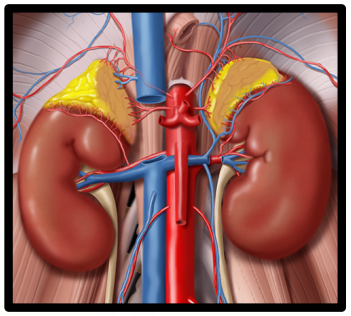
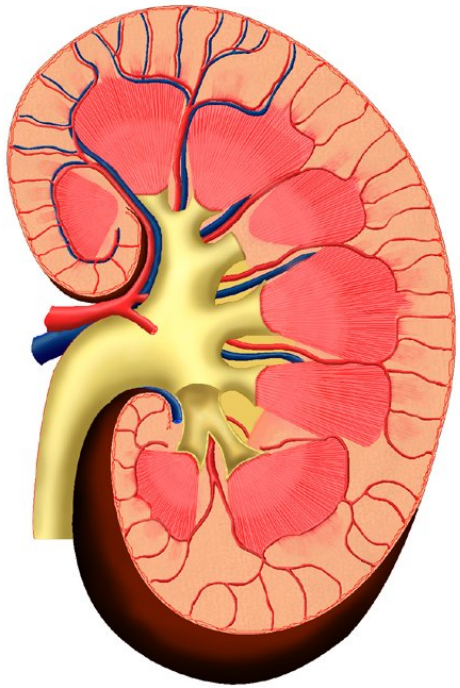


Inborn Errors of Amino Acid Metabolism

Lecture 4



Renal Block
Biochemistry433@hotmail.com

Objectives:

Biochemistry of:

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

Abbreviation:

- aa- amino acid
- Phe-Phenylalanine
- Tyr-Tyrosine
- Trp- Tryptophan
- Leu- Leucine
- Ile- Isoleucine
- Val- Valine
- Met- Methionine
- PKU- Phenylketonuria
- MSUD- Maple Syrup Urine Disease

Inborn Errors of Amino acid Metabolism

Caused by enzyme loss or deficiency due to gene loss (no aa) or gene mutation (abnormal aa)

Enzyme + Substrate —(Cofactors)→ **Product**

Enzyme: Lost or mutated; Substrate: Excess; Product: Deficient

Phenylketonuria (PKU)

✓ Conversion of **Phe** (phenylalanine) to **Tyr** requires **phenylalanine hydroxylase** and **tetrahydrobiopterin (BH4)**

✓**Most common** disease of amino acid metabolism

✓ Results in h**yperphenylalaninemia**

✓Tyrosine is not an essential aa and we can get it through the diet.

Classic PKU:

