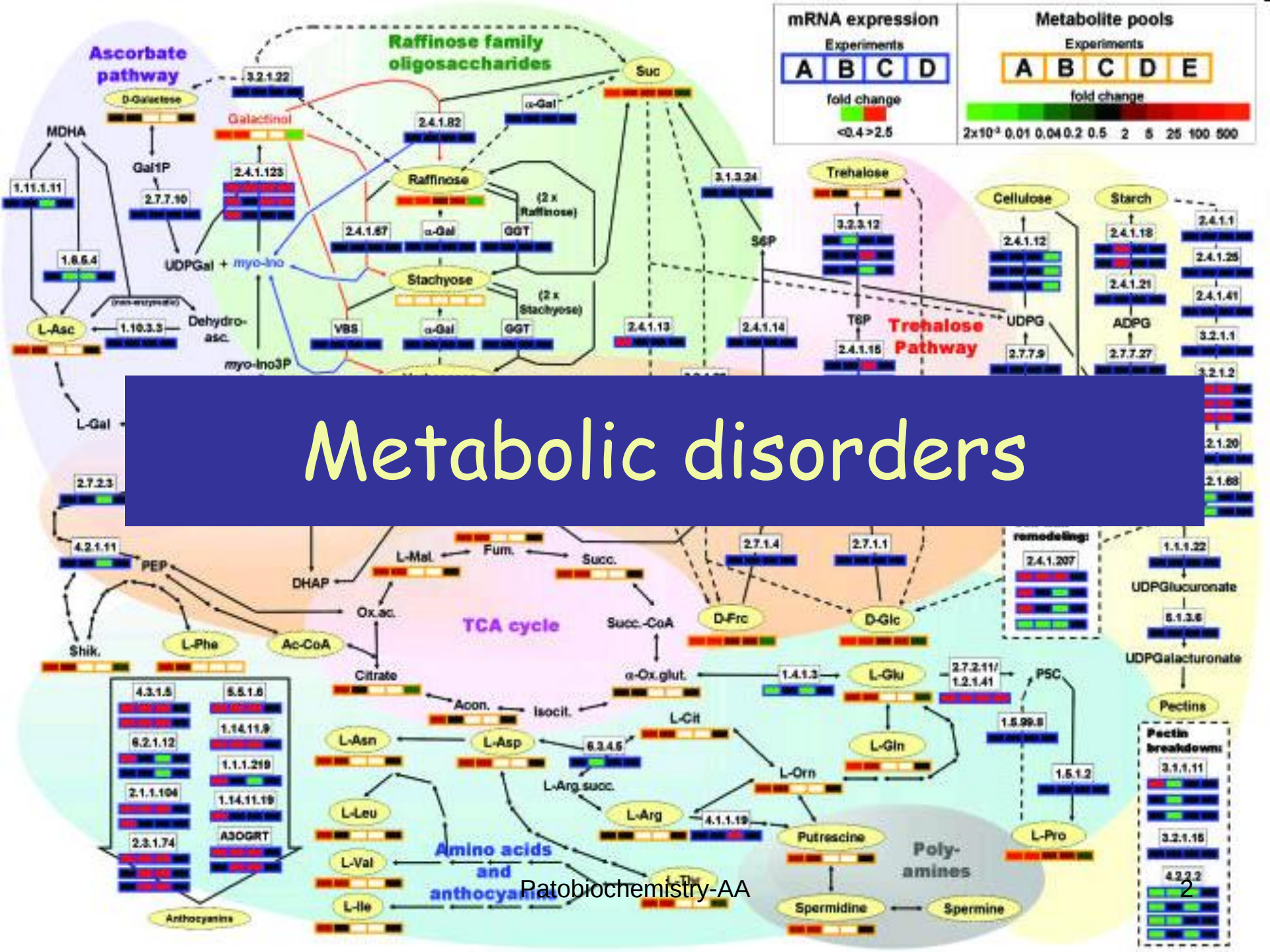
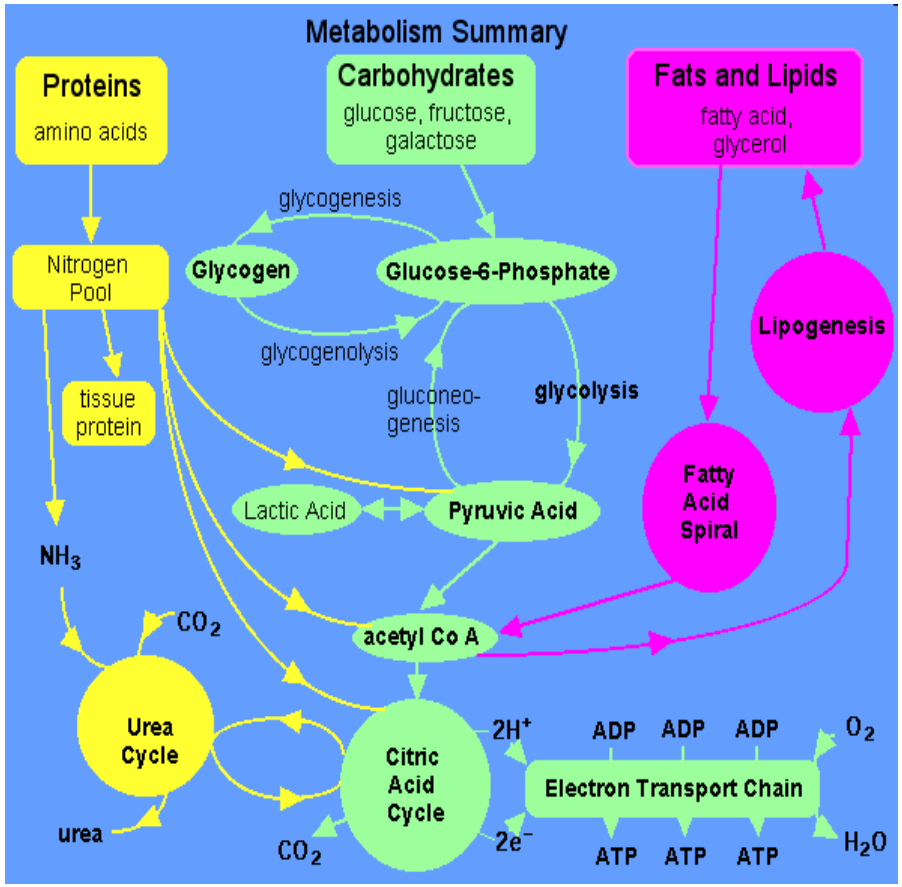
University of Veterinary and Pharmaceutical Sciences Brno
Faculty of Pharmacy

