Metabolism of Aromatic Amino Acids

4

Mária Stančíková and Jozef Rovenský

Content

Phenylalanine and tyrosine are the simplest aromatic amino acids derived from alanine. Phenylalanine is an essential amino acid that our body cannot synthesise. This does not apply to tyrosine, which the body can synthesise only if there is a sufficient amount of phenylalanine – and availability of the enzyme participating in conversion of phenylalanine to tyrosine (Fig. 4.1). There is a close mutual relationship between phenylalanine and tyrosine; phenylalanine converts to tyrosine in the liver and to phenylpyruvic acid in the kidneys. Aromatic amino acids have a common intermediary metabolism, and conversion of phenylalanine to tyrosine and its further metabolism is controlled by a complicated enzymatic system. Disorder of the conversion of phenylalanine to tyrosine is called phenylketonuria, and it is one of the most frequently occurring recessive inherited diseases (approximately 1 patient per 10,000 newborns). In phenylketonuria, either the phenylalanine hydroxylase that converts phenylalanine to tyrosine (Fig. 4.1) or its cofactor tetrahydrobiopterin is absent (Blau et al. 2005; Crone et al. 2005). Treatment of children with phenylketonuria has to start in the 3rd month of life, because unrecognised phenylketonuria results in mental retardation, seizures, excessive tremor and hyperactivity.

M. Stančíková
National Institute of Rheumatic Diseases, Piešťany, Slovakia
e-mail: marika.stancikova@gmail.com

J. Rovenský (✉)
National Institute of Rheumatic Diseases, Piešťany, Slovakia

Institute of Physiotherapy, Balneology and Therapeutic Rehabilitation, University of SS Cyril and Methodius Trnava, Piešťany, Slovakia
e-mail: jozef.rovensky@nurch.sk

J. Rovenský et al. (eds.), *Alkaptonuria and Ochronosis*,
DOI 10.1007/978-3-319-15108-3_4

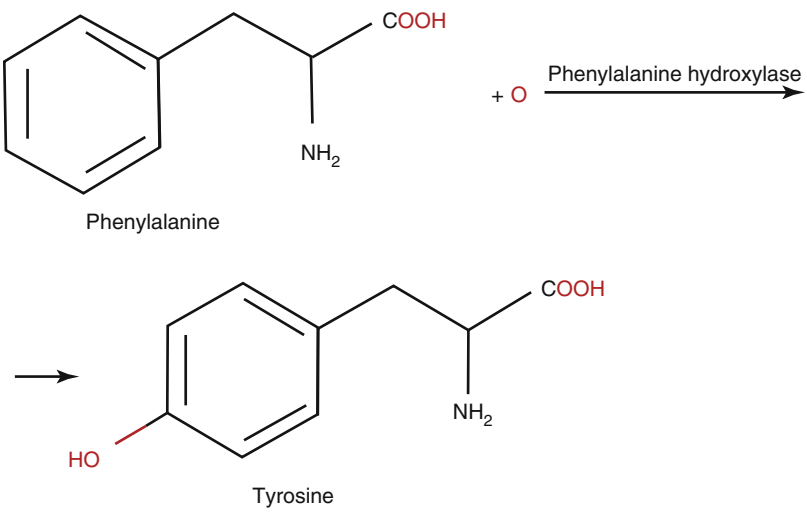

Fig. 4.1 Conversion of phenylalanine to tyrosine

Phenylalanine has to be considerably reduced in food, and on the other hand tyrosine has to be added. Several types of hyperphenylalaninaemia that do not fulfill the criteria of the classical forms of phenylketonuria have been revealed during the examinations aimed at early diagnostics of phenylketonuria. In the case of the mild form of phenylketonuria, the body tolerates a higher intake of phenylalanine in food when compared to typical phenylketonuria. Tyrosine plasma concentration also increases. In cases of transient phenylketonuria, clinical and biochemical signs regress or completely vanish. In a special form of hyperphenylalaninaemia, without ketonuria, phenylalanine plasma concentration is slightly increased; however, phenylpyruvate is not excreted. After phenylalanine intake, its concentration increases; then it decreases, and tyrosine concentration can also increase. In both forms, decreased activity of phenylalanine hydroxylase to 10–20 % of normal values has been demonstrated. Disorders of phenylalanine metabolism are also present in Hartnup disease and generalised aminoaciduria. Approximately 90 % of phenylalanine in the body converts to tyrosine. The remaining 10 % of phenylalanine is used for protein synthesis. Tyrosine, which forms from phenylalanine under normal circumstances, can further be metabolised via various pathways with the formation of:

1. Fumarate and acetoacetate
2. Dopamine, adrenaline and noradrenaline
3. Melanins
4. Thyroid hormones – thyroxin and triiodothyronine

Degradation of tyrosine to fumarate and acetoacetate starts with transamination of tyrosine (Figs. 4.2 and 4.3) to para-hydroxyphenylpyruvic acid, while a-ketoglutarate is the cofactor. The change of the lateral chain to the ortho position, oxidative

