Inborn Errors of Amino Acid Metabolism (Renal Block)

Biochemistry of:

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

Inborn Errors of aa Metabolism

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

Phenylketonuria (PKU)

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

Phenylketonuria (PKU)

- Classic PKU:
  - Due to deficiency of phenylalanine hydroxylase
- 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

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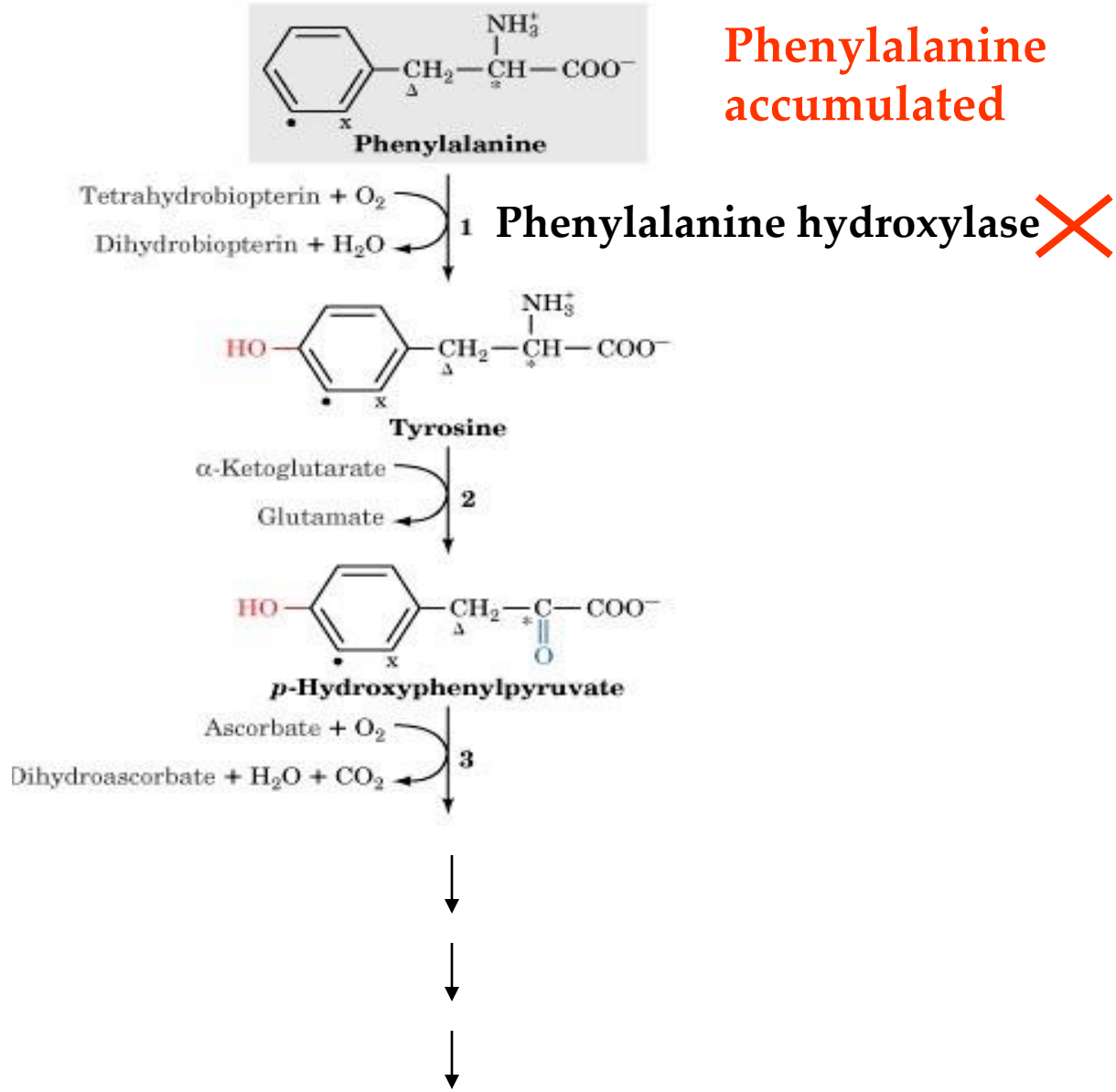

The pathway of phenylalanine degradation

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Phenylketonuria (PKU)

Atypical hyperphenylalaninemia:

- Due to deficiency of BH_4
- Caused by the deficiency of:
  - Dihydropteridine reductase
  - Dihydrobiopterin synthetase
  - Carbinolamine dehydratase

