Lecture 2: Inborn Errors of aminoacid Metabolism

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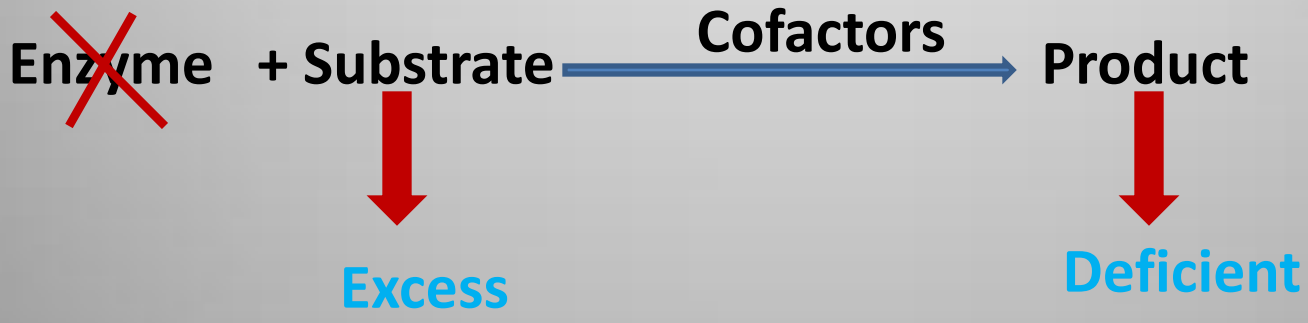
Inborn Errors of amino acid Metabolism

- Caused by enzyme loss or deficiency due to gene mutation



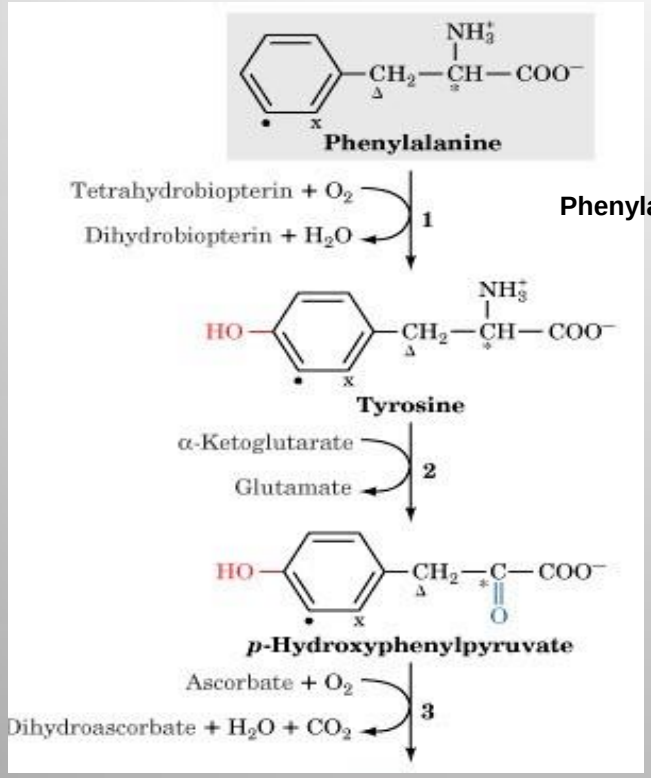
Inborn diseases of amino acid metabolism

- Phenylketonuria
- Maple syrup Urine Disease
- Albinism
- Homocystinuria
- Alkaptonuria

Phenylketonuria (PKU)

- Most common disease of aminoacid metabolism
- Due to deficiency of phenylalanine hydroxylase enzyme
- Results in hyperphenylalaninemia and tyrosine deficiency

