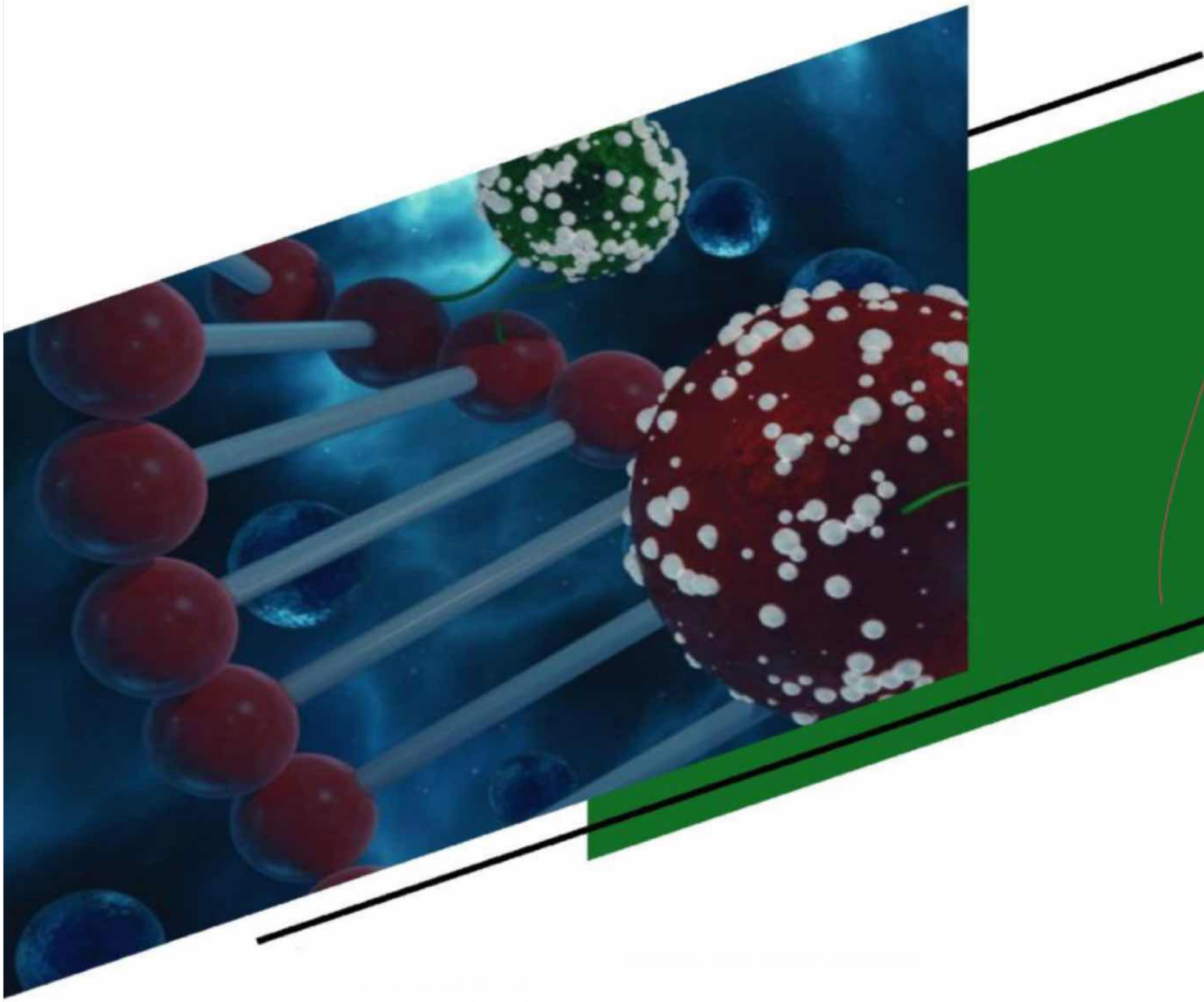
Doctor 021

METABOLISM

Sheet no. 30



Doctor : Diala Abu-Hassan

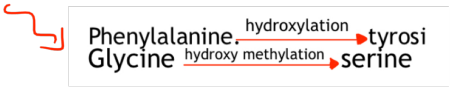
Amino Acid Synthesis

We already discussed some synthetic processes during degradation pathways of amino acids. Note that we have only **Biosynthesis of Nonessential Amino Acids**.

