Inborn errors of amino metabolism

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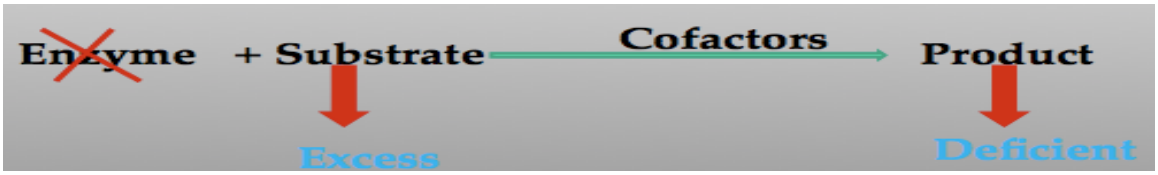
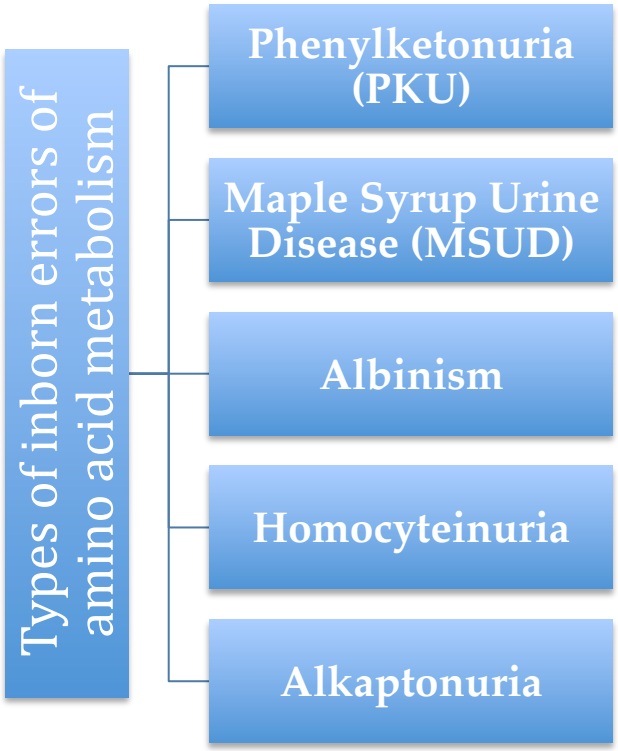
Team biochemistry 430

Inborn Errors of amino acid Metabolism

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

When there is cofactors deficiency the enzyme will be not effective so this leads to substrate accumulation and product deficiency which both lead to harmful effect.



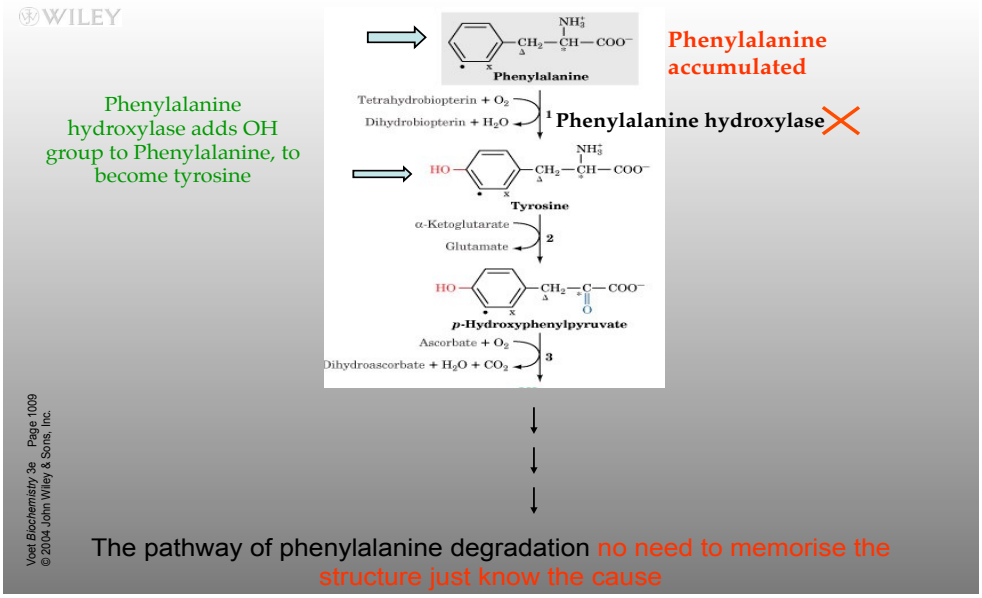


Phenylketonuria (PKU):

- Due to deficiency of phenylalanine hydroxylase enzyme
- Most common disease of aa metabolism
- Results in hyperphenylalaninemia

It is 2 types:

