# Catabolism of Phenylalanine and Thyrosine

- Under normal conditions, degradation of phenylalanine mostly occurs through tyrosine.
- Phenylalanine is hydroxylated at para-position by phenylalanine hydroxylase to produce tyrosine(p-hydroxy phenylalanine)

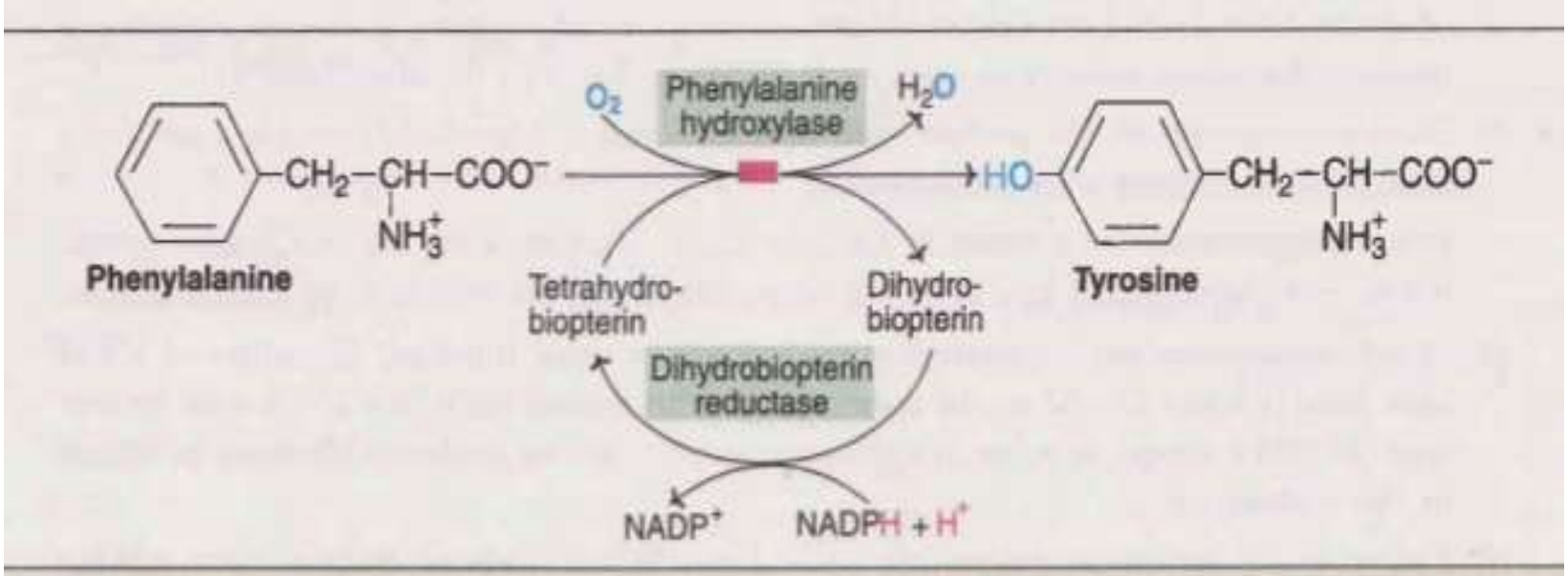


*Fig. 15.18 : Synthesis of tyrosine from phenylalanine ( —Block in phenylketonuria).*

## DEGRADATION OF TYROSINE:

- The metabolism of phenylalanine and tyrosine is considered together.
- Tyrosine first undergoes transamination to give p-hydroxy phenyl pyruvate, catalysed by tyrosine transaminase.
- p-Hydroxyphenylpyruvate hydroxylase catalyses oxidative decarboxylation as well as hydroxylation of the phenyl ring of p-hydroxyphenylpyruvate to produce homogentisate.
- Homogentisate oxidase cleaves the benzene ring of homogentisate to form 4-maleylacetoacetate.
- Maleylacetoacetate undergoes isomerization to form 4-fumaryl acetoacetate and this reaction is catalysed by maleyl acetoacetate isomerase.
- Fumaryl acetoacetase brings the hydrolysis of fumaryl acetoacetate to liberate fumarate and acetoacetate.