Classical PKU



Phenylalanine accumulated

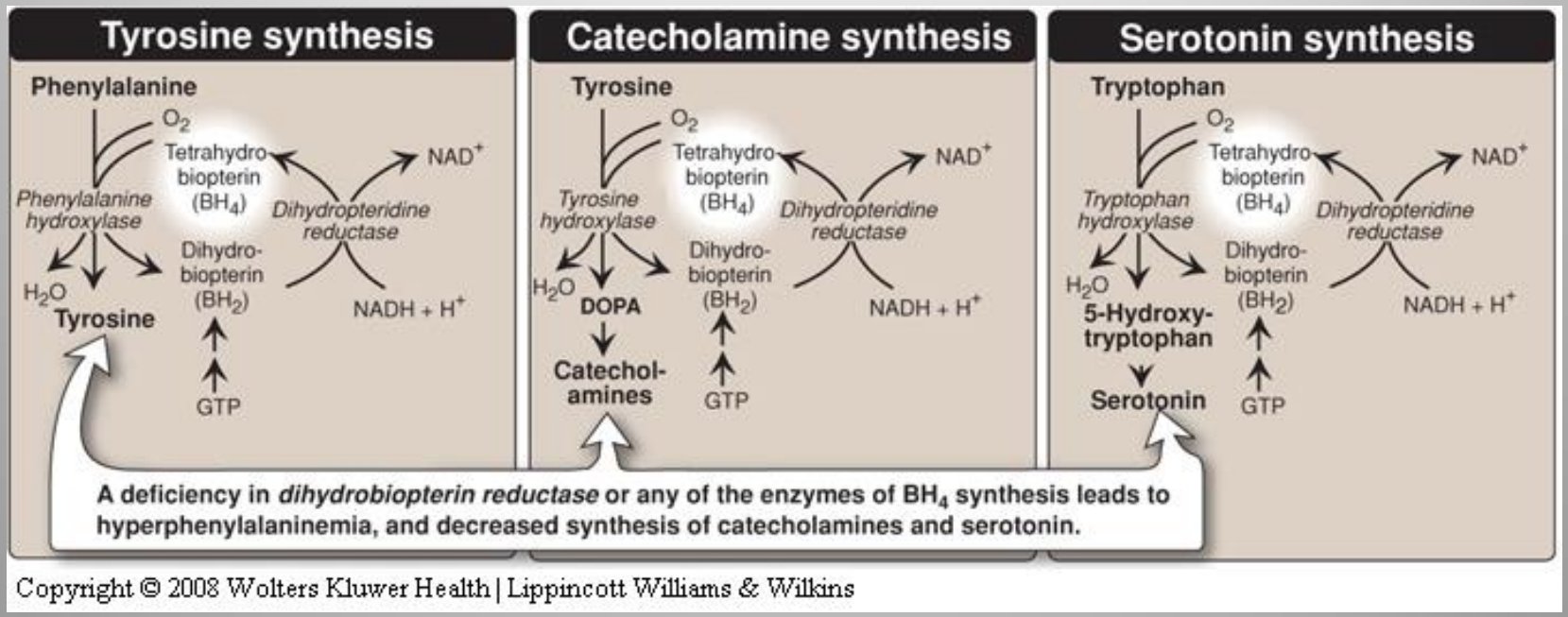
Phenylalanine hydroxylase

The pathway of phenylalanine degradation

Other reasons for hyperphenylalanemia PKU contd..

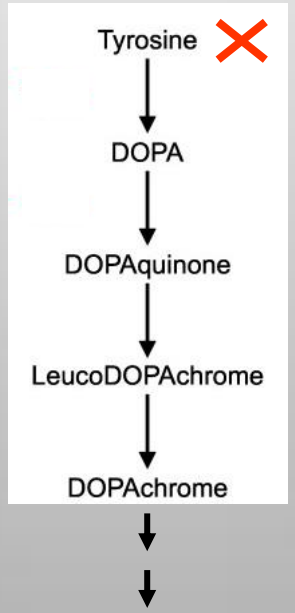
- Conversion of Phe to Tyr requires tetrahydrobiopterin (BH_4)
- Even if phenylalanine hydroxylase level is normal
- The enzyme will not function without BH_4
- Hence Phe is accumulated
- **Atypical hyperphenylalaninemia**:
  - Due to deficiency of dihydropteridine reductase, dihydrobiopterin synthetase enzymes