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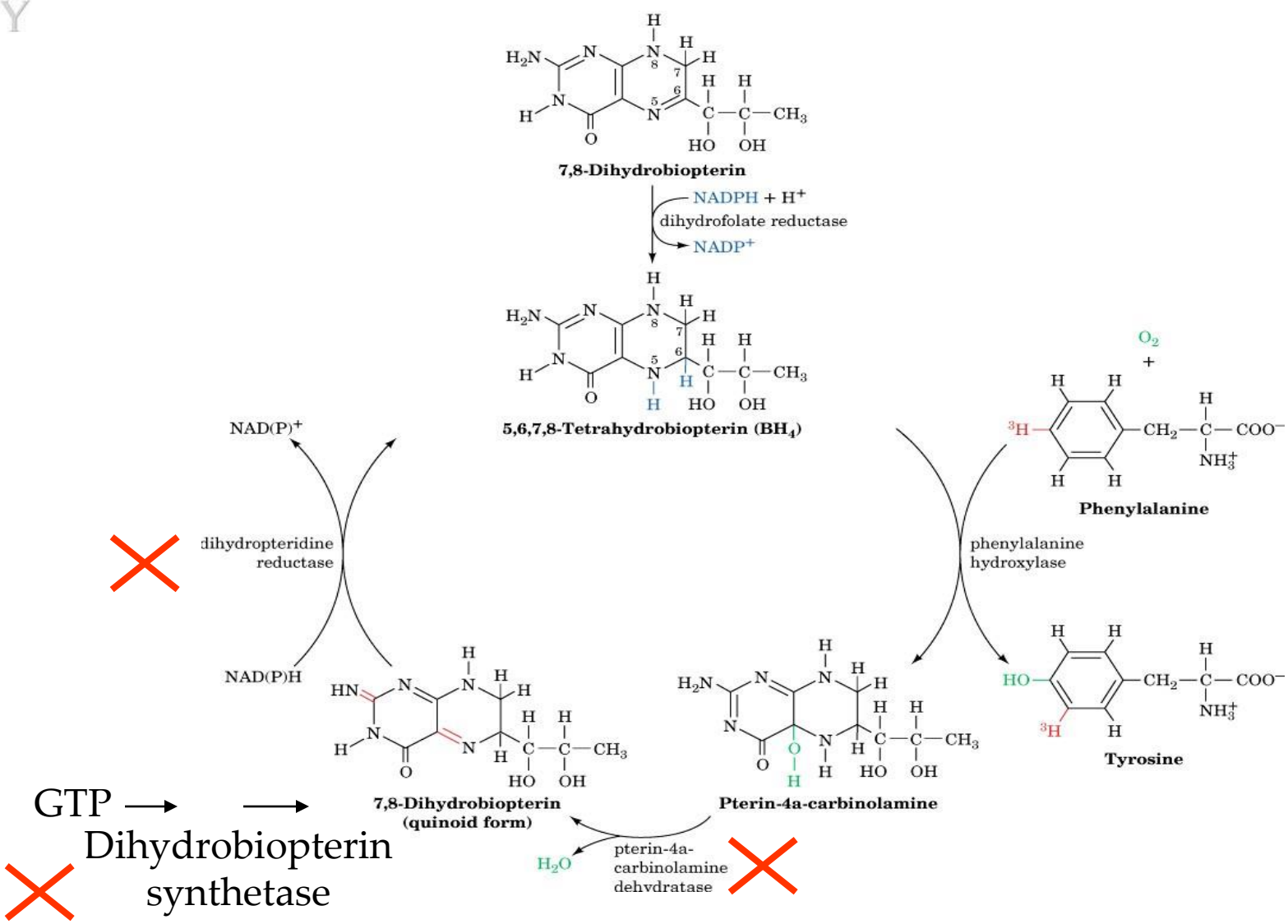

Formation, utilization, and regeneration of 5,6,7,8-tetrahydrobiopterin (BH_4) in the phenylalanine hydroxylase reaction

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Characteristics of PKU

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

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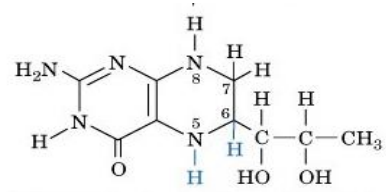
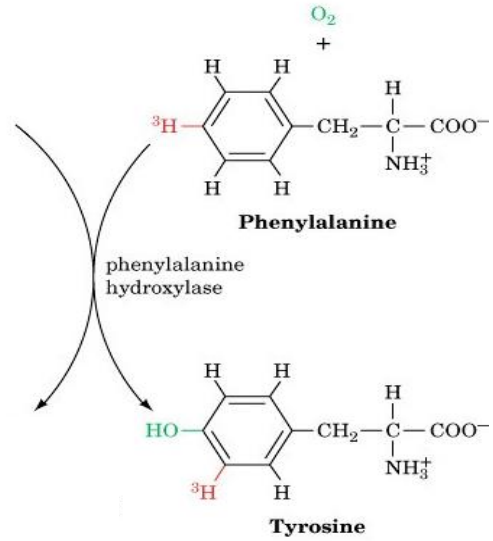


5,6,7,8-Tetrahydrobiopterin (BH_4)