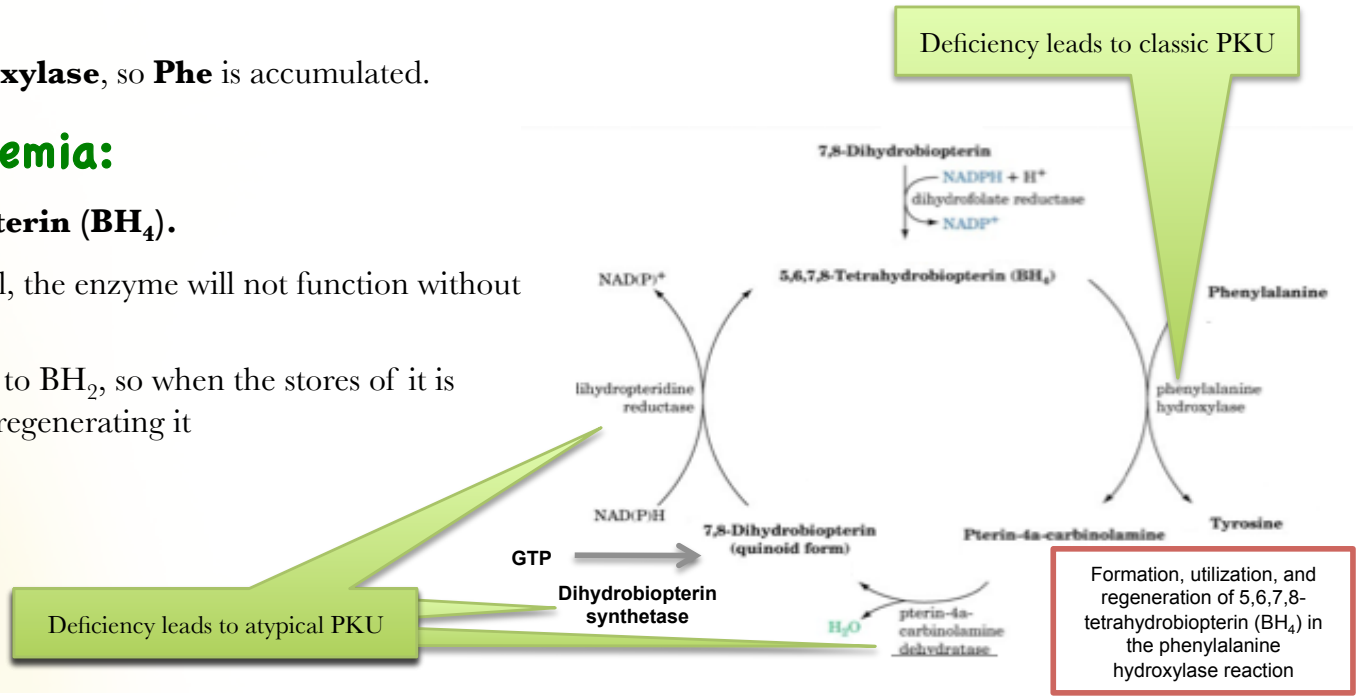
Due to deficiency of **phenylalanine hydroxylase**, so **Phe** is accumulated.

Atypical hyperphenylalaninemia:

- Due to deficiency of **tetrahydrobiopterin (BH_4).**
- Even if **Phe** hydroxylase level is normal, the enzyme will not function without BH_4.
- In the normal pathway BH_4 is oxidized to BH_2, so when the stores of it is depleted 3 enzymes are responsible for regenerating it

Caused by the deficiency of:

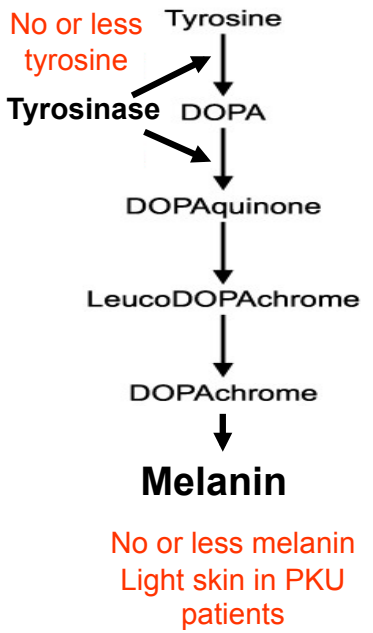
- Dihydropteridine reductase
- Dihydrobiopterin synthetase
- Carbinolamine dehydratase



Characteristics of PKU

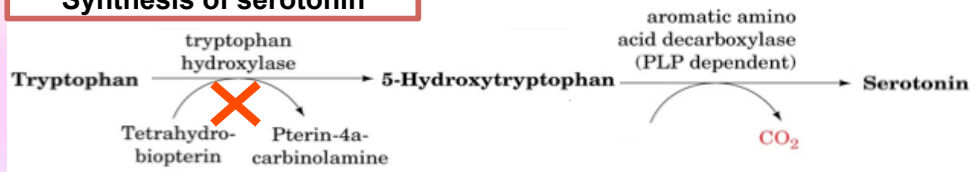
✓**Tyr** will not be converted to **catecholamine** (neurotransmitter), which requires BH_4
✓**Trp** will not be converted to **serotonin** (a neurotransmitter) as it requires BH_4
✓Elevated phenylalanine in tissues, plasma, urine.
✓Phe is degraded to phenyllactate, phenylacetate, and phenylpyruvate, which gives urine a **mousy** odor (like a mouse).
✓ excess phe **competatively inhibits tyrosinase** (the first two steps) , that is why even though tyr is given in the patient's diet it is not efficient to produce melanin.
✓So the patient is given tyr and DOPA and forbidden from phe.
✓**CNS symptoms**: Mental retardation, failure to walk or talk, seizures, etc.
✓ **Hypopigmentation :** due to deficiency of melanin, and hydroxylation of tyrosine by tyrosinase is inhibited by high phe conc.