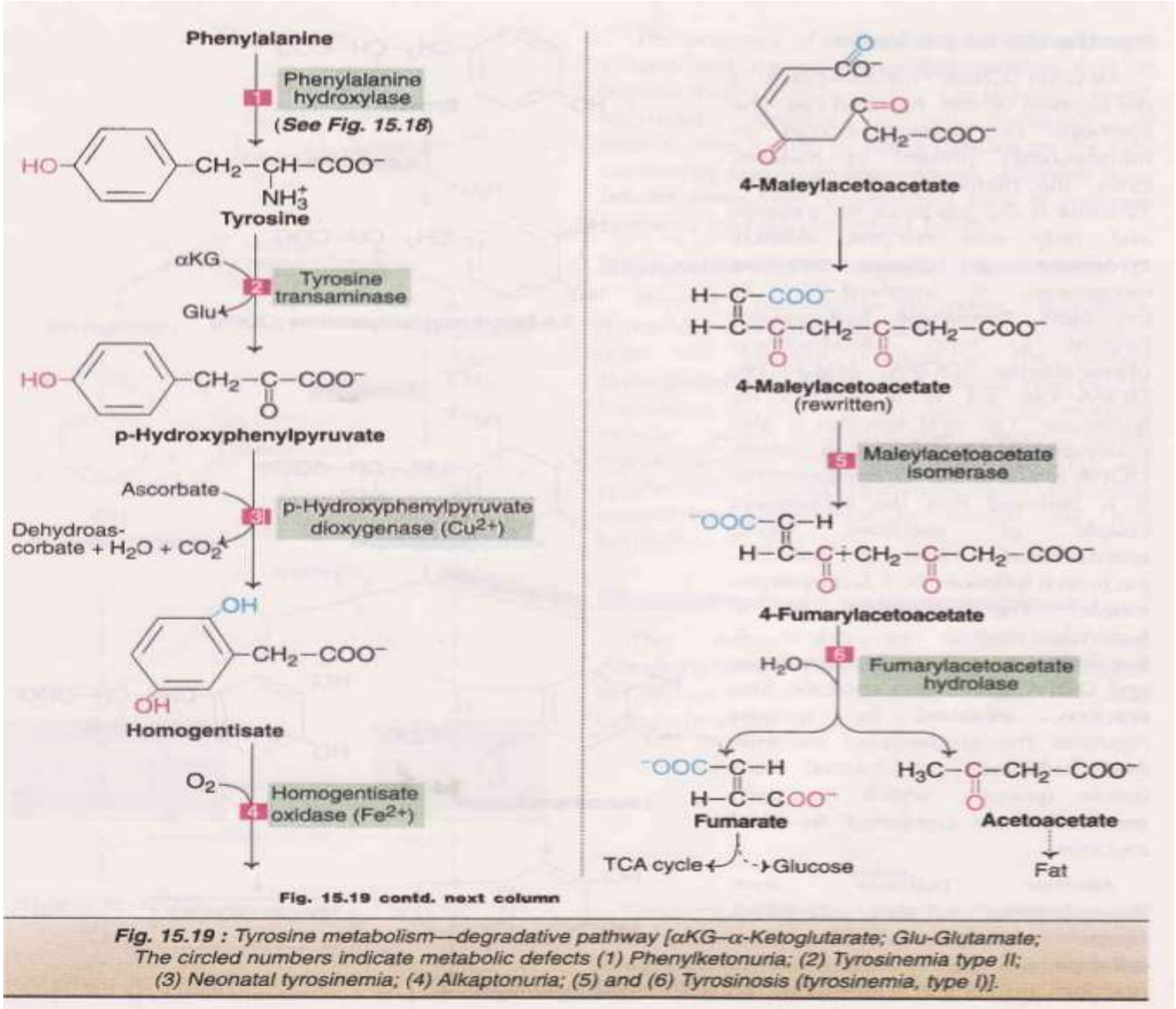


***Fig. 15.19 :*** *Tyrosine metabolism—degradative pathway [αKG–α-Ketoglutarate; Glu-Glutamate; The circled numbers indicate metabolic defects (1) Phenylketonuria; (2) Tyrosinemia type II; (3) Neonatal tyrosinemia; (4) Alkaptonuria; (5) and (6) Tyrosinosis (tyrosinemia, type I)].*