BH_2



Phe accumulated

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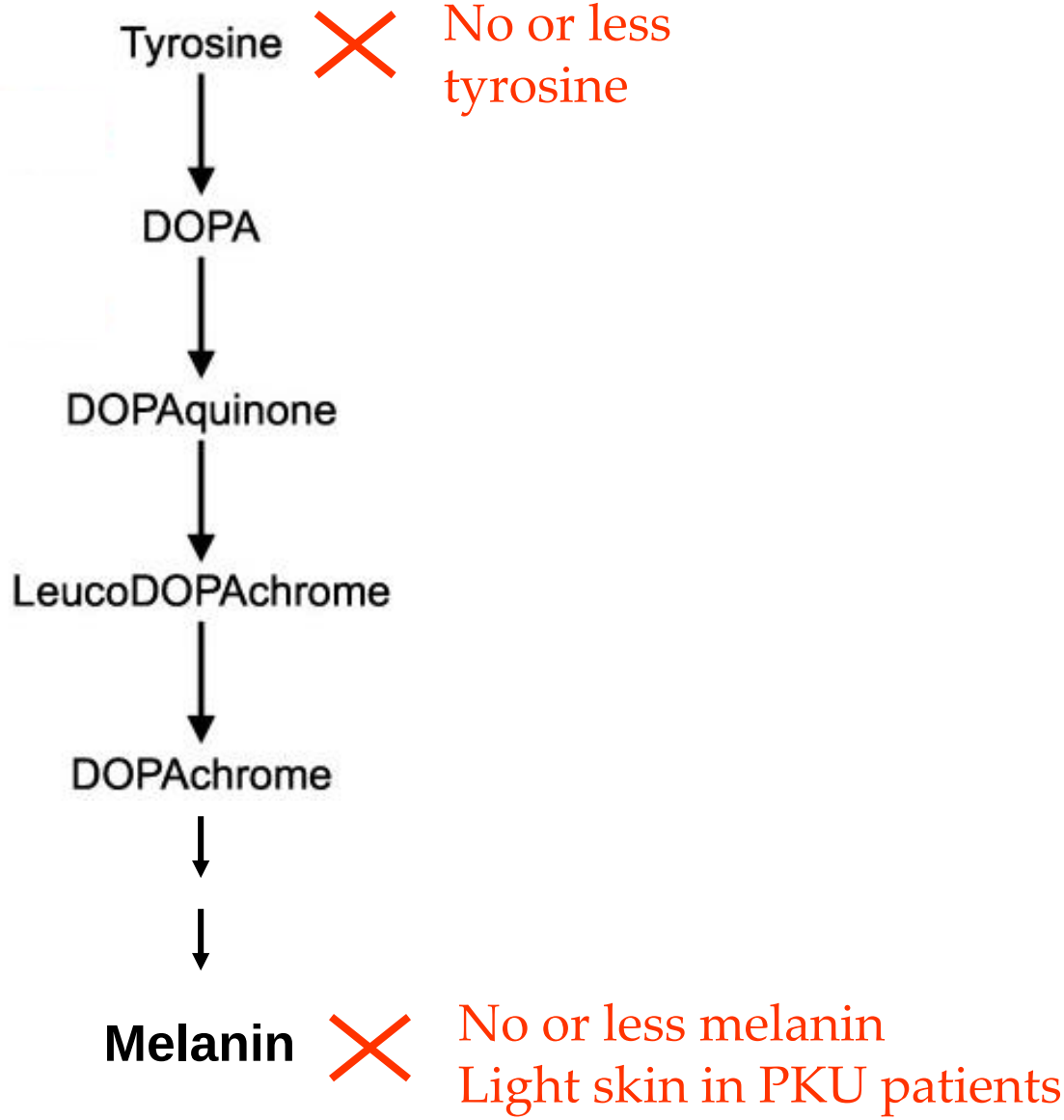

Melanin biosynthesis from tyrosine

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Characteristics of PKU

- Tyr will not be converted to catecholamine neurotransmitters
- Synthesis of catecholamines requires BH_4