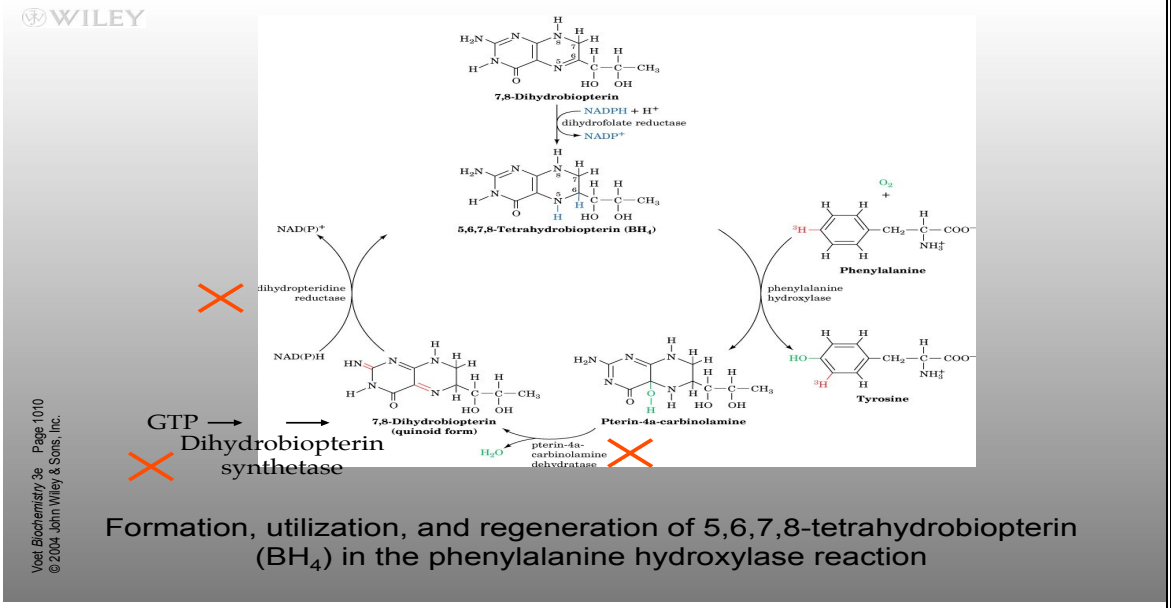
- 1- Classic PKU: Due to deficiency of phenylalanine hydroxylase.
- Hence Phe is accumulated.



2- Atypical hyperphenylalaninemia:

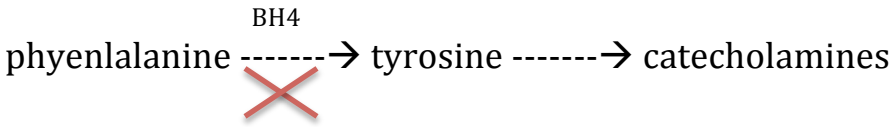
Due to deficiency of BH_4.

- Conversion of Phe to Tyr(tyrosine) requires tetrahydrobiopterin (BH_4)
- Even if phenylalanine hydroxylase level is normal, the enzyme will not function without BH_4
  - Caused by the deficiency of:
    - ★ Dihydropteridine reductase (which converte BH2 to BH4) most common+imp we must memorise this one.
    - ★ Dihydrobiopterin synthetase (synthisis)
    - ★ Carbinolamine dehydratase (synthisis)



Characteristics of PKU

- In the absence of BH_4, Phe will not be converted to Tyr
- Tyr will not be converted to catecholamine (neurotransmitter)
- There for Synthesis of catecholamines requires BH_4
- consequently if BH2 not converted to BH4 there will be no catecholamine (dopamine and serotonin)



- Elevated phenylalanine in tissues, plasma, urine
- Phe is degraded to phenyllactate, phenylacetate, and phenylpyruvate instead
  - Gives urine a mousy odor (smell of mouse)

- CNS symptoms: Mental retardation, failure to walk or talk, seizures, etc.
- Hypopigmentation
  - Deficiency of melanin (because melanin comes from tyrosine)

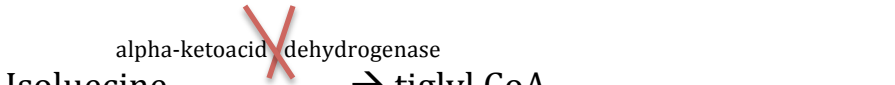
Hydroxylation of tyrosine by tyrosinase is inhibited by high phe conc.

Diagnosis and Treatment of PKU

- 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
  - Tyr supplementation.

Maple Syrup Urine Disease

- Due to deficiency of alpha-ketoacid dehydrogenase
- The enzyme complex decarboxylates leucine, isoleucine and valine
- These aa accumulate in blood
- Symptoms: mental retardation, physical disability, metabolic acidosis, etc.
- Maple syrup odor of urine



Deficiency of this enzyme causes accumulation of these aa

Types:

- Classic type: Most common, due to little or no activity of alpha-ketoacid dehydrogenase (more severe).
- Intermediate and intermittent forms: Some enzyme activity, symptoms are milder.
- Thiamin-responsive form: High doses of thiamin increases alpha-ketoacid
  dehydrogenase activity (we give thiamin if he response to it he will be this type but if not he will be the second).

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 (can not open there eye exposure to light)
- May lead to skin cancer.

tyrosinanse
Tyrosine----------→ melanin
Deficiency of tyrosinase leads to albinisim.

Homocystinuria

- Due to defects in homocysteine metabolism
- Deficiency of cystathionine beta-synthase
  - Converts homocysteine to cystathione
- 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 (ectopia lenses)
- Oxidative stress +inflammation

cystathionine beta-synthase
Methionine <----------Homocysteine ----------X----> cystathione

Accumulation of homocysteine could result in build of methionine as well.

Hyperhomocysteinemia is also associated with:

- Neural tube defect (spina bifida) (inproper clouser of nural tube"in spine"
- Vascular disease (atherosclerosis)
- Heart disease

Treatment:

- Oral administration of vitamins B_6, B_{12} and folate
- Vitamin B_6 is a cofactor for cystathionine b-synthase
- Methionine-restricted diet.

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

Characteristics of Alkaptonuria

- 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 of alkaptonuria

- Restricted intake of tyrosine and phenylalanine (bec it give Tyr) reduces homogentisic acid and dark pigmentation.

Summery

	Disease	Enzyme	Aminoacids involved
1	Phenylketonuria	Phenylalanine hydroxylase	Phenylalanine
2	Maple syrup urine disease	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