DOCTOR 2020 | JU

METABOLISM

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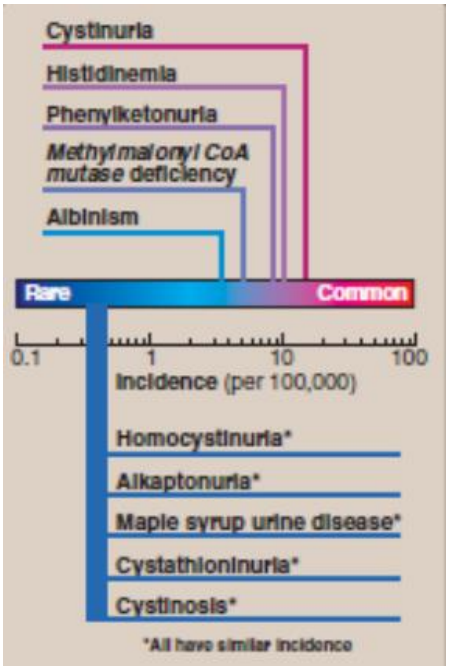
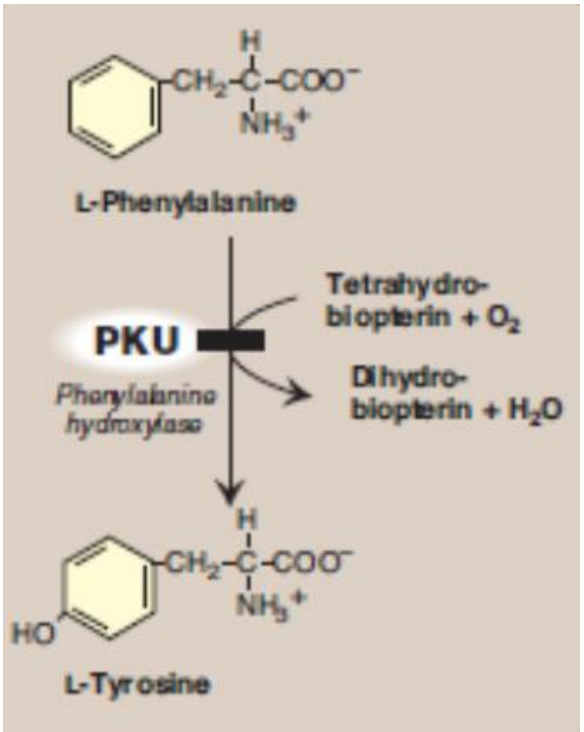
Metabolic defects in amino acid metabolism

The inherited defects of AA metabolism if stay untreated result in mental retardation or other developmental abnormalities because of the harmful accumulation of metabolites.



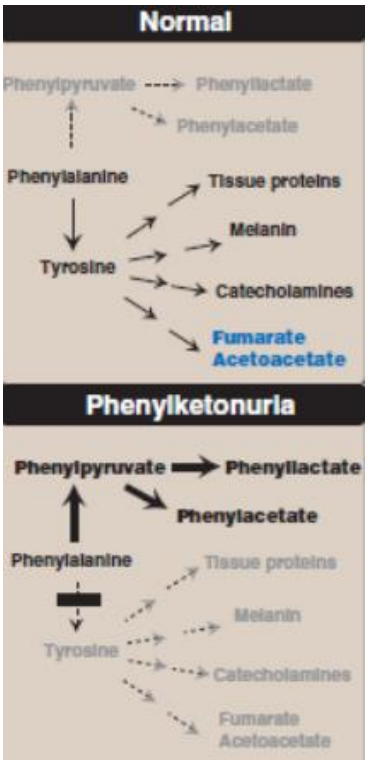
1.Phenylketonuria (PKU)