Essential: Phe, Val, Thr, Trp, Met, Leu, Ile, Lys & His

Nonessential: Ala, Arg, Asp, Asn, Cys, Glu, Gln, Gly, Pro, Ser & Tyr.

We know that phenylalanine is hydroxylated to tyrosine, and hydroxymethylation of glycine produces serine.



Nonessential amino acids are synthesized from:

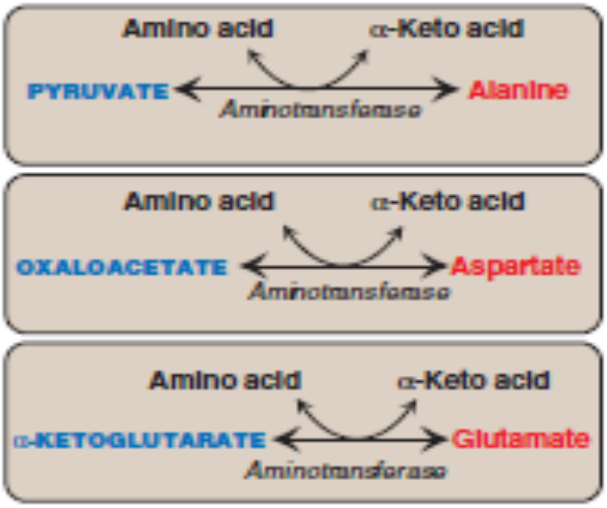
1. Metabolic intermediates (mostly).

2. from the essential amino acids.

-- Example: Tyr and Cys are synthesized Phe and Met, respectively. ((Tyr from Phe,, Cys from Met.))

Synthesis from α-keto acids

We can synthesize amino acids from their α-keto acids by reversing transamination

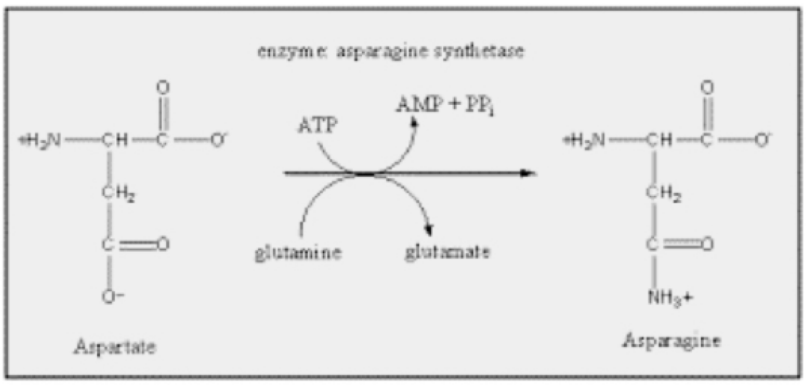


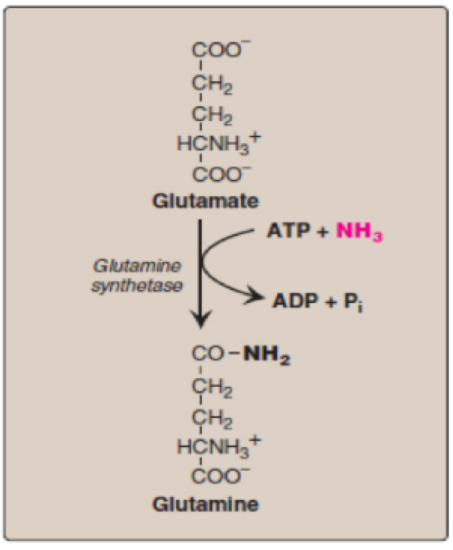
→ Ala, Asp, and Glu are synthesized by transfer of an amino group to the α-keto acids pyruvate, oxaloacetate, and α-ketoglutarate, respectively.