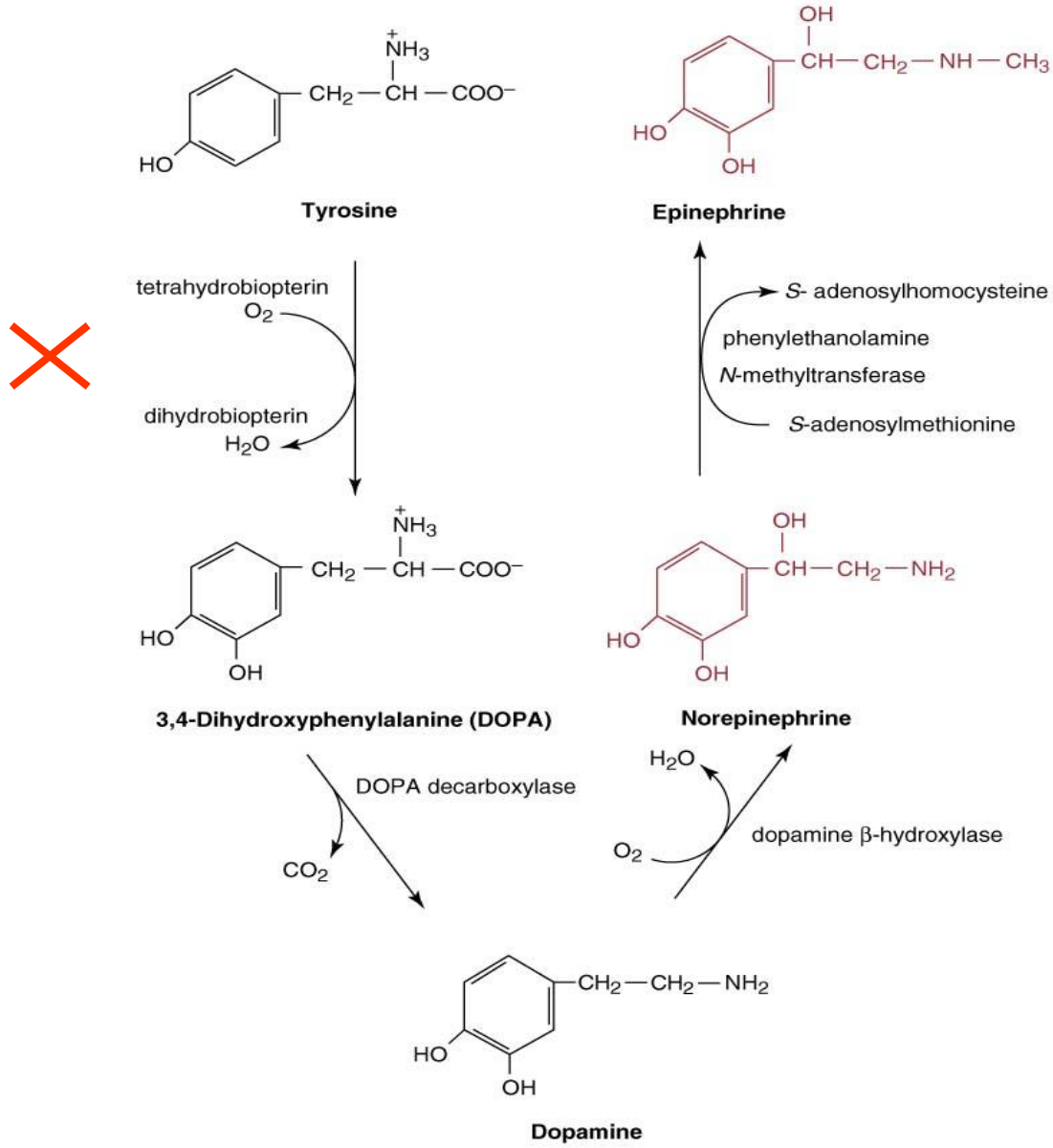

Figure 19.50. Synthesis of catecholamines.

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Characteristics of PKU

- Trp will not be converted to serotonin (a neurotransmitter) as it requires BH_4

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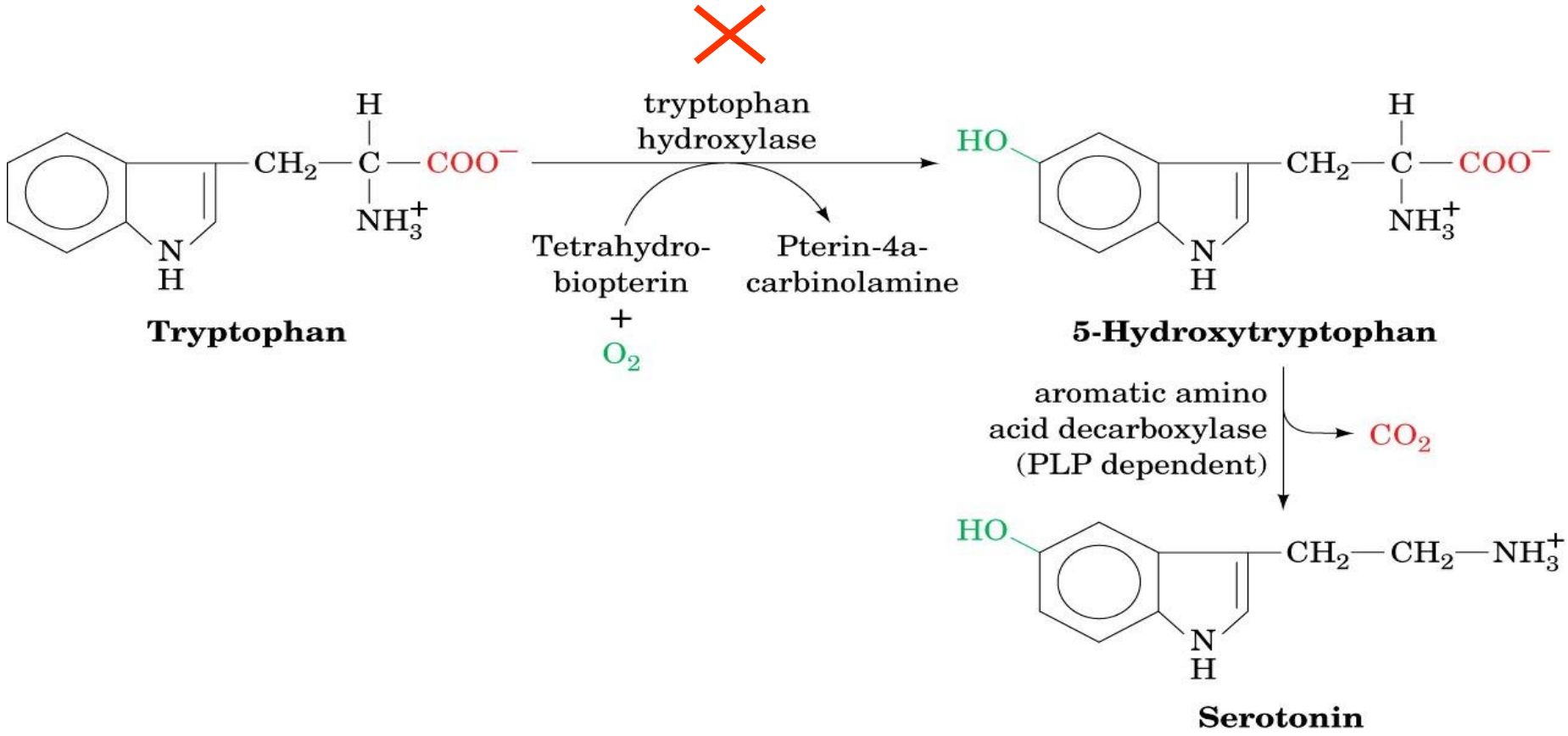