Synthesis of melanin



No or less melanin
Light skin in PKU patients

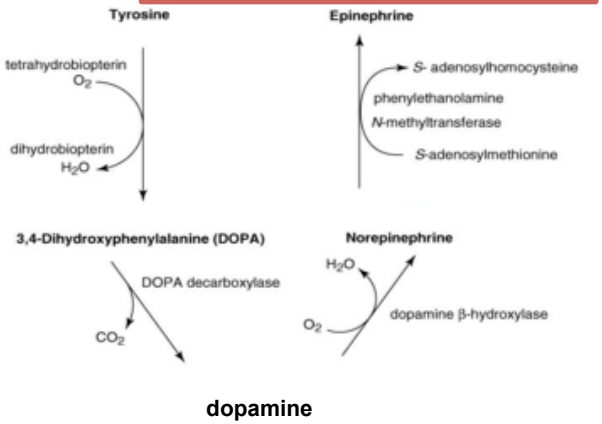
Synthesis of serotonin



Diagnosis and treatment

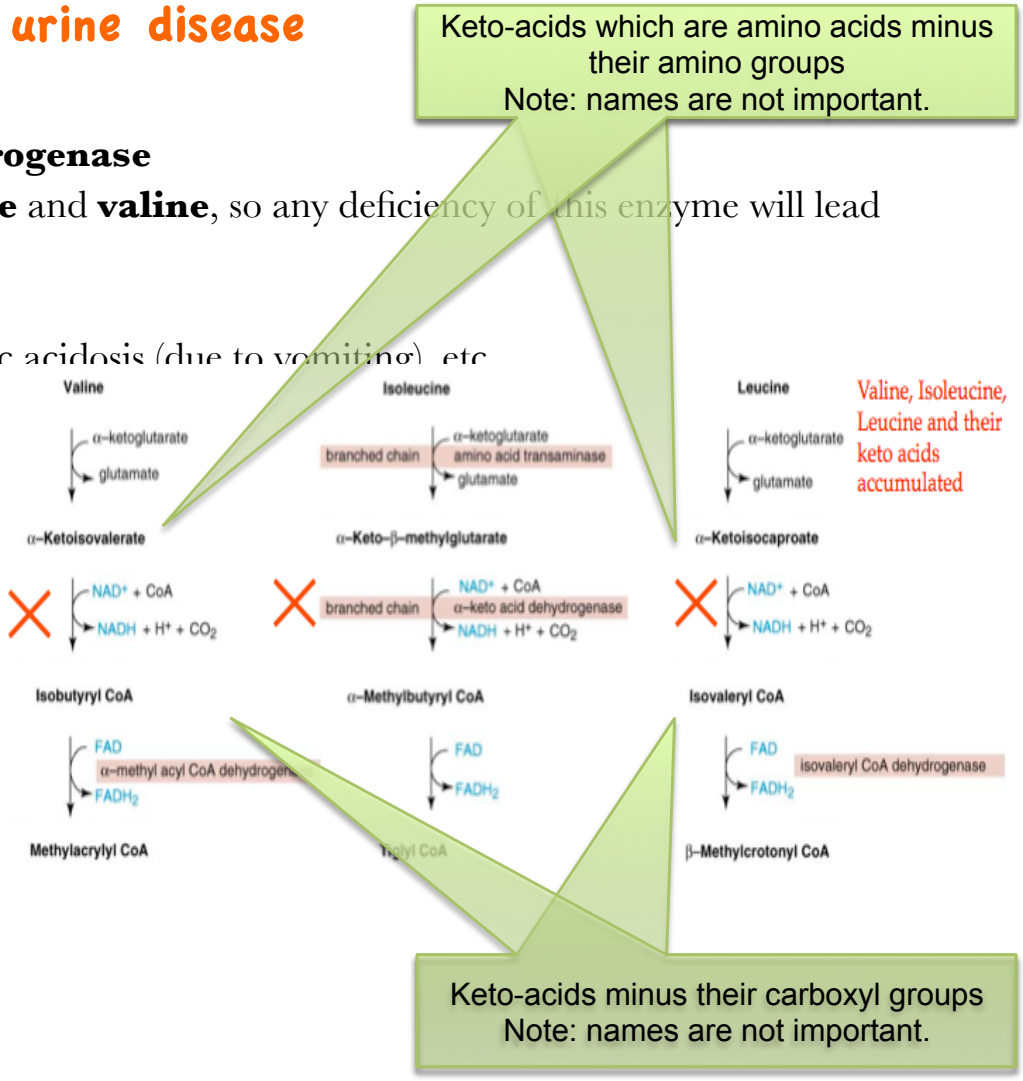
✓Prenatal diagnosis is done by **detecting gene mutation** in fetus
✓Neonatal diagnosis in infants is done by **measuring blood phe levels**
✓**Treatment**: Life long **phe-restricted diet (low)**
✓If a pregnant mother is affected, the fetus is affected but the opposite will not affect the mother because the mother's system will clear it.