→ Glu can also be synthesized by the reverse of oxidative deamination, catalyzed by glutamate dehydrogenase

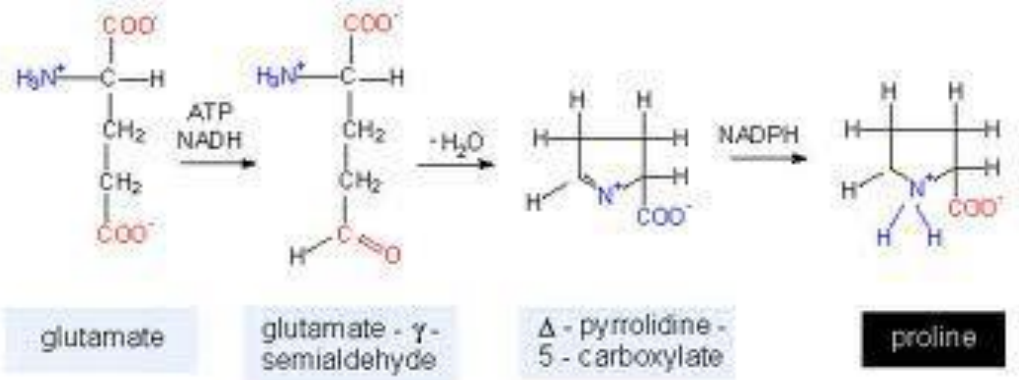
Synthesis by amidation

1. **Gln** formed from Glu by **glutamine synthetase.**
2. **Asn** formed from Asp by **asparagine synthetase**, using glutamine as the amide donor.





Proline



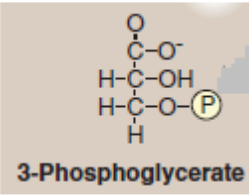
The proilne AA is metabolized to produce α-ketoglutarate via glutamate, so I can use glutamate to synthesize proline (reverse reaction).

Proline have a ring structure connected to amino group in the backbone.

So, we start of removing carboxyl group by reduction to aldehyde to become glutamate semialdehyde, then by dehydration we remove the oxygen atom, and connect the R group with the aminogroup in the backbone, and finally reduced to proline**. (so the reaction is cyclation and reduction).**

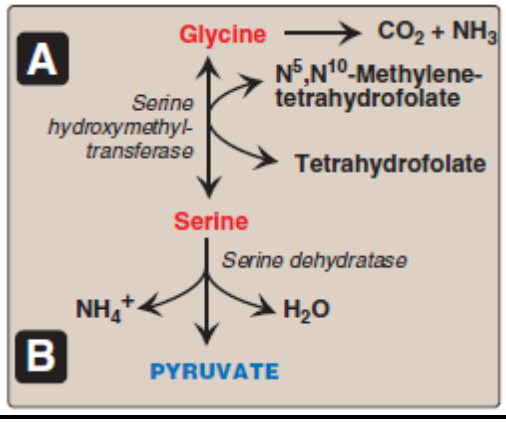
Serine and glycine

Serine arises **from 3-phosphoglycerate** (glycolytic intermediate) that is oxidized to 3-phosphopyruvate, and then transaminated to 3-phosphoserine. Serine is formed by hydrolysis of the phosphate ester.

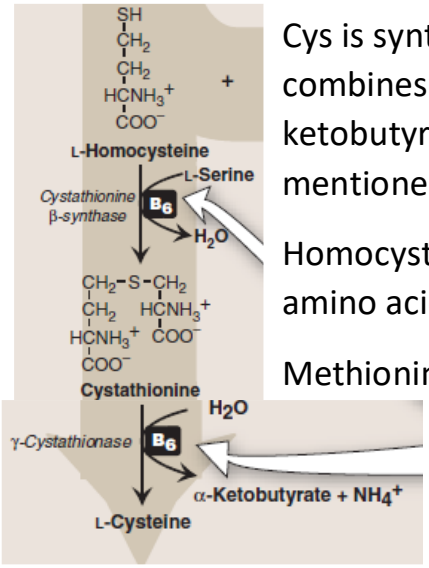


Serine can also be formed from glycine through transfer of a hydroxymethyl group by **serine hydroxymethyl transferase** (<u>N^5 , N^{10} -methylene- THF is the one carbon donor).</u>