Disorders of amino acid metabolism

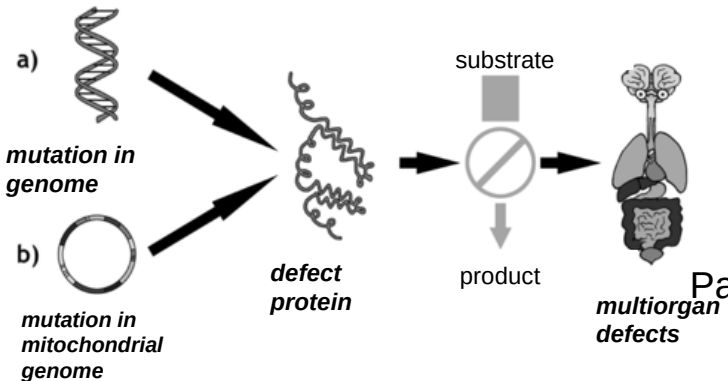

mRNA expression
Experiments
A B C D
fold change
<0.4 >2.5
Metabolite pools
Experiments
A B C D E
fold change
2x10-3 0.01 0.04 0.2 0.5 2 5 25 100 500
Ascorbate pathway
Raffinose family oligosaccharides
Trehalose Pathway
TCA cycle
Amino acids and anthocyanins
Poly-amines
Pectin breakdown
Metabolic disorders

Metabolic disorders

- metabolic changes of proteins, carbohydrates, fats and water management (mostly mental or physical disability)
- 7000 described metabolic disorders (7% of total population), 700-800 -inherited
- Heredity - genetically determined enzyme defect causes metabolic block with pathological consequences
- enzymopathy- most often is a metabolic disorder caused by a defect in the enzyme - defective enzyme has reduced enzymatic aktivity or activity is completely missing
- primary - genetic background
  secundary – due to other disorders



