

# Disorders of aromatic and branched chain amino acid metabolism

Disorders of AMK metabolism are divided into branched and aromatic AMK disorders.

## A quick review of biochemistry

Amino acids can be divided into aromatic and branched. With the exception of tyrosine (Tyr), both aromatic and branched AMK are essential, Tyr is conditionally essential (if phenylalanine is deficient).

- **aromatic:** phenylalanine (Phe), tyrosine (Tyr)
- **branched:** valine (Val), isoleucine (Ile), leucine (Leu)

Furthermore, AMKs can be divided into **ketogenic** and **glucogenic**.

- *ketogenic*
  - acetyl-CoA → Leu, Ile
  - acetoacetate → Phe, Tyr, Leu
- *glucogenic*
  - fumarate → Phe, Tyr
  - succinyl-CoA → Val, Ile

## Overview of branched AMK metabolism

The first three reactions - *transamination*, *decarboxylation* and *dehydrogenation* - are common to **all** these AMKs. AMK crosses the **liver**.

### Common reactions

**Transamination** (1st reaction) by common transaminase (activity highest in the myocardium and skeletal muscle, low in the liver) - appropriate 2-oxoacids are formed (val → 2-oxoisovalerate, leu → 2-oxocaproate, ile → 2-oxomethylvalerate); block in **hypervalinemia**

**Decarboxylation** (2nd reaction) and **dehydrogenation** (3rd reaction) - takes place in mitochondria → specific multienzyme dehydrogenase → acyl-CoA is formed one carbon shorter than the original oxo acid; block (2 - decarboxylation) in **maple syrup disease**; block (3 - dehydrogenation) in **isovaleric acidemia**

### Result:

- Val → methylcrotonyl-CoA
- Leu → β-methylcrotonyl-CoA
- Ile → tigloyl-CoA

### Specific reactions of individual branched AMK intermediates

#### VALINE

methylcrotonyl-CoA → β-hydroxyisobutyryl → β-hydroxyisobutyrate → methylmalonate semialdehyde → methylmalonyl-CoA → **enzyme cofactor deficiency - vit. B12 in methylmalonic aciduria** → succinyl-CoA

#### LEUCINE

β-methylcrotonyl-CoA → methylglutakonyl → β-hydroxy-β-methylglutaryl-CoA → acetoacetyl-CoA + acetyl-CoA

#### ISOLEUCINE

tigloyl-CoA →  $\alpha$ -methyl- $\beta$ -hydroxybutyryl-CoA →  $\alpha$ -methylacetyl-CoA → acetyl-CoA + propionyl-CoA

## Overview of aromatic AMK metabolism

1. tyrosine is formed from **phenylalanine** by the action of phenylalanine hydroxylase (monooxygenase), **tetrahydrobiopterin** (hydrogen donor) needs as a cofactor
2. transamination of tyrosine to p-hydroxyphenylpyruvate - hydroxylase (dioxygenase) converted to homogentate (aromatic ring)
3. disruption of the aromatic ring of homogentisate → **homogentisatoxygenase**
4. the final products are fumarate and acetoacetate

Hydroxylase is **active only after birth**. Aromatic AMKs are the starting product of the synthesis of catecholamines, melanin and hormones of the thyroid gland.

PHENYLALANINE → **block in PKU** (phenylalanine hydroxylase or cofactor deficiency); **delayed enzyme activity in delayed hyperphenylalaninemia** → tyrosine → **block in type II tyrosinemia**. (tyrosine transaminase) → p-hydroxyphenylpyruvate → homogentisate → **block in alkaptonuria** (homogentisatoxygenase) → 4-maleinylacetylacetate → **block in tyrosinemia type I**. (maleinylacetylacetate hydrolase) → 4-fumarylacetylacetate → **block in tyrosinemia type I**. (fumarylacetylacetate hydrolase)

## Disorders of branched AMK metabolism

Disorders of branched AMK metabolism include hypervalinemia, leucinoses and its intermittent forms, *isovaleric acidemia*, and *methylmalonic aciduria*.

### Hypervalinemia

There is low common transaminase activity for valine. This is a very rare disease.