Synthesis of serotonin

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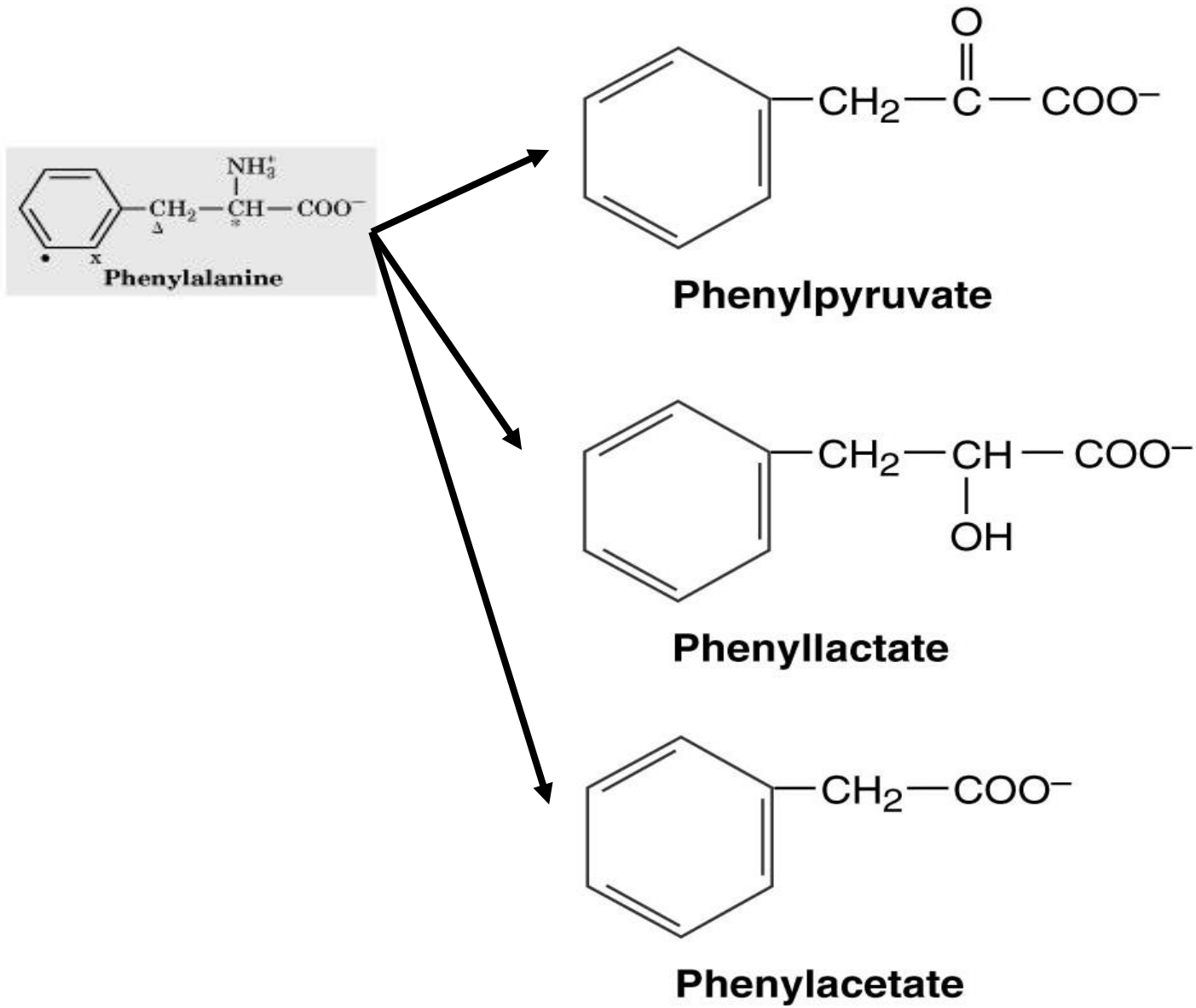
Characteristics of PKU

- CNS symptoms: Mental retardation, failure to walk or talk, seizures, etc.
- Hypopigmentation
  - Deficiency of melanin
  - Hydroxylation of tyrosine by tyrosinase is inhibited by high phe conc.