- **The most common inborn error of amino acid metabolism (prevalence 1:15,000).**
- **Due to phenylalanine hydroxylase deficiency**
- **Biochemical changes: accumulation of phenylalanine (and a deficiency of tyrosine).**
- **Tyr cannot be synthesized from Phe and becomes an essential amino acid.**
    - Patients should obtain Tyrosine from diet.
- **Caused by any of 100 or more different mutations in the gene that codes for phenylalanine hydroxylase (PAH).**
- **Due to the accumulation of Phe it will be converted to other metabolites such as: phenyllactate, phenylacetate, and phenylpyruvate that can cross the BBB and cause mental retardation.**



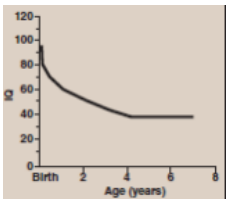
Characteristics of classic PKU:

1. Elevated phenylalanine in tissues, plasma, and urine.
2. The characteristic musty "mousey" urine odor due to phenyllactate, phenylacetate, and phenylpyruvate
3. CNS symptoms: Mental retardation (IQ < 50), failure to walk or talk, seizures, hyperactivity, tremor, microcephaly, and failure to grow
4. Hypopigmentation: fair hair, light skin colour, and blue eyes because the hydroxylation of Tyr by tyrosinase (the first step in melanin formation) is competitively inhibited by the high levels of Phe.



After birth does the neonatal has mental retardation?

Not yet. Why?



At birth, infants with PKU have normal blood levels of Phe because the mother clears the extra Phe through placenta thus PKU neonatal lack of symptoms.

PKU is a genetic disease but can we reduce its symptoms and avoid mental retardation?

Yup, through neonatal screening programmes, after birth usually a several screening is done one of them to measure the phenylalanine hydroxylase so we can early diagnose the PKU neonatal.

Exposure protein feeding for 24–48 hours elevates Phe, thus, screening should be done after this to avoid false negatives.

Treatment:

Dietary restriction: synthetic amino acid preparations low in Phe, supplemented with natural foods low in Phe content (fruits, vegetables, and certain cereals).

Dietary restriction isn't only during the childhood and if the patient consumes a lot of Phe his IQ will decrease with his age, but he will never reach the mental retardation (IQ <50).

PKU neonatal must receive milk without Phe.

Earlier treatment (prevents neurologic damage days of life) prevents neurologic complications (mental retardation).

Recall from BioChem the artificial sweetener Aspartame should be avoided since it contains Phe.

Nice question: PKU patients' proteins contain Phe what's its source since we avoid them from it? Actually the retraction isn't 100% and remember we have protein degradation so we can reuse the Phe to make new proteins.

Maternal PKU

Baby with Microcephaly

Pregnant woman with a PKU doesn't control its diet can this affect the fetus?

Yeah, because accumulation of Phe will lead to accumulation of Phe metabolites as we mentioned and these metabolites will cross the placental barrier and cause serious symptoms even though the fetus doesn't have PKU because the problem with Phe metabolites not Phe itself.

High blood Phe levels in the mother cause microcephaly, mental retardation, and congenital heart abnormalities in the fetus.

Phenlyalanine is a teratogen (an agent or factor which causes malformation of an embryo).

Dietary control of blood phenylalanine must begin prior to conception, and must be maintained throughout the pregnancy.