### Maple syrup disease (leucinoses)

This disease is caused by a **deficiency or insufficient activity of the decarboxylase** (in the second joint reaction). It is manifested by urine smelling of burnt sugar. Furthermore, the levels of Val, Leu and Ile and their 2-oxo acids are increased (there are corresponding hydroxy equivalents of 2-oxo acids in the urine). It is important to detect this disease as soon as possible, otherwise, it is fatal. People who survive have brain damage, failure to thrive, drowsiness, coma, later vegetative nerve problems (heart disorders - bradycardia, hypothermia to apnea) and severe dehydration. The treatment consists of a **diet in which branched-chain AMKs are eliminated from the diet**.

### Intermittent forms of leucinoses

Intermittent forms of leucinoses are caused by **less severe decarboxylase modifications**. The metabolism of **Val, Ile** and **Leu** is reduced but maintained. Symptoms of leucinoses appear later and occasionally (after ingestion of large amounts of these AMKs).

### Isovaleric acidemia

Isovaleric acidemia is caused by a **dehydrogenase disorder** in step 3 of the common pathway. **Isovaleryl-CoA dehydrogenase deficiency** occurs, and the accumulated isovaleryl-CoA is hydrolyzed to isovaleryl and excreted. It is manifested by metabolic acidemia (pH 7.3), ketonuria, hyperammonaemia, hypocalcaemia, hyperlactatemia, odor of the breath and body fluids, coma after ingestion of large amounts of protein and general pancytopenia. The disease is included in neonatal screening.

### Methylmalonic aciduria

Methylmalonic aciduria is caused by **avitaminosis B12**. B12 is a cofactor of the enzyme that converts methylmalonyl-CoA to succinyl-CoA (radical isomerization), and metabolic acidosis occurs. It is treated with vitamin B12.

## Disorders of aromatic AMK metabolism

Disorders of aromatic AMK metabolism include phenylketonuria, maternal phenylketonuria, transient hyperphenylalaninemia, tyrosinemia I and II. type and alkaptonuria.

### Phenylketonuria (PKU, Folling's disease)

1. **phenylalanine hydroxylase** defect = classic PKU, PKU I (enzyme activity is less than 25%) - 98-99% of

cases, AR hereditary disease

2. **dihydrobiopteridine reductase** defect = PKU II and III
3. **dihydrobiopteridine biosynthesis** defect = PKU IV and V

Monooxygenase is formed from phenylalanine hydroxylase (it involves only one oxygen, water is formed from the other). The H<sub>2</sub> donor for water formation is tetrahydrobiopteridine (THBP), after the release of H<sub>2</sub>, dihydrobiopteridine (DHBP) is formed, which is reduced by DHBP-reductase back to THBP. Phe accumulates (hyperphenylalaninemia - up to 150-630mg / l plasma) and is converted to phenylpyruvate and phenylacetate and excreted in the urine, often excreted as phenylacetylglutamine.

The consequences of the untreated form (PKU I) are **irreversible mental retardation** (high levels of Phe damage to the brain), **seizures, psychoses, eczema, urine odor**, and **light pigmentation** (blonde hair and blue eyes, even if there are no genetic conditions ).

The disease is included in neonatal screening, which is a method of tandem mass spectrometry (since October 1, 2009). Previously, the Guthrie test was used, in which the blood collected from the baby was added to the *Bacillus subtilis* colony (days 4-5 after postpartum) (the bacillus survives only in blood rich in Phe).

Phenylketonuria is treated with **the diet** until the end of CNS development (ie until about the age of 20).

**Saptoterin** (Kuvan), a synthetic version of natural THBP that increases phenylalanine hydroxylase activity (both in enzyme failure and THBP problems), L-DOPA (substitution for catecholamine formation) and LNAA transporter (large neutral amino acids transporter) are also given), which aims to block the passage of Phe at high levels through the blood-brain barrier.

## Maternal / maternal phenylketonuria (PKU)

In maternal phenylketonuria, the mother is a phenylketonuric who **does not follow a diet**, the child is healthy. **High levels of Phe damage the child's CNS** and **mental retardation** occurs with a picture of PKU, which is **negative for the gene mutation**.