Aminoacids and Tetrahydrobipterin



Characteristics of PKU

- **In the absence of BH_4, Phe will not be converted to Tyr**



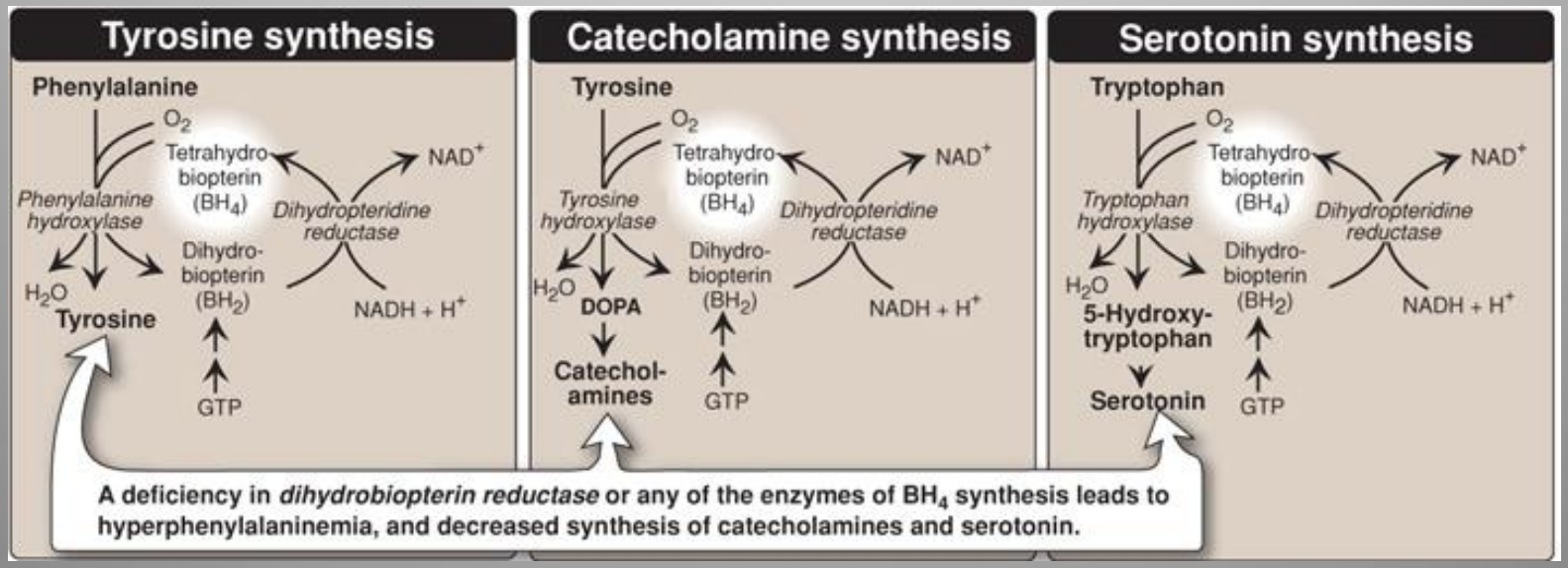
No or less Tyrosine/ also inhibited by excess Phe