Characteristics of PKU

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



Cause of mousy urine smell in PKU

Characteristics of PKU

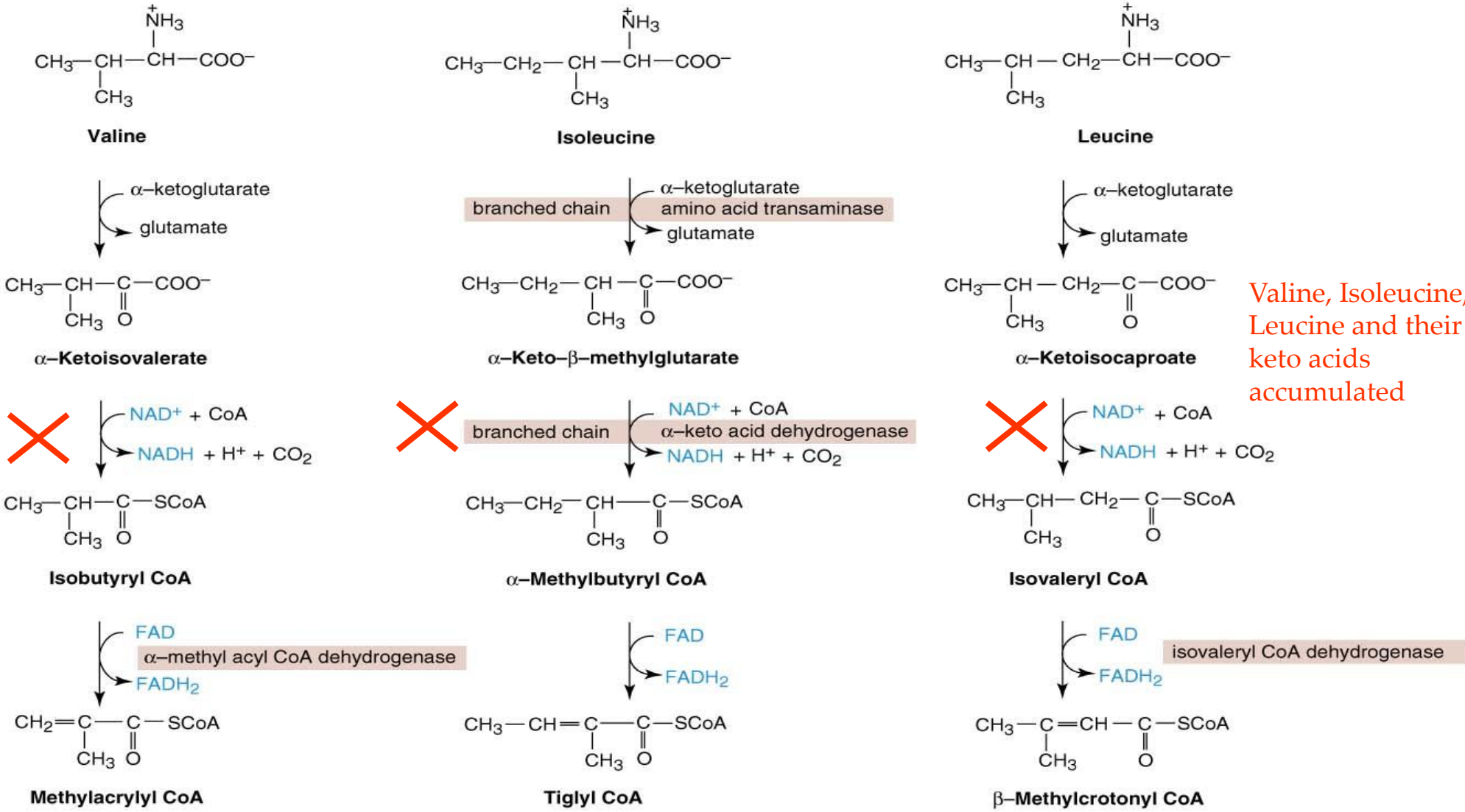
- Prenatal diagnosis is done by detecting gene mutation in fetus
- Neonatal diagnosis in infants is done by measuring blood phe levels
- Treatment:
  - Life long phe-restricted diet

Maple Syrup Urine Disease

- Due to deficiency of branched chain α-ketoacid dehydrogenase
- The enzyme decarboxylates leucine, isoleucine and valine
- These aa 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 α-ketoacid dehydrogenase
  - Intermediate and intermittent forms: Some enzyme activity, symptoms are milder
  - Thiamin-responsive form: High doses of thiamin 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

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

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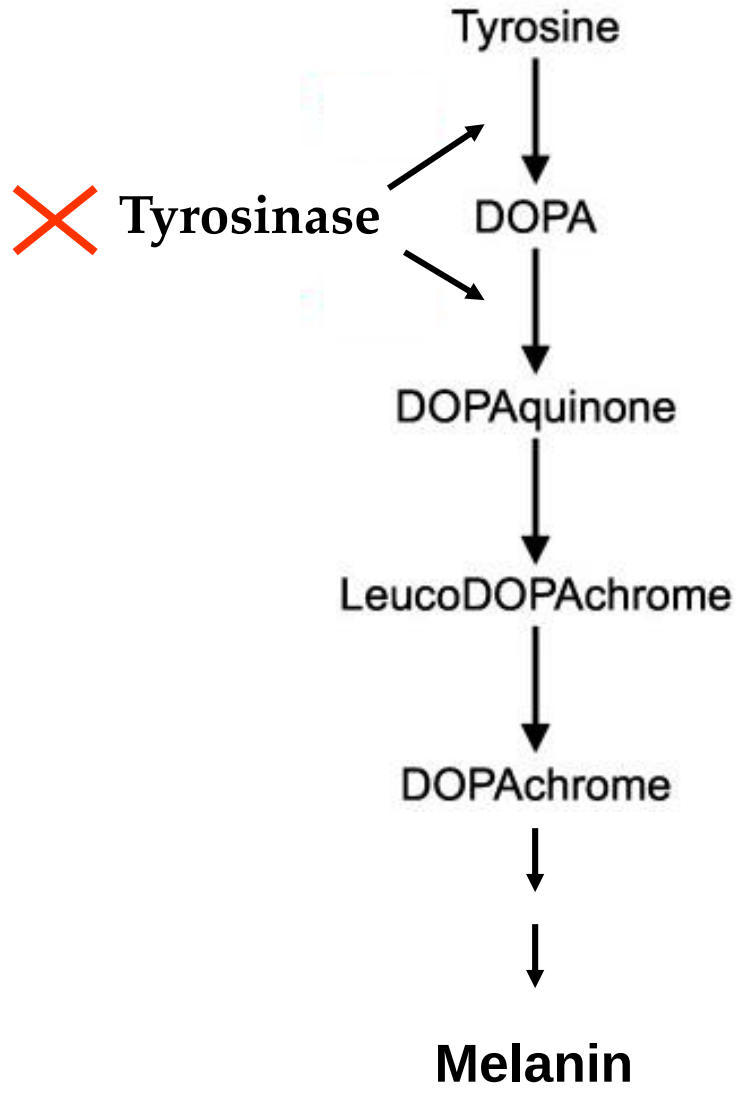

