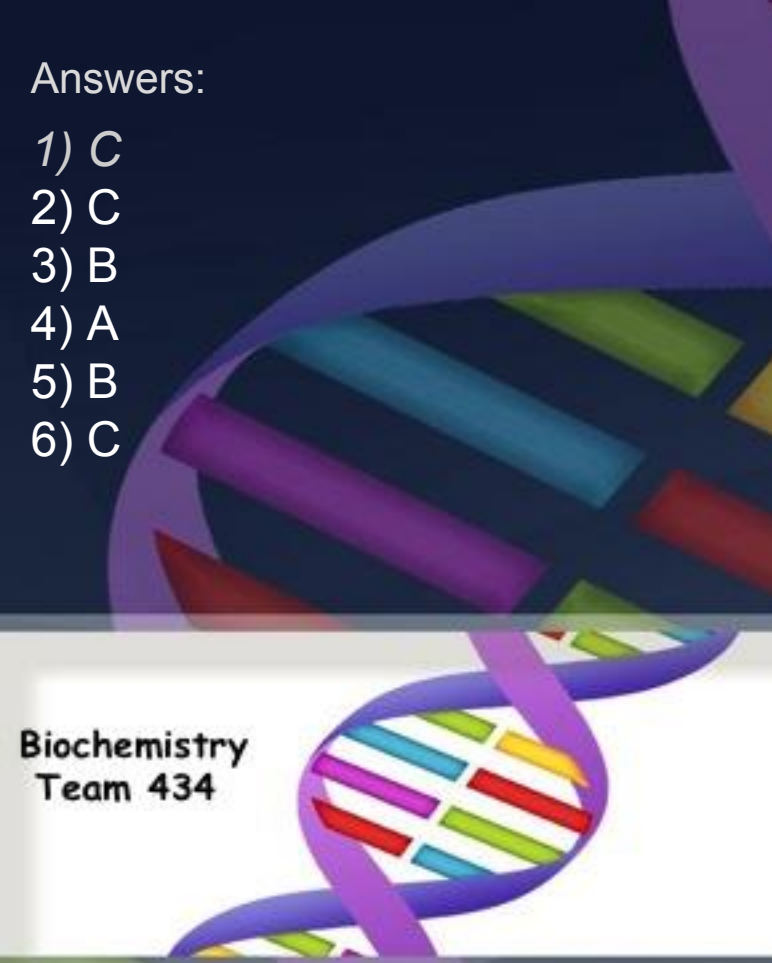
MSUD:
https://www.youtube.com/watch?v=ZM3WNCmSk_w

Alkaptonuria:

https://www.youtube.com/watch?v=t5EgHvSY

Answers:

1) C
2) C
3) B
4) A
5) B
6) C



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