Glycine is synthesized from serine by removal of a hydroxymethyl group, also by **serine hydroxymethyl transferase** <u>(THF is the one carbon acceptor removed from serine).</u>



Cysteine



Cys is synthesized by two consecutive reactions in which homo cysteine combines with serine, forming cystathionine that is hydrolyzed to α-ketobutyrate and Cys (vitamin B is needed) remember enzymes that are mentioned in methionine metabolism.

Homocysteine is derived from Methionine, Because Met is an essential amino acid, Cys can be synthesized the Met dietary intake is adequate.

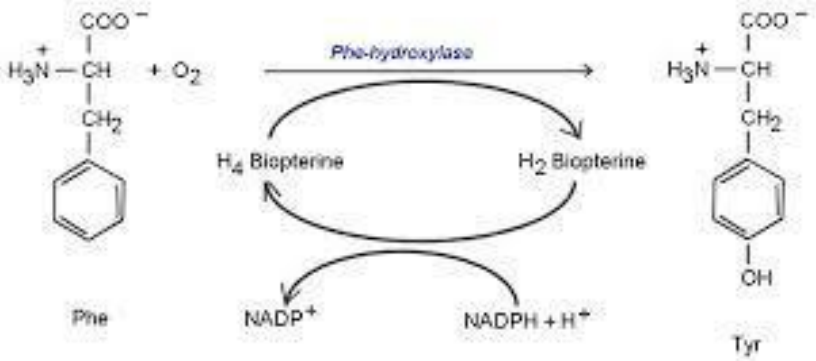
Methionine is essential but Cys in non-essential (we can produce it).

Tyrosine

Tyr (non essential AA) is formed from Phe (essential AA) by phenylalanine hydroxylase. The reaction requires molecular oxygen and the coenzyme **tetrahydrobiopterin (BH4)**.

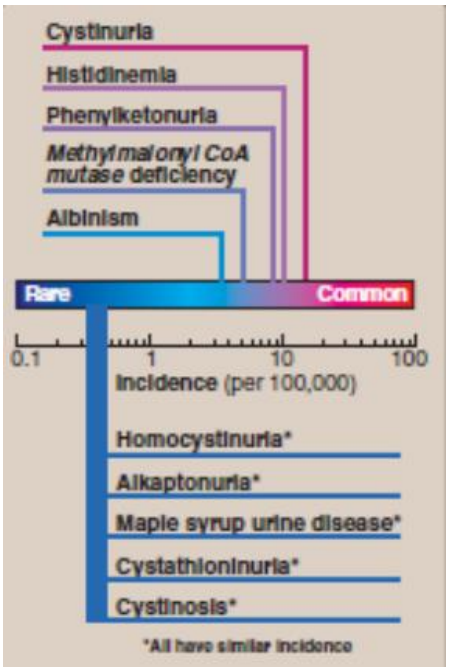
BH4 is oxidized to dihydrobiopterin (BH2).

BH4 is regenerated from BH2 by the enzyme **NADH-requiring dihydropteridine reductase**.



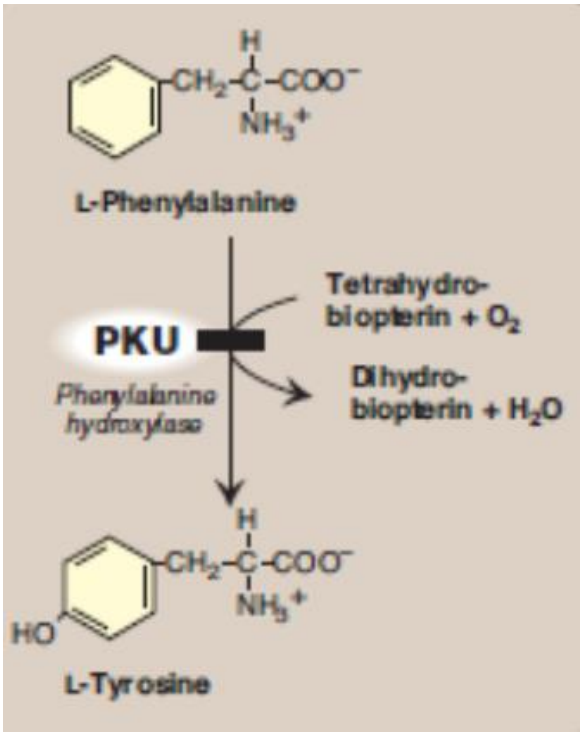
Metabolic defects in amino acid metabolism