No or less melanin
Light skin in PKU patients

Melanin biosynthesis from tyrosine: Deficiency of tyrosinase leads to albinisim

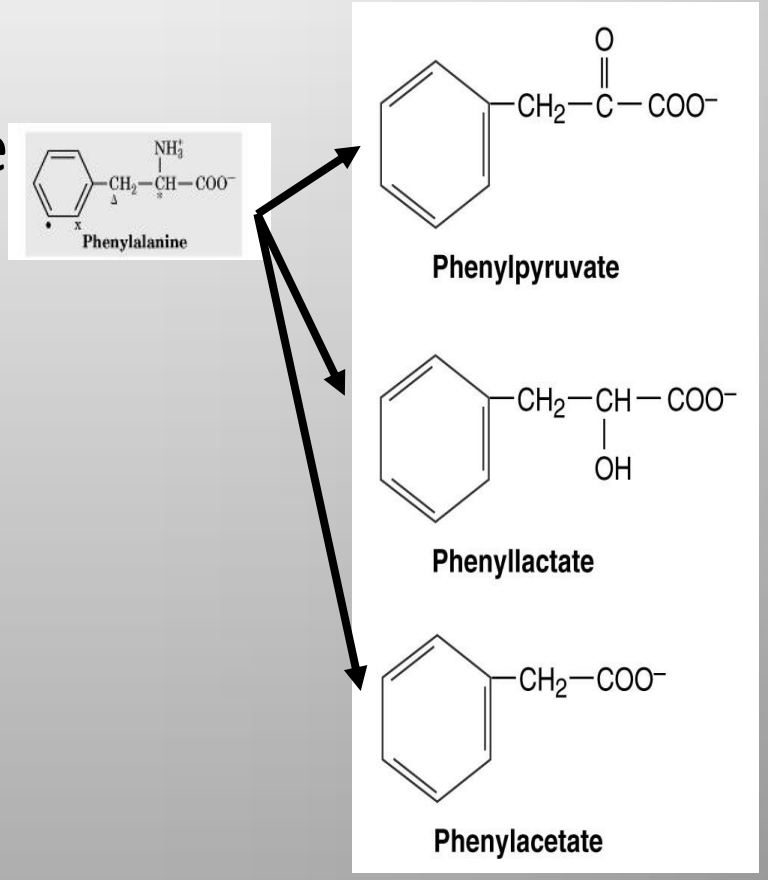
Characteristics of PKU

- Tyr will not be converted to catecholamines and Trp will not be converted to serotonin as they require BH_4
- Catecholamines and serotonin are **neurotransmitters**



Characteristics of PKU

- Elevated phenylalanine in tissues, plasma, urine
- Phe is degraded to phenyllactate, phenylacetate, phenylpyruvate
- Gives urine a mousy odor



Cause of mousy urine smell in PKU

Characteristics of PKU

- **CNS symptoms**: Mental retardation, failure to walk or talk, seizures, microcephaly etc.
- **Hypopigmentation** – fair hair, light skin colour and blue eyes
- Urine has a musty (mousey) odor

Diagnosis and treatment of PKU

- Prenatal diagnosis is done by detecting gene mutation in fetus
- Neonatal diagnosis in infants is done by measuring levels of blood phe
- Treatment: Life long phe-restricted diet and tyrosine supplementation