Principes of metabolic disorders



Types of metabolic disorders

- Enzymopathy - totaly described more than 200 defect enzymes function -phenylketonurie
  - acummulation – spatial problem (glycogen storage disease, lipidosis)
  - increased toxicity (cysteinuria, gout)
  - conversion to other harmful metabolite
  - inhibits the metabolism of another enzyme, transporter, lack of product
- Receptors and their disorders- receptor - familial hyperlipidemia (hypercholesterolaemia)
- Disorders of molecular transport- cystic fibrosis
- Defect of structure of cells - muscular dystrophy
- Regulation of sex differentiation- gen SRY
- Mitochondrial disease- Leber´s optic atrophy
- Genes with so far unknown mechanism of action- Syndrome of fragile X (triplet disease)
- Wrong endocrine regulation- diabetes mellitus

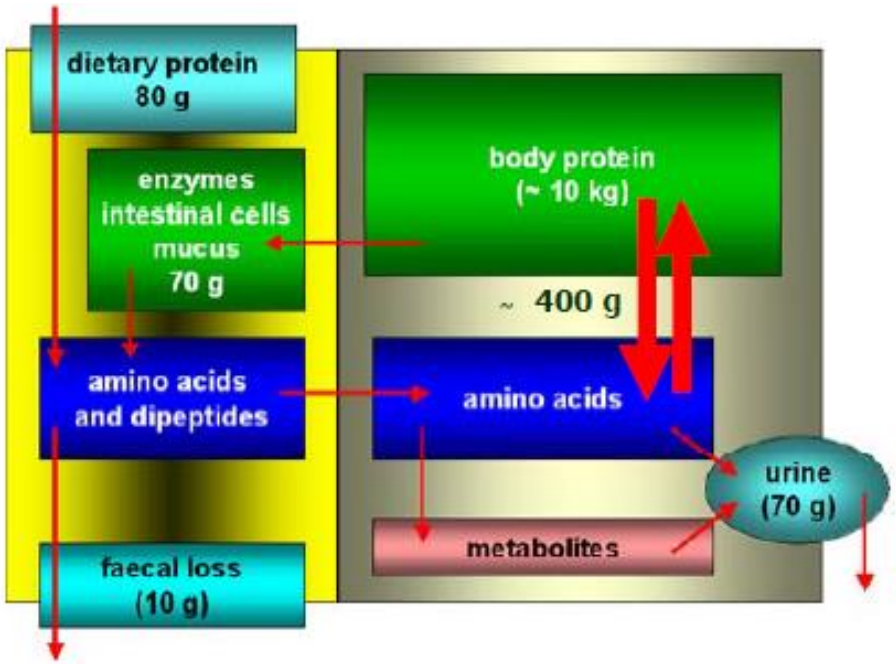
Type of defect	Disability examples
Defect of enzymes	PKU, galactosemia, adenosine deaminase deficiency
Defect of receptors	testicular feminization, hypercholesterolaemia
Defect of molecular transport	cystic fibrosis, hypertension
Defect of cell structure	Duchenn and Becker´s muscular dystrophy
Defect of homeostasis	antihemophilic globulin, immunoglobulins
Defect of regulation of growth and differentitation	sex determination, inactivation of X chromosome, tumor suppressors
Defect of intercellular communication	inzuline, growth hormone, sex differentiation
Defect of mitochondria	Leber´s optic atrophy

Metabolism of AA and proteins

- **proteins from AA linked by peptide bonds (CO-NH) structure:**
- – primary - 20 AA
- – secundary – hydrogen and disulfide bonds - globulin, β-sheet
- – tertiary – conformation in space
- – quaternary – association of several protein subunits
- **under physiol. pH mostly negative charge**
- – buffers (capability of binding H+)
- constant renewal and degradation of proteins associated with the synthesis and catabolism AA
- proteins significantly differ its **half-life**
- regulatory proteins, enzymes and transcription factors, usually several hours
- - albumin 10 days
- - muscle proteins ~180 days
- - hemoglobin ~120 days
- - collagen several years
- – **turnover in a 70 kg human of about 300 g proteins/day**
- – about 30g/day per day is required for the substrates for synthesis of nucleotides, glucose, ketone bodies and neurotransmitters
- – about 35 – 55g/day is oxidized to water, CO2 and nitrogen (irreversibly eliminated as urea) there is no storage form of proteins
- – ***AA* "pool" is just such as it is an immediate need**
- – rest is oxidized and eliminated
- **losses (and essential *AA*) must be paid by dietary protein intake**
- – essential: His, Val, Leu, Ile, Lys, Met, Thr, Phe, Trp
- – nonessential *AA* may be formed esp. of intermediates of citric acid cycle
- nitrogen release from the *AA* in the form of ammonia and ammonium salts is toxic, therefore it is in the liver processed in the urea cycle to a non-toxic urea, which is excreted in the urine