Melanin biosynthesis from tyrosine: Deficiency of tyrosinase leads to albinisim

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Homocystinuria

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

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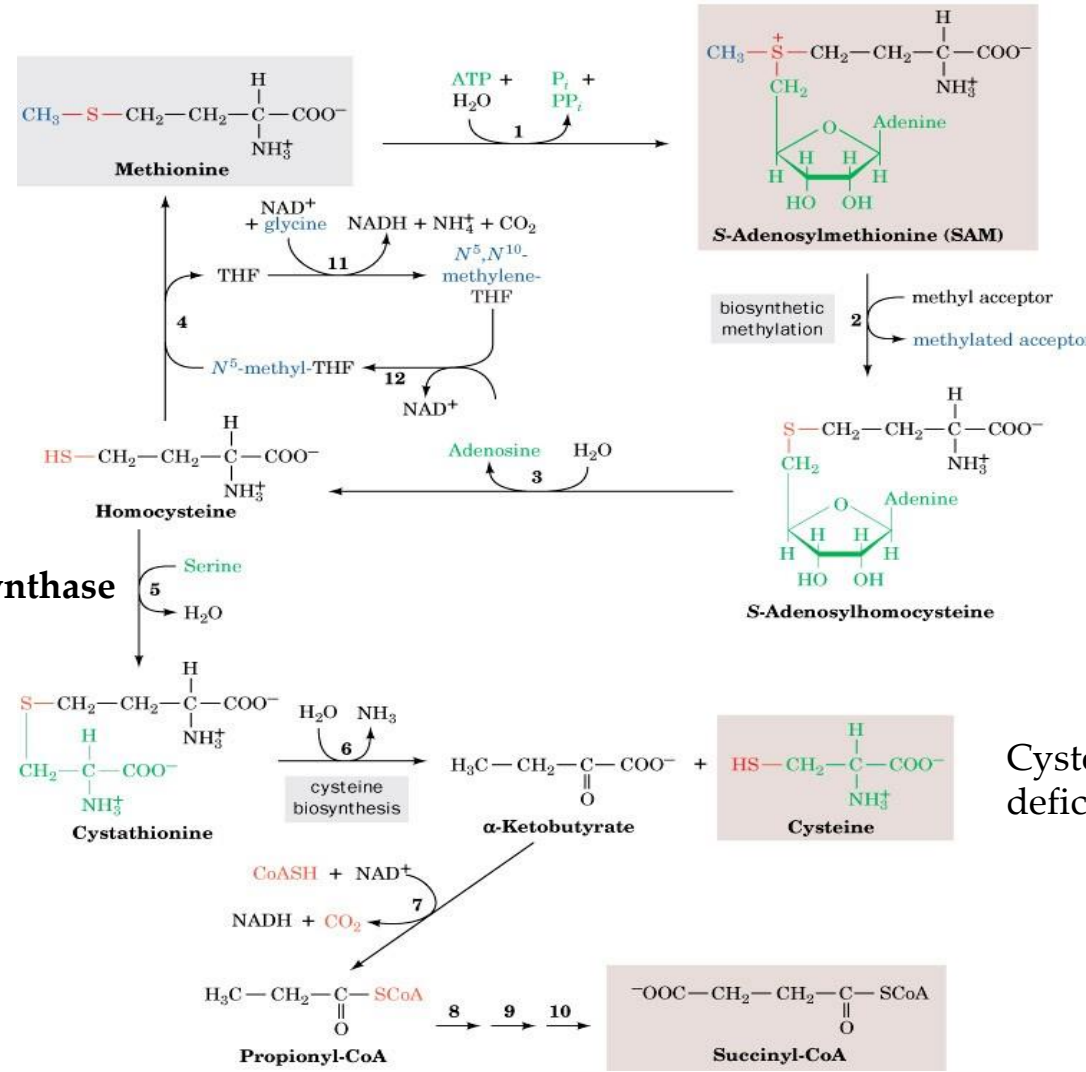
Methionine and its metabolites are accumulated



Cysteine becomes deficient

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

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Homocystinuria

Treatment:

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

Homocysteinemia

Hyperhomocysteinemia is also associated with:

- Neural tube defect (spina bifida)
- Vascular disease (atherosclerosis)
- Heart disease