# Disorders of Thyrosine (phenyl alanine) metabolism

## Phenylketonuria( PKU):

- Due to the deficiency of the hepatic enzyme, phenylalanine hydroxylase, caused by an autosomal recessive gene.
- This enzyme deficiency impairs the synthesis of tetrahydro biopterin required for the action of phenylalanine hydroxylase
- Phenylketonuria causes the accumulation of phenylalanine in tissues and blood, and results in its increased excretion in urine.
- Effects on central nervous system : Mental retardation, failure to walk or talk, failure of growth, seizures and tremor.
- Effect on pigmentation: hypopigmentation that causes light skin colour, fair hair, blue eyes etc (ie, inhibit melanin formation)

- PKU is mostly detected by screening the newborn babies for the increased plasma levels of phenylalanine( PKU, 20-65 mg/dl; normal 1-2mg/dl) - Guthrie test.
- plasma phenylalanine concentration can be maintained within the normal range by selecting foods with low phenylalanine content and/or feeding synthetic amino acid preparations, low in phenylalanine.
- In some seriously affected PKU patients, treatment includes administration of 5-hydroxytryptophan and dopa

## Albinism:

- Occurs due to the lack of synthesis of the pigment melanin.
- It is an autosomal recessive disorder

## Causes for Albinism:

1. Deficiency or lack of the enzyme tyrosinase (enzyme most responsible for the synthesis of melanin).
2. Decrease in melanosomes of melanocytes.
3. Impairment in melanin polymerization.
4. Lack of protein matrix in melanosomes.
5. Limitation of substrate(tyrosine) availability.
6. Presence of inhibitors of tyrosinase.

- Lack of melanin in albinos makes them sensitive to sunlight.
- Increased susceptibility to skin cancer (carcinoma) is observed.
- Photophobia (intolerance to light) is associated with lack of

## Alkaptonuria:

- Defect in enzyme homogentisate oxidase.
- Homogentisate accumulates in tissues and blood, and is excreted into urine.
- Homogentisate gets oxidized to the corresponding quinones, which polymerize to give black or brown colour (due to the presence of pigment alkapton).
- For this reason, the urine of alkaptonuric patients resembles coke in colour.
- Alkapton deposition occurs in connective tissue, bones and various organs (nose, ear etc.) resulting in a condition known as ochronosis.
- consumption of protein diet with relatively low phenyl alanine content is recommended as treatment.

## Tyrosinosis or Tyrosinemia Type I

- This is due to the deficiency of the enzymes fumaryl aceto acetate hydroxylase and/or maleyl acetoacetate isomerase.
- It causes liver failure, rickets, renal tubular dysfunction and polyneuropathy.
- In acute tyrosinosis, the infant exhibits diarrhea, vomiting, and 'cabbage-like' odor.
- Death may even occur due to liver failure within one year.
- For the treatment, diets low in tyrosine, phenylalanine and methionine are recommended.

## Tyrosinemia type II (Richner- Hanhart syndrome)

- This is due to a defect in the enzyme tyrosine transaminase.
- Blockade in the routine degradative pathway of tyrosine.
- Accumulation and excretion of tyrosine and its metabolites(p-hydroxy phenyl pyruvate, p-hydroxyphenyl acetate, N-acetyltyrosine and tyramine ) are observed.
- The absence of the enzyme p-hydroxyphenylpyruvate dioxygenase causes neonatal tyrosinemia.