Synthesis of catecholamines



Maple syrup urine disease

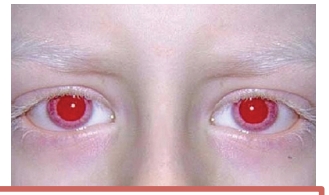
- ✓ Due to deficiency of **branched chain α-ketoacid dehydrogenase**
- ✓ The enzyme complex **decarboxylates leucine**, **isoleucine** and **valine**, so any deficiency of this enzyme will lead to accumulation of the amino acids.
- ✓ These amino acids **accumulate** in blood
- ✓ **Symptoms**: mental retardation, physical disability, metabolic acidosis (due to vomiting), etc
- ✓ **Maple syrup odor** of urine
- ✓ **Types**:
- ✓ **Classic type:** Most common, due to little or no activity of a-ketoacid dehydrogenase (severe)
- ✓ **Intermediate and intermittent forms: 3-15%** Some enzyme activity, symptoms are milder (intermediate)
- ✓ **Thiamin-responsive form:** High doses of thiamin, which is a vitamin B1, increases a-ketoacid dehydrogenase activity (mild)



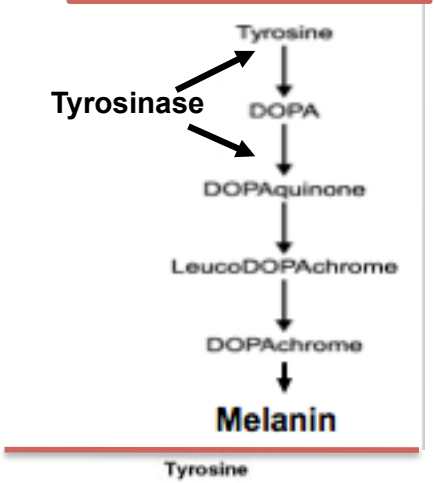
Treatment

Limited intake of leucine, isoleucine and valine

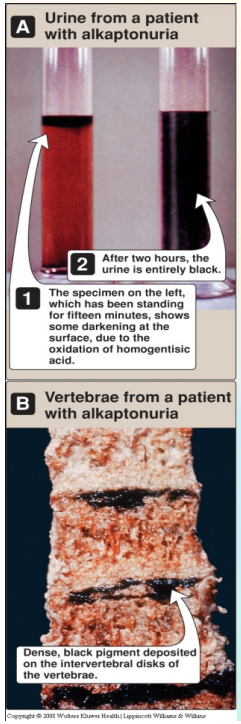
Albinism



- ✓A disease of **tyrosine** metabolism
- ✓Tyrosine is involved in **melanin production**
- ✓Melanin is a pigment of **hair, skin, eyes**
- ✓Due to **tyrosinase deficiency**
- ✓Melanin is **absent** in albino patients
- ✓Hair and skin appear **white**
- ✓**Vision defects, photophobia**
- ✓Prone to skin cancer



Alkaptonuria



- ✓A rare disease of **tyrosine degradation**
- ✓Due to **deficiency of homogentisic acid oxidase**
- ✓Homogentisic acid is **accumulated** in tissue and cartilage
- ✓**Characteristics:**

✓Homogentisic aciduria: elevated homogentisic acid in urine which is oxidized to dark pigment over time

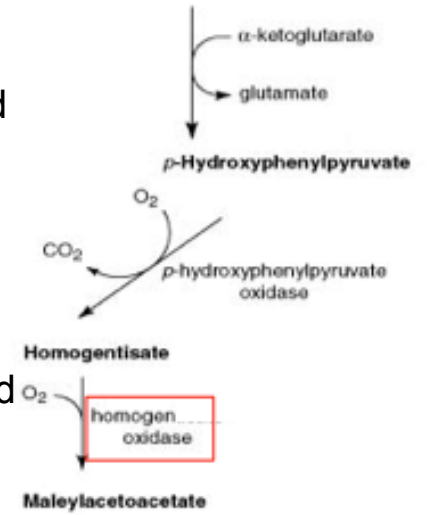
✓Arthritis

✓Black pigmentation of cartilage, tissue

✓Usually asymptomatic until adulthood

✓**Treatment:**

Restricted intake of tyrosine and phenylalanine reduces homogentisic acid and dark pigmentation