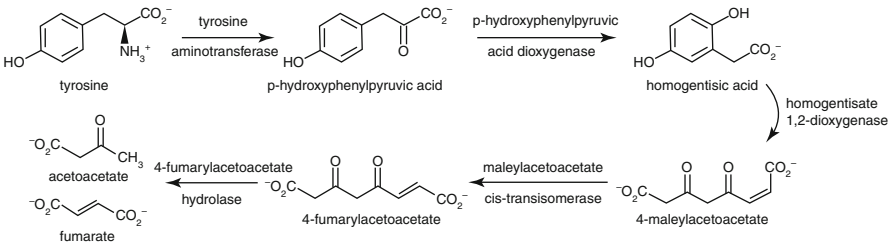

Fig. 4.2 Degradation of tyrosine to acetoacetate and fumarate

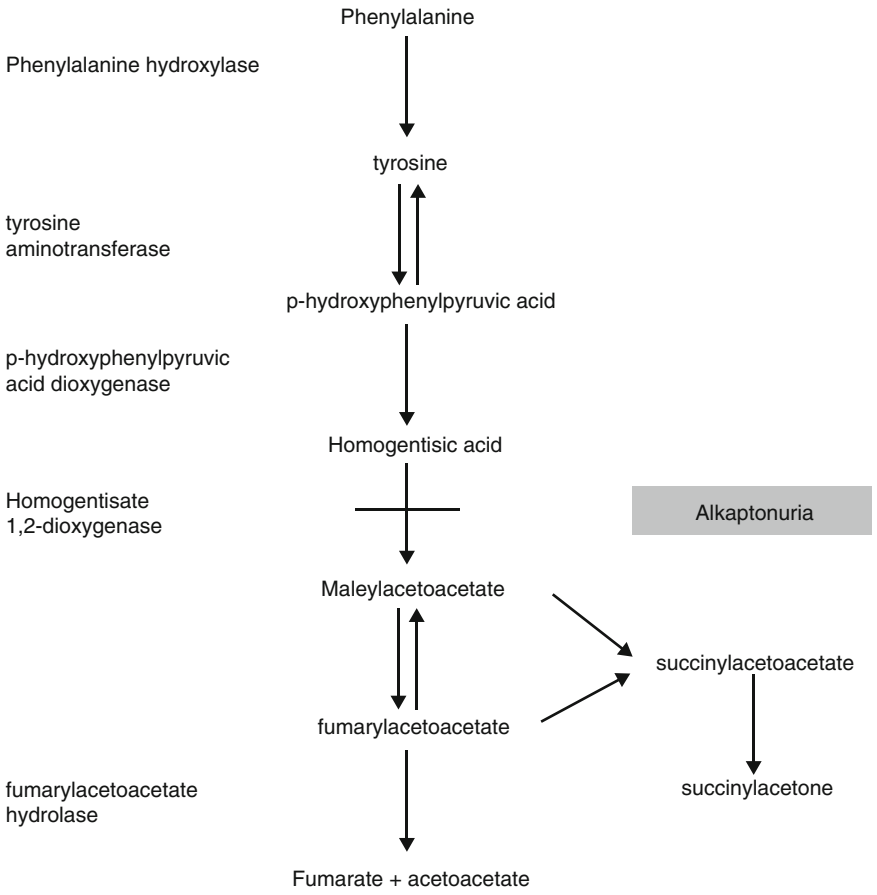

Fig. 4.3 Metabolic pathway of phenylalanine and tyrosine degradation. Disorder of conversion of homogentisic acid to maleylacetoacetate, cause of alkaptonuria

decarboxylation and hydroxylation results in the formation of homogentisic acid. The next step of tyrosine metabolism is degradation of homogentisic acid.

The aromatic ring of homogentisic acid is opened up by means of homogentisate 1,2-dioxygenase with the participation of an oxygen molecule with subsequent formation of maleylacetoacetate. Fumarylacetoacetate forms by means of maleylacetoacetate cis-trans-isomerase and rotation of the carboxyl group arising from the hydroxyl group. Glutathione serves as cofactor in this step. Fumarylacetoacetate is subsequently degraded by fumarylacetoacetate hydrolase with the participation of a water molecule to the final products – fumarate and acetoacetate. These products enter the metabolic pathway of citric acid. Another pathway of tyrosine conversion is formation of dopamine and catecholamines. By means of tyrosine hydroxylase, tyrosine converts to DOPA-3,4-dihydroxyphenylalanine. Dopamine forms by means of DOPA-decarboxylase. Subsequently adrenaline and catecholamines that have the role of neurotransmitters form from dopamine. Tyrosine can also be metabolised to melanins that protect us against UV radiation. Tyrosine oxidises in the presence of oxygen to DOPA. DOPA dehydrogenates with the formation of dopaquinone. Further reactions result in the formation of indolequinone (indole-5,6-quinone) via several intermediate products. Brown-black eumelanin arises by its polymerisation. Eumelanin is the pigment found in hair, eyes and skin. Dopaquinone can also bind SH-groups of cysteine and further be oxidised to polymeric quinones. Yellow pheomelanin forms by this pathway. Tyrosine is also part of thyroglobulin (the protein found in the thyroid gland), thyroxine and triiodothyronine. These thyroid hormones have multiple effects; in general, they accelerate reactions taking place in cells.

References

Blau, N., Koch, R., Matalon, R., Stevens, R.C.: Five years of synergistic scientific effort on phenylketonuria therapeutic development and molecular understanding. Mol. Genet. Metab. **86**(Suppl 1), 1 (2005)

Crone, M.R., van Spronsen, F.J., Oudshoom, K., Bekhof, J., van Rijn, G., Verkerk, P.H.: Behavioural factors related to metabolic control in patients with phenylketonuria. J. Inherit. Metab. Dis. **28**, 627–637 (2005)