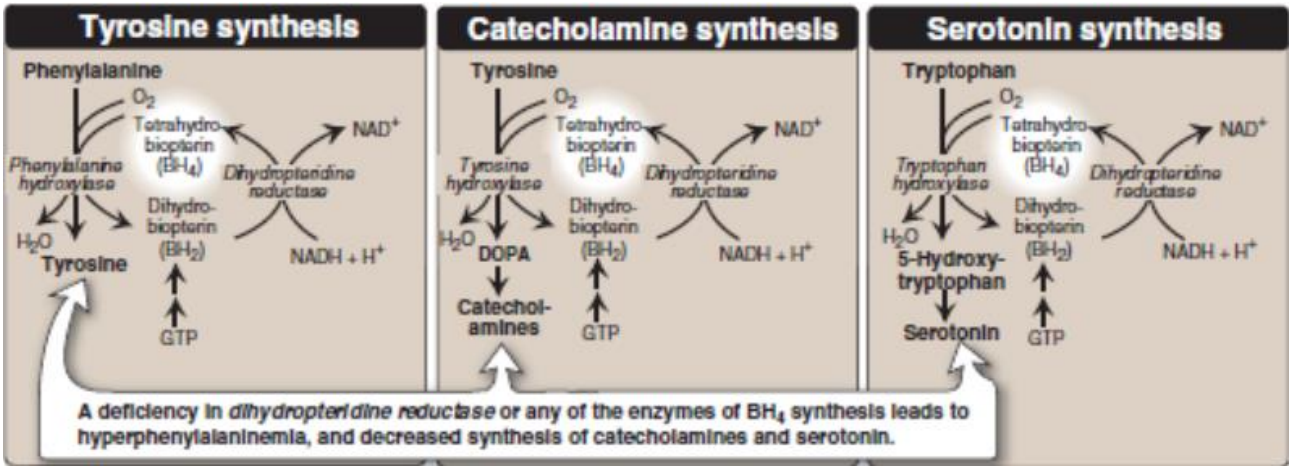
2.Hyperphenylalaninemia

Dihydropteridine reductase deficiency

Dihydropteridine reductase is the responsible enzyme for recycle the co-enzyme BH4 now remember that BH4 is required by phenylalanine hydroxylase as well as Tyrosine hydroxylase (for catecholamine synthesis) and Tryptophan hydroxylase (for Serotonin synthesis) thus these path ways will be affected.

Restricting dietary Phe does not reverse the CNS effects due to deficiencies in neurotransmitters.

Replacement therapy with BH4 or L-DOPA and 5-hydroxytryptophan (products of the affected tyrosine hydroxylase–and tryptophan hydroxylase–catalyzed reactions) improves the clinical outcome



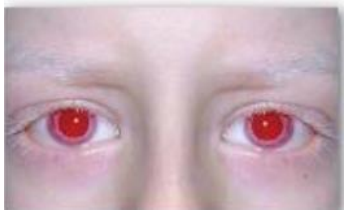
3.Albinism

A group of conditions in which a defect in Tyr metabolism results in a deficiency in the production of melanin.

Partial or full absence of pigment from the skin, hair, and eyes.

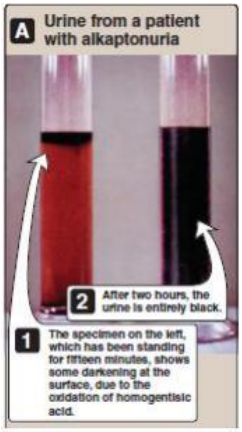
Inheritance modes: Autosomal recessive (primary mode), Autosomal dominant, or X-linked.

Complete albinism (tyrosinase-negative oculocutaneous albinism) results from a deficiency of copper-requiring tyrosinase

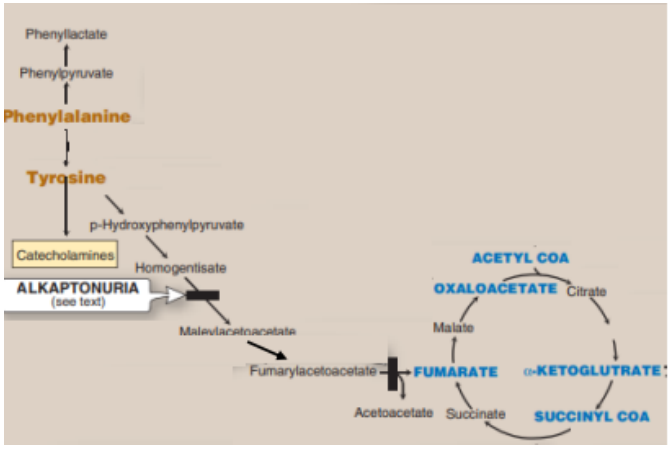


Complete albinism:
The most severe form.
Total absence of pigment from the hair, eyes, and skin, vision defects and photophobia (sunlight hurts their eyes).
Higher risk for skin cancer.