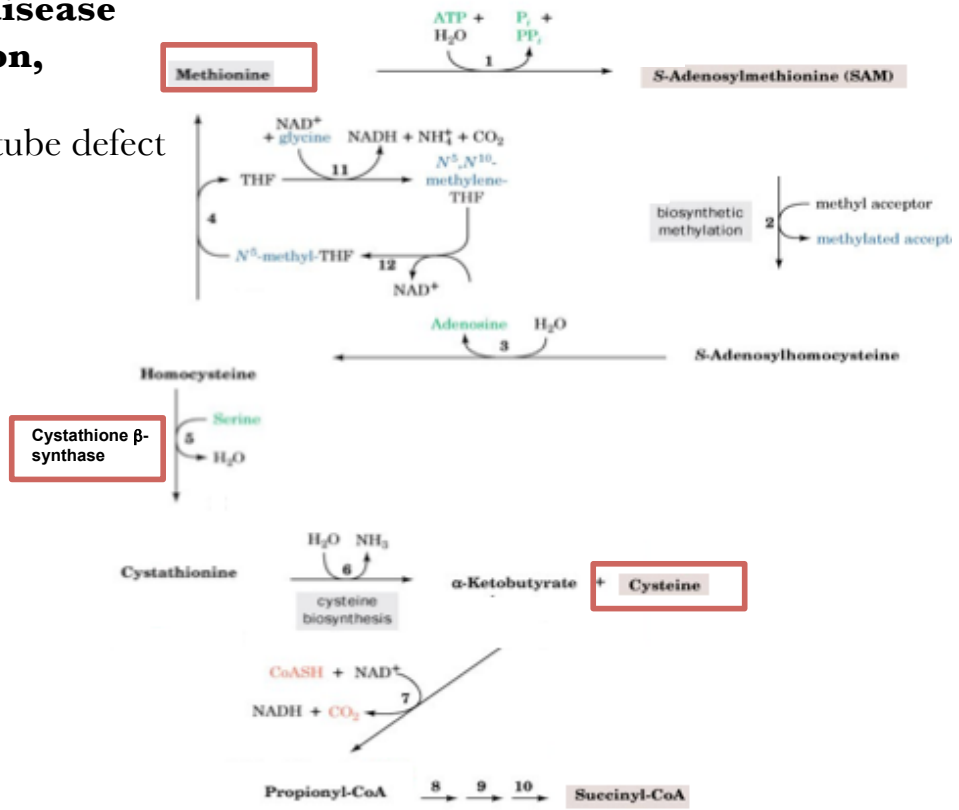


Homocystinuria

- ✓ Synthesized during the degradation of methionine
- ✓ Due to defects in **homocysteine** metabolism
- ✓ Deficiency of **cystathionine b-synthase**

- ✓ Converts **homocysteine** to **cystathionine**
- ✓ **High plasma and urine** levels of homocysteine
- ✓ Homocysteine is a risk factor for **atherosclerosis and heart disease**
- ✓ **Skeletal abnormalities, osteoporosis, mental retardation, displacement of eye lens**
- ✓ **Hyperhomocysteinemia is also associated with:** Neural tube defect (spina bifida), Vascular disease (atherosclerosis), Heart disease
- ✓ because their endothelial lining is more prone to injury

- ✓ **Treatment:**
- ✓ Oral administration **of vitamins B6, B12 and folate**
- ✓ Vitamin B6 is a cofactor for **cystathionine b-synthase**
- ✓ **Methionine-restricted diet**



Neural tube defect: deficiency of
- Tetrahydrofolate
- Methionine synthase
- Vitamin B6, B12
- Folic acid

+ Hyperhomocysteinemia

SUMMARY

	Disease	Enzyme	Aminoacids involved	pathway	What is accumulated or deficient
1	Phenylketonuria	Phenylalanine hydroxylase	Phenylalanine	The pathway of phenylalanine degradation	Tyr def. Phe is accumulated
2	Maple syrup urine disease	Branched chain α-ketoacid dehydrogenase	Isoleucine, leucine and valine	Degradation of branched-chain amino acids: valine, isoleucine and leucine.	Isoleucine, leucine and valine and their keto acid is accumulated
3	Albinism	Tyrosinase	Tyrosine	Melanin biosynthesis from tyrosine	Melanin is deficient and tyrosine is accumulated
4	Homocystinuria	Cystathionine β-synthase	Methionine	Methionine degradation pathway	Methionine and homocystine are Accumulated and cystine deficiency
5	Alkaptonuria	Homogentisic acid oxidase	Tyrosine and phenylalanine	Degradation of tyrosine	homogentisic acid is accumulated

MCQs

1- a patient was presented with atherosclerosis and complicated heart disease, after the doctor had a few tests done, which of the following could be one of his findings:

A- a-ketoacid dehydrogenase deficiency
B- tyrosinase deficiency
C- cystathionine b-synthasedeficiency

2 – tyrosinase deficiency ia associated with:

A- Albinism
B- PKU
C- Alkaptonuria

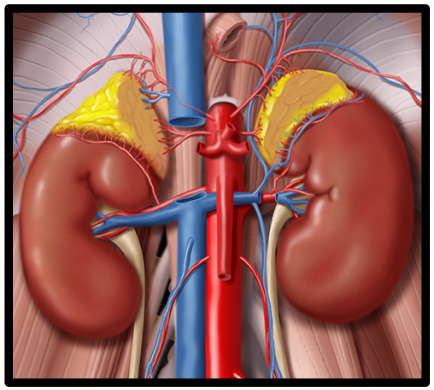
3- A mother came to the emergency room with her new baby born complaining of his urine color that she found dark in his diapers, the most likely dignosis:

A- Albinism
B- PKU
C- Alkaptonuria

4- the best way to treat alkaptanuria is to:

A- screen fetuses
B- limit the patient's intake of
C-

ANS : 1- C 2 - A 3 - C 4 - A



GOOD LUCK

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