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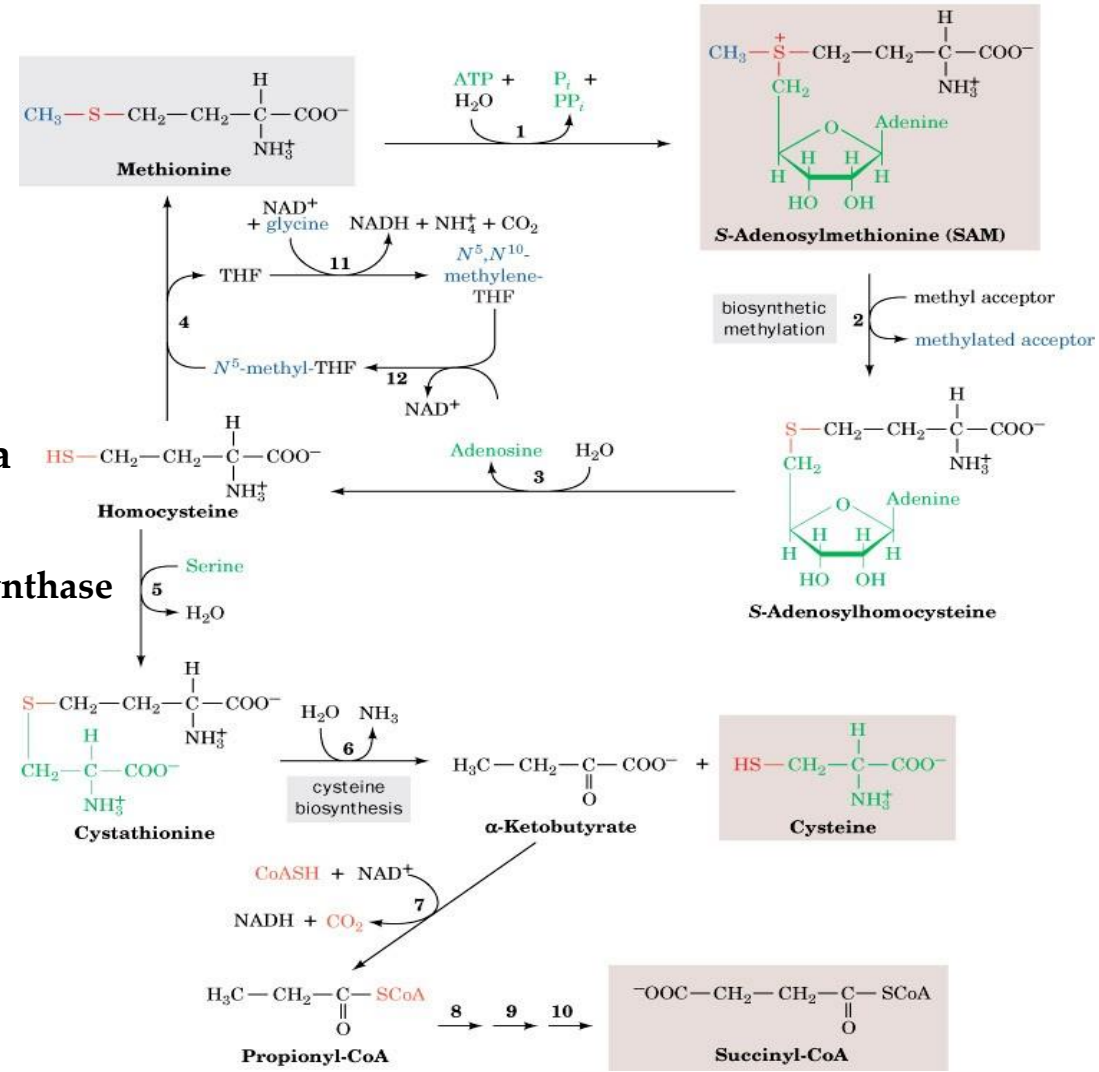
Neural tube defect

Deficiency of:
- **Tetrahydrofolate**
- **Methionine synthase**
- **Vitamin B_6, B_{12}**
- **Folic acid**

+

Hyperhomocysteinemia

✕ Cystathione β-synthase



Methionine degradation pathway: Deficiency of cystathione β-synthase leads to hyperhomocystinuria / hyperhomocysteinemia

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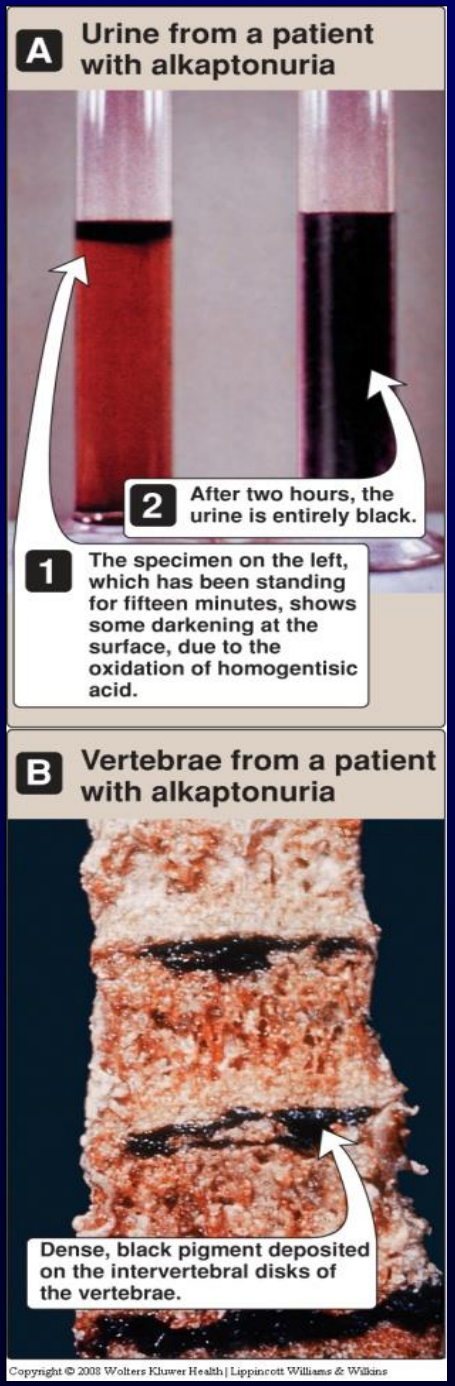
Alkaptonuria

- 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

Alkaptonuria

- Homogentisic acid is oxidized to dark pigment in urine over time
- Arthritis, black pigmentation of cartilage and tissue
- Usually asymptomatic until adulthood
- Restricted intake of tyrosine and phenylalanine reduces homogentisic acid and dark pigmentation



Degradation of tyrosine
Deficiency of homogentisic acid oxidase leads to alkaptonuria