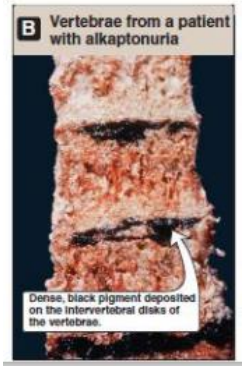
4. Alkaptonuria (Alcaptonuria)



A rare metabolic condition, however, cases were found in Jordan



A deficiency in homogentisic acid oxidase, resulting in the accumulation of homogentisic acid (a reaction that occurs in the degradative pathway of Tyr).



Characteristic symptoms: Not life threatening Patients are usually asymptomatic until age 40.

Homogentisic aciduria

Large joint arthritis

Black ochronotic pigmentation of cartilage and collagenous tissue

Dark staining of the diapers can indicate the disease in infants

The black urine takes a long time to occur that's why the infants not diagnosed early.

Treatment: diets low in protein—especially in Phe and Tyr reduce homogentisic acid levels, and the pigment deposited in body tissues.

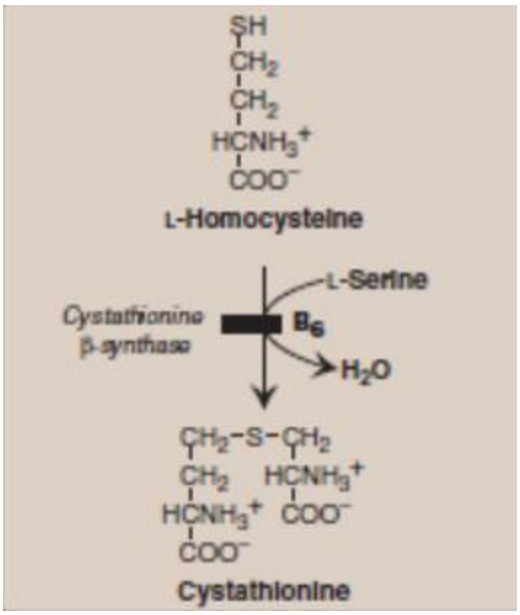
5. Homocystinuria

Defects in the metabolism of homocysteine.

Mode of inheritance: Autosomal recessive.

High plasma and urinary levels of homocysteine and Met and low levels of Cys.

The most common cause is a defect in cystathionine β-synthase that converts homocysteine to cystathionine



6. Maple syrup urine disease (MSUD)

Rare (1:185,000), autosomal recessive (AR) disorder, most cases are heterozygotes

Partial or complete deficiency in branched-chain α-keto acid dehydrogenase complex that decarboxylates Leu, Ile, and Val

Remember from last lecture we said that branched amino acids have a special pathway that induce decarboxylation reactions and these branched amino acids are important for the synthesis of different neurotransmitters such as glutamate and GABA.

Branched-chain amino acids are an important energy source in times of metabolic need

Accumulation in the blood causes a toxic effect that interferes with brain functions.

Signs and symptoms: feeding problems, vomiting, dehydration, severe metabolic acidosis, and a characteristic maple syrup odor to the urine.

If untreated, MSUD leads to mental retardation, physical disabilities, and even death.

Screening and diagnosis: prenatal diagnosis and neonatal screening are available.

Treatment: a synthetic formula that contains limited amounts of Leu, Ile, and Val to provide the branched-chain amino acids necessary for normal growth and development without producing toxic levels.

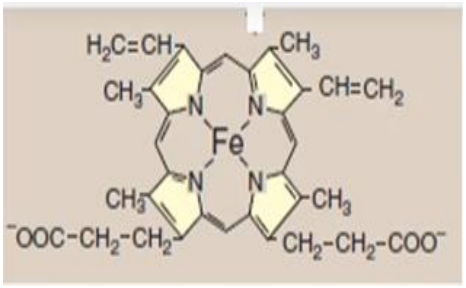
Early diagnosis and lifelong dietary treatment is essential for child normal development.