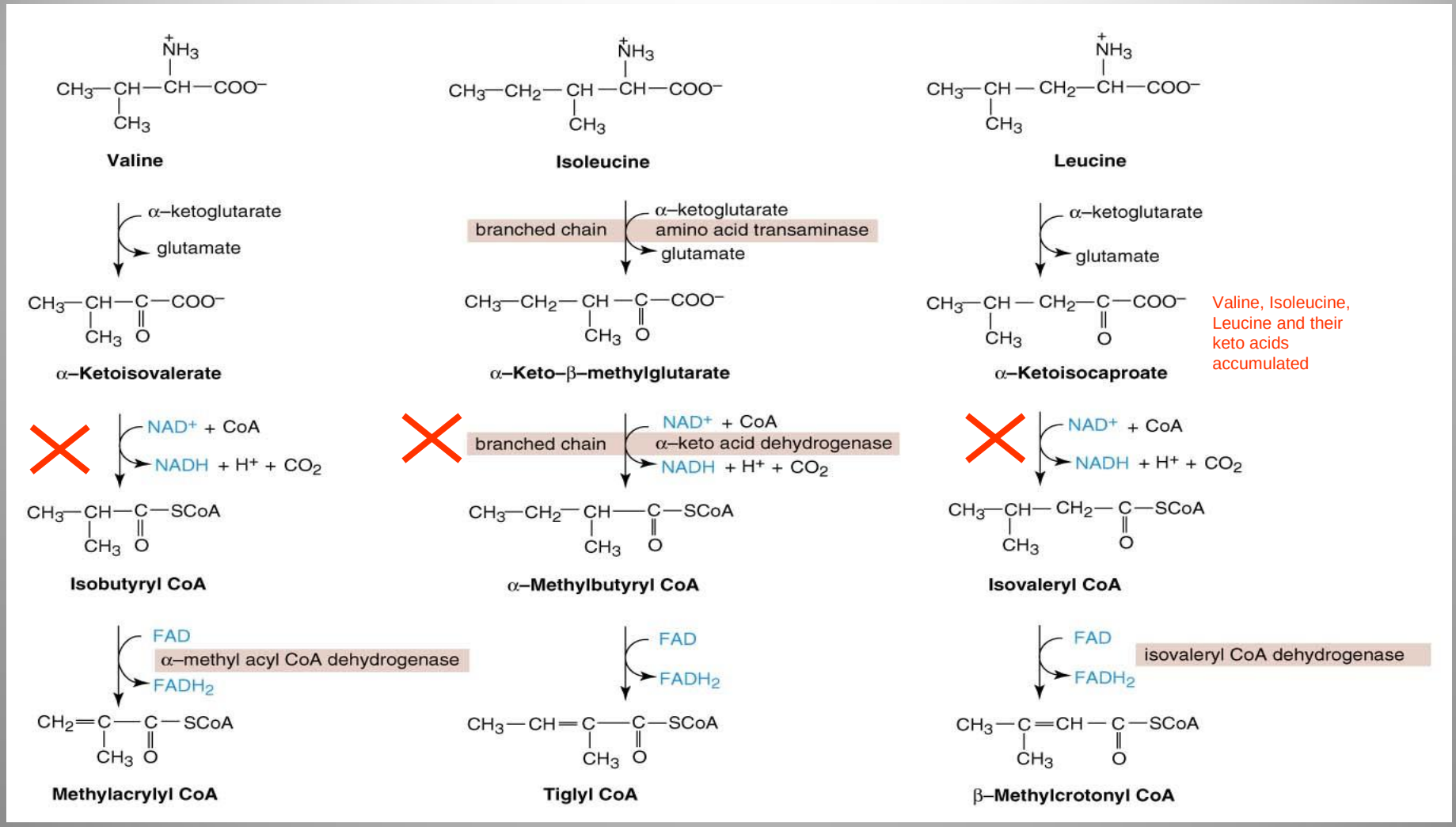
Maple Syrup Urine Disease

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

Maple Syrup Urine Disease

Types:

- **Classic type:** Most common, due to little or no activity of branched chain α-ketoacid dehydrogenase
- **Intermediate and intermittent forms:** Higher enzyme activity, symptoms are milder
- **Thiamine-responsive form:** High doses of thiamine increases α-ketoacid dehydrogenase activity



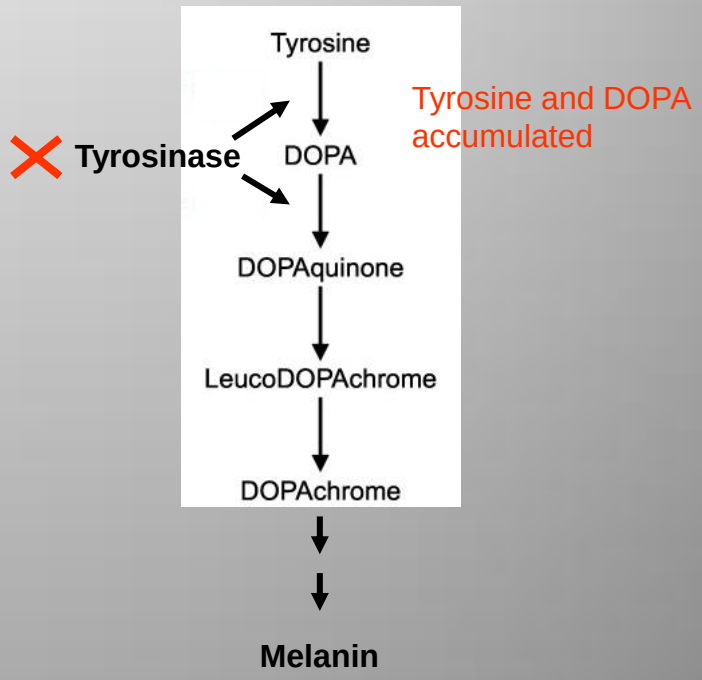
Degradation of branched-chain amino acids: valine, isoleucine and leucine.
Deficiency of branched chain a-keto acid dehydrogenase leads to MSUD.

Maple Syrup Urine Disease

- **Treatment: Limited intake of leucine, isoleucine and valine causes no toxic effects**

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, skin, eyes appear white
- Vision defects, photophobia