## Transient hyperphenylalaninemia

Transient hyperphenylalaninemia is caused by a **delayed onset of phenylalanine hydroxylase enzyme activity**. It is treated with a temporary reduction in protein intake.

## Type I tyrosinemia (tyrosinosis)

Type I tyrosinemia is caused by a defect in fumarylacetoacetate hydrolase, which is expressed mainly in the liver and kidneys, and probably also in maleylacetoacetate hydrolase, AR is hereditary.

It is manifested by high levels of **Tyr** (60-120 mg / l plasma) and **Met** and high levels of metabolites affect the activities of other enzymes and transport systems that cause severe pathologies such as **hepatorenal failure** (liver cirrhosis, hepatomegaly, coagulopathy, Fanconi's syndrome) renal tubules, phosphate excretion → hypophosphatemic rickets), CNS involvement (convulsions, hyperextension, self-harm, respiratory arrest), ascites or tissue damage radicals (accumulated metabolites (maleyl acetoacetate, fumarylacetoacetate) and their derivatives (succinylacetone and succinate elimination of one antioxidant).

When left untreated, **acute** tyrosinosis manifests itself in diarrhea, vomiting, and infant failure. The smell of head cabbage dies within 6 to 8 months of liver failure. In **chronic** tyrosinemia, the symptoms are the same but weaker. Individuals die within 10 years. The treatment used includes a diet based on the absence of Phe and Tyr, today NTBC (p-hydroxyphenylpyruvate hydroxylase blocker) is used.

## Tyrosinemia II. type (Richter-Hanhart syndrome)

Tyrosinemia II. type, otherwise called Richter-Hanhart syndrome, is caused by a **defect in liver tyrosine transaminase**. This is a very rare disease where **AR** is hereditary. Tyrosine levels increase (40-50mg / l plasma).

It is manifested by **mild mental retardation, hyperkeratosis** (on the palms and soles of the feet), **conjunctivitis, corneal ulceration, nystagmus** and **glaucoma** (turbidity of tyrosine crystals). Tyrosine and its metabolites are present in the urine. He is being treated with a diet.

## Alkaptonuria

Alkaptonuria occurs in the absence of **homogentisatoxygenase**. Manifestations are **darkening of the urine in the air, ochronosis** (oxidation of the homogentate to benzoquinoline acetate → generalized pigmentation of the binder, sclera, arches, skin), arthritis (hips, ankles, spine), kidney damage (urolithiasis) and heart valves (aortic or mitral valve regurgitation and aortic calcification).

It is treated with diet, administration of ascorbic acid (vitamin C), which prevents the binding of homogentisic acid to the binder, and administration of NTBC.

## Links

## Related articles

- Hereditary disorders of amino acid metabolism

## Literature

- MURRAY, Robert K., Daryl K. GRANNER a Peter A. MAYES, et al. *Harperova biochemie*. 23. vydání. Jinočany : H+H, 2002. ISBN 80-7319-013-3.
- LEDVINA, M., A. STOKLASOVÁ a J. CERMÁN. *Biochemie pro studující medicíny I. díl*. 1. vydání. Praha : Karolinum, 2004. ISBN 80-246-0849-9.

## Extern links in Czech

- Souhrn údajů o přípravku Kuvan ([http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Summary\\_for\\_the\\_public/human/000943/WC500045034.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/000943/WC500045034.pdf))
- Fenylketonurie na [www.stefajir.cz](http://www.stefajir.cz) (<http://www.stefajir.cz/?q=fenylketonurie>)
- Fenylketonurie na [vitalion.cz](https://nemoci.vitalion.cz/fenylketonurie/) (<https://nemoci.vitalion.cz/fenylketonurie/>)
- Poruchy metabolismu aminokyselin – přednáška ÚLB 1. LF UK ([http://che1.lf1.cuni.cz/html/2009\\_Poruchy\\_metabolismu\\_aminokyselin\\_sm.pdf](http://che1.lf1.cuni.cz/html/2009_Poruchy_metabolismu_aminokyselin_sm.pdf))
- Medicabáze – lékařské repetitorium (<http://www.medicabaze.cz/index.php?sec=welcome>)