صلّ على النبي

A new topic ☺, amino acids are used to produce special products such as porphyrins.

Porphyrins

Ring structure molecules composed of 4 repeated 5-memberd rings called pyrrole rings that contain N oriented toward the canter, where Fe is going to bind –in the case of heme it should be in the ferrous sate- Fe+2 and on each pyrrole ring 2 side chains and these side chains make the deference between porphyrins.



Porphyrins are cyclic compounds that readily bind metal ions (Fe+2 or Fe+3).

The most prevalent metalloporphyrin in humans is heme.

Another example of porphyrins is coporphrins.

Heme is found in hemoglobin, myoglobin, the cytochromes, catalase, nitric oxide synthase, and peroxidase.

Hemeproteins are rapidly synthesized.

6-7 proteins are synthesized each day to replace heme lost through the normal turnover of erythrocytes.

Structure of Porphyrins

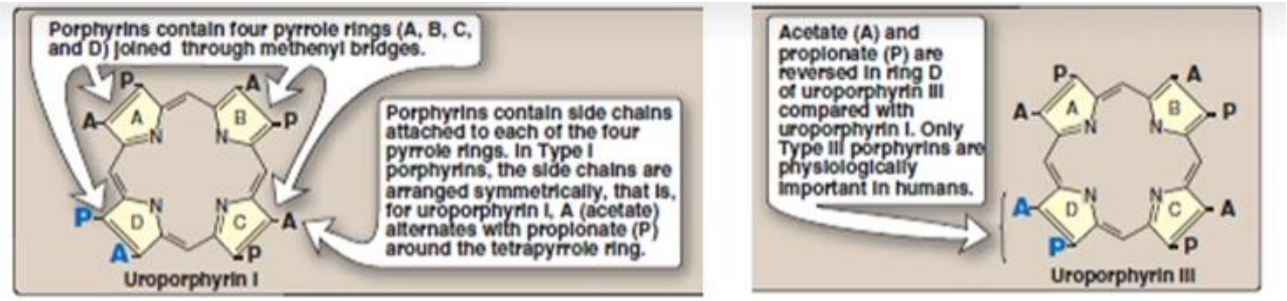
The medical significance of porphyrins is related to the following structural features of these molecules:

1. Nature of the side chains that are attached to each of the four pyrrole rings.
Uroporphyrin contains acetate (–CH2–COO–) and propionate (–CH2–CH2–COO–)
Coproporphyrin contains methyl (–CH3) and propionate groups
Protoporphyrin IX (and heme) contains vinyl (–CH=CH2), methyl, and propionate groups.

2. Distribution of side chains around the tetrapyrrole nucleus. Four different ways (I to IV) Only Type III porphyrins (asymmetric substitution on ring D) are physiologically important in humans.

3. Porphyrinogens (porphyrin precursors) exist in a chemically reduced, colorless form, and serve as intermediates between porphobilinogen and the oxidized, colored protoporphyrins in heme biosynthesis.

Notice these 2 different porphyrins they have the same side chains but they differ in the distribution and that results in different molecules.



Biosynthesis of heme

Synthesis of heme occurs continually because the proteins that contain heme are also degraded continually one example is the hemoglobin when the RBCs reaches 120 days and die.

The major sites of heme biosynthesis are:

1.Liver (cytochrome P450), variable rate depending on demand of heme proteins.

2.Eryhrocyte-producing cells (progenitor cells) of the bone marrow (hemoglobin), more than 85% of all heme synthesis.

The heme synthesized in bone marrow for hemoglobin and from the liver for other proteins.

The initial and last step in porphyrins formation occurs in mitochondria

The intermediate steps occur in the cytosol.

Mature RBCs lack mitochondria and are unable to synthesize heme.

تم بحمد الله