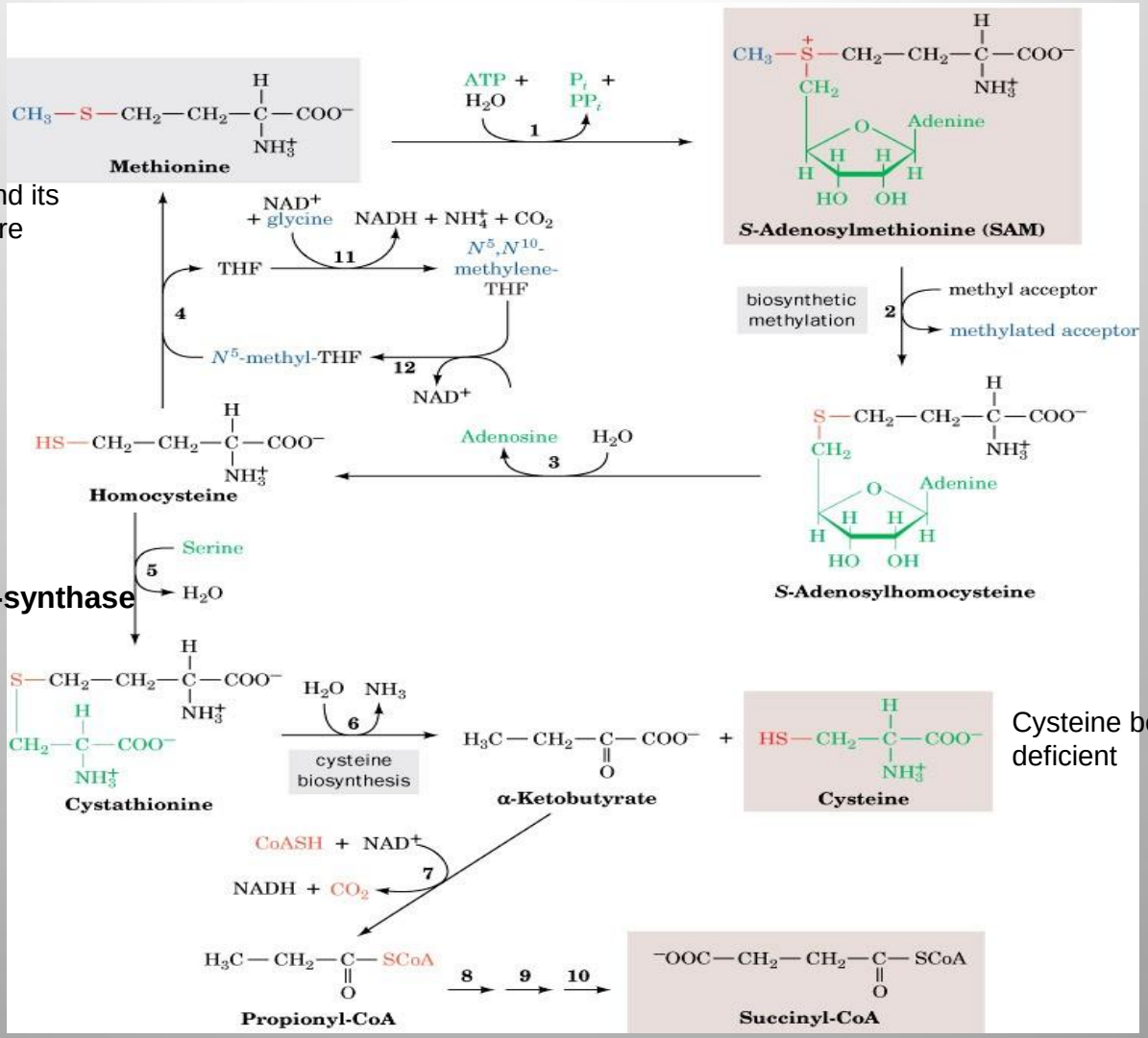
Melanin biosynthesis from tyrosine: Deficiency of tyrosinase leads to albinisim

Homocystinuria

- Due to defects in homocysteine metabolism
- Deficiency of cystathionine β-synthase
- Converts homocysteine to cystathionine
- High plasma and urine levels of homocysteine and methionine and low levels of cysteine
- Homocysteine is a risk factor for atherosclerosis and heart disease
- Skeletal abnormalities, osteoporosis, mental retardation, displacement of eye lens

Methionine and its metabolites are accumulated

Cystathione b-synthase



Cysteine becomes deficient

Methionine degradation pathway: Deficiency of cystathione b-synthase leads to homocystinuria / homocysteinemia