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



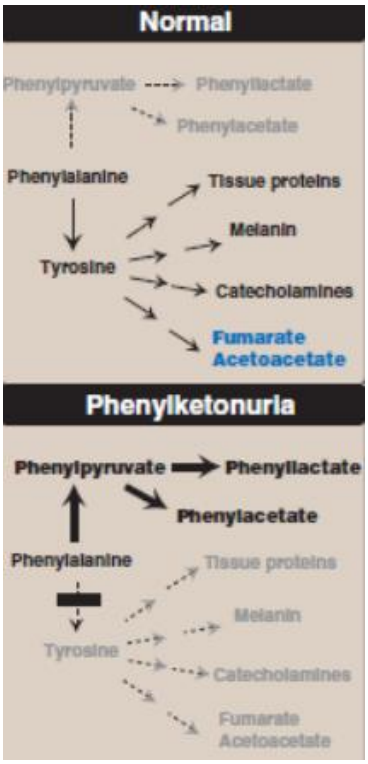
1.Phenylketonuria (PKU)

- **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:

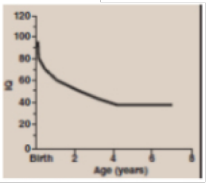
1. **Elevated phenylalanine in tissues, plasma, and urine.**
2. **The characteristic musty "mousey" urine odor due to phenyllactate, phenylacetate, and phenylpyruvate**
3. **CNS symptoms: Mental retardation (IQ < 50), failure to walk or talk, seizures, hyperactivity, tremor, microcephaly, and failure 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.**



|Neonatal screening programs |

After birth does the neonatal has mental retardation?

Not yet. Why?



-- Neonatal screening programs- one of the most important infant tests after a couple days from birth.
-- The artificial sweetener Aspartame should be avoided due to Phe- containing.

-- Another Reason

|Neonatal screening and diagnosis of PKU |

… PKU is treatable by dietary restriction.
… Lack of neonatal symptoms

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.