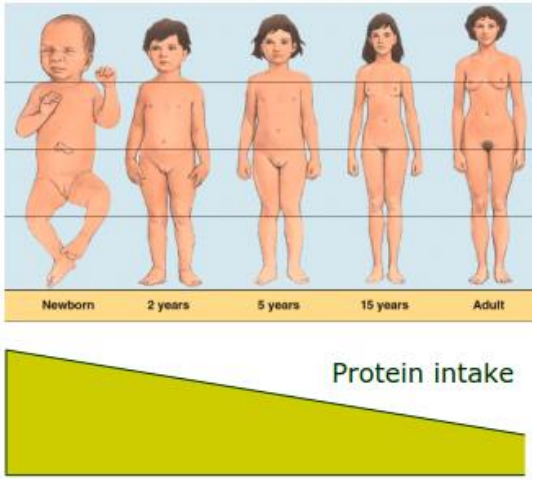
Energy store	tissue	amount (g)	energy (kj)	(kcal)
Glycogen	liver	70	1176	280
Glycogen	muscle	120	2016	480
Glucose	blood	20	336	80
Triacylglycerols	fat	15 000	567 000	135 000
Proteins	muscle	6000	100 800	24 000

http://www.studentconsult.com/content/default.cfm?ISBN=9780323053716



http://uk.geocities.com/david.bender@btinternet.com/images/proteinoverview.png

Protein requirements at diet



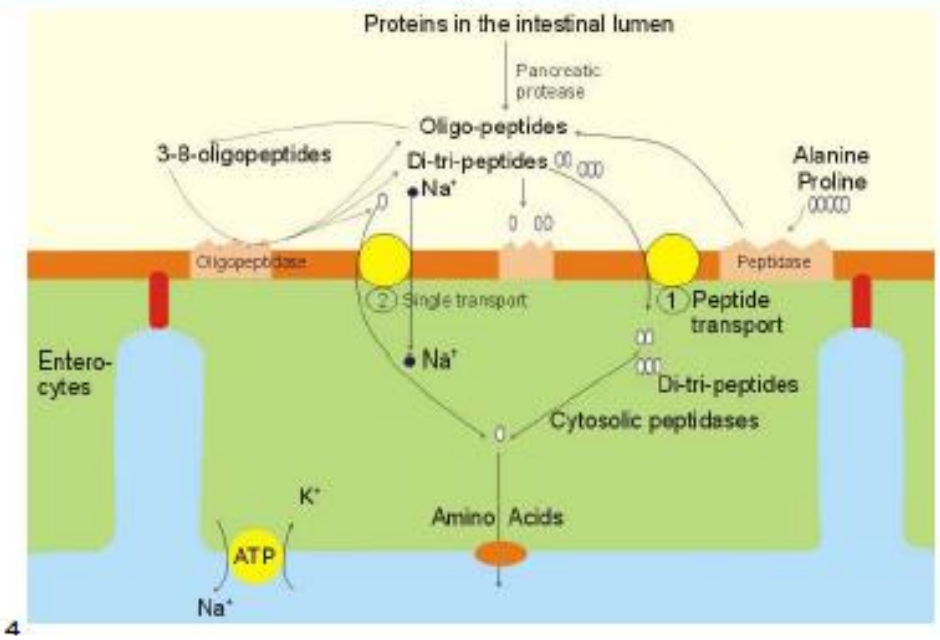
Protein digestion and resorption AA in GIT

proteins in GIT – ~50% from diet, **very different "digestibility" proteins - little digested elastin, keratin, mucin**

enzyme digestion of proteins, resorption AA and di- and tripeptides by enterocytes of small intestine via transporters (SLC, solute carriers – many types), **concentration AA in cell is generally much higher than extracellularly therefore is active maintaining**

- – Na+ -dependent transport – act. transport Na+ facilitated diffusionNa+/AK (=symport)
- – Na+ -independent

– facilitated diffusion(=uniport)