Treatment of Homocystinuria

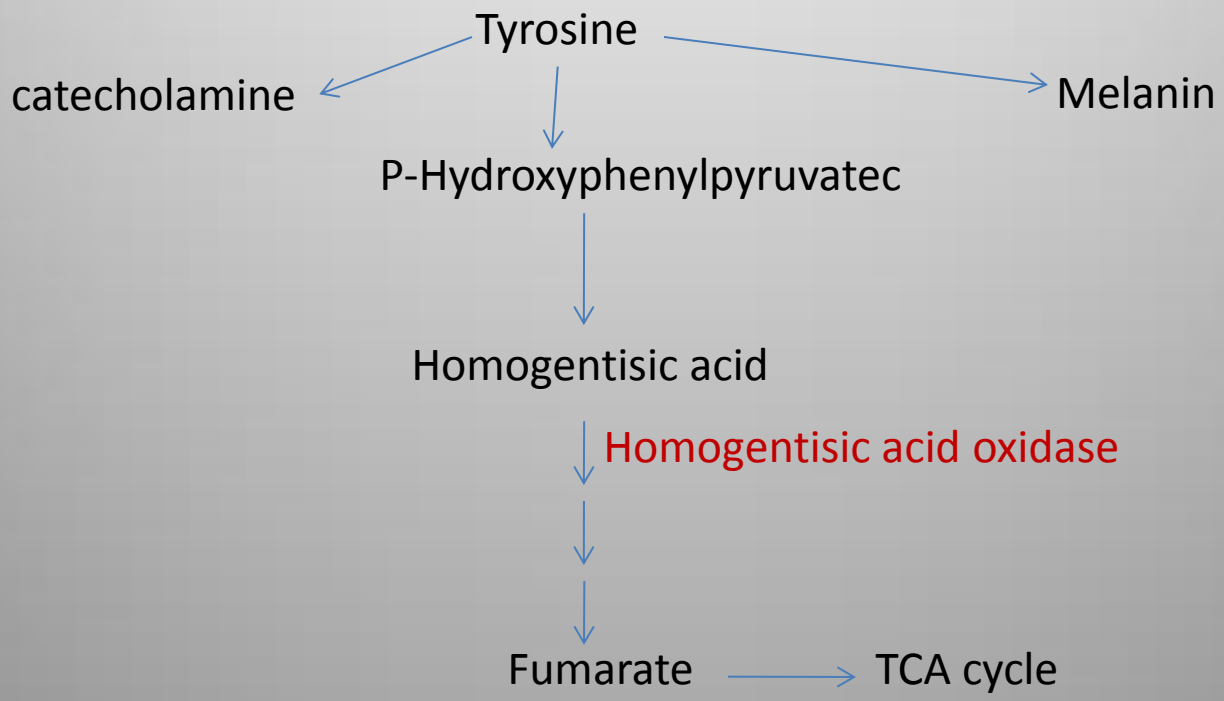
- Oral administration of vitamins B_6, B_{12} and folate
- Vitamin B_6 is a cofactor of cystathionine β-synthase
- Methionine-restricted diet

Homocystinuria

- Hyperhomocysteinemia is also associated with:
- Neural tube defect (spina bifida)
- Vascular disease (atherosclerosis)
- A risk factor of heart disease

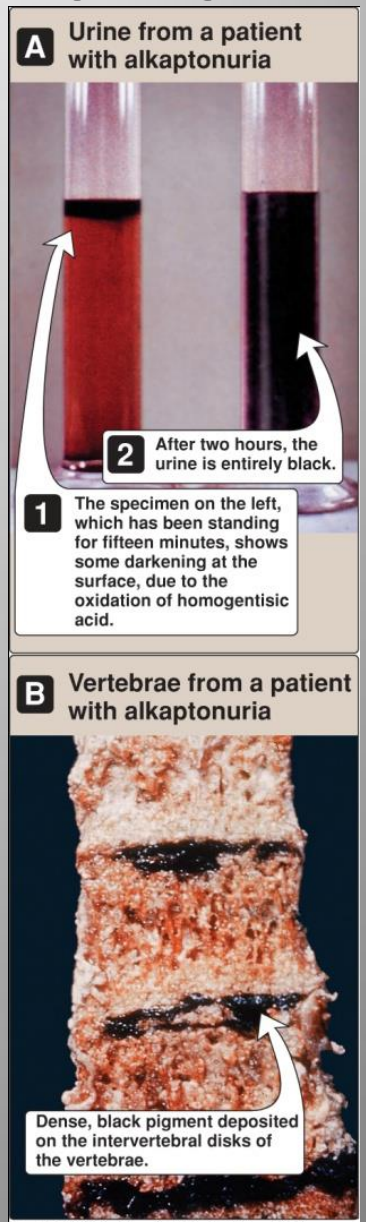
Alkaptonuria

- A rare disease of tyrosine degradation
- Due to deficiency of homogentisic acid oxidase



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 reduces homogentisic acid and dark pigmentation

Summary

	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