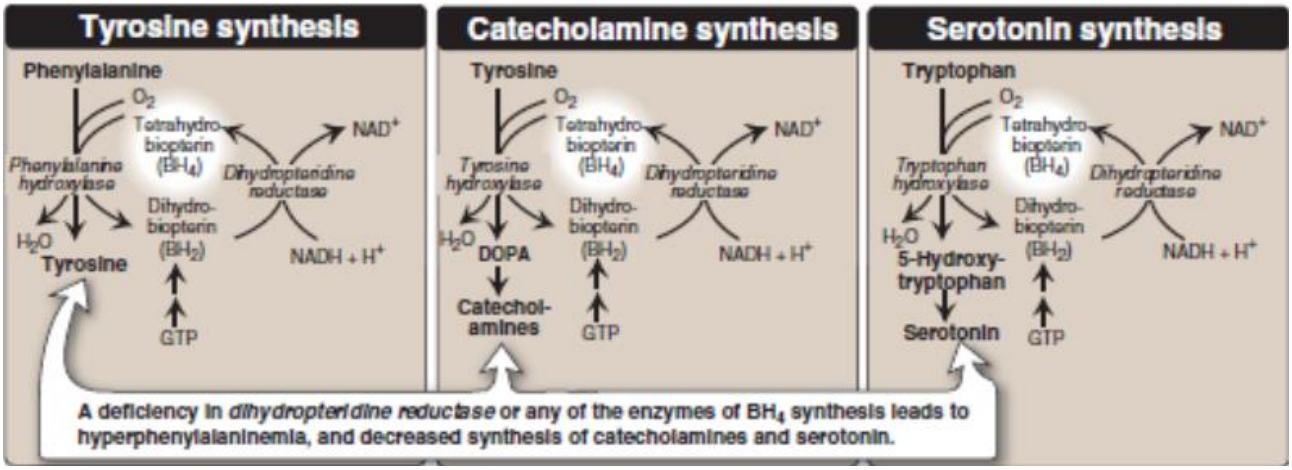
2.Hyperphenylalaninemia

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



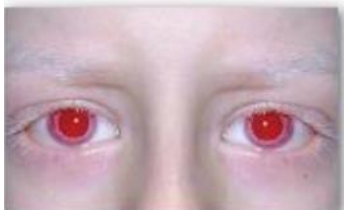
3.Albinism

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.

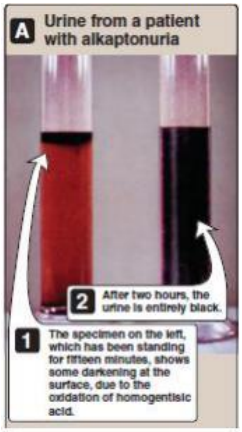
Inheritance modes: Autosomal recessive (primary mode), Autosomal dominant, or X-linked.

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

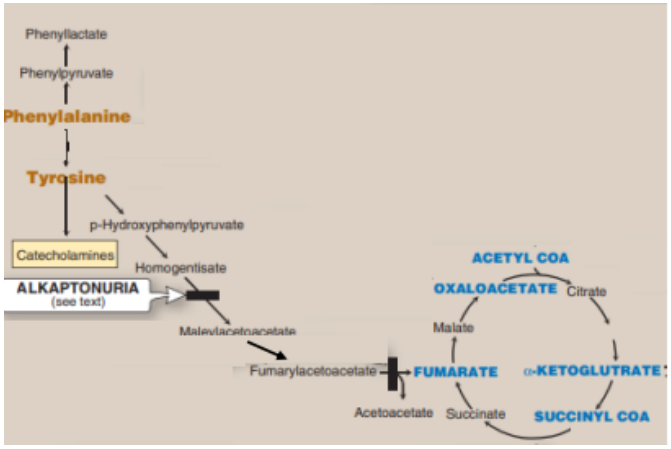


Complete albinism:
The most severe form.
Total absence of pigment from the hair, eyes, and skin, vision defects and photophobia (sunlight hurts their eyes).
Higher risk for skin cancer.

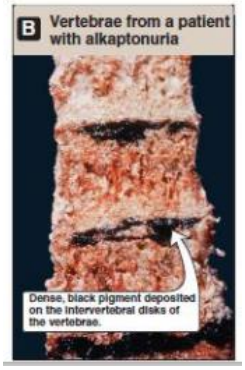
4. Alkaptonuria (Alcaptonuria)



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.

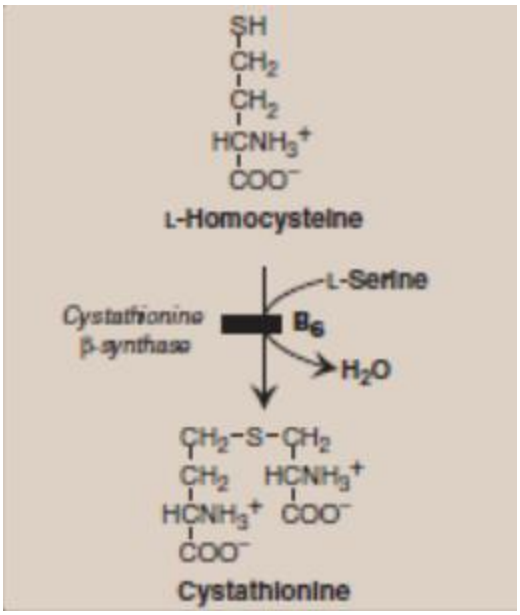
5. Homocystinuria

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

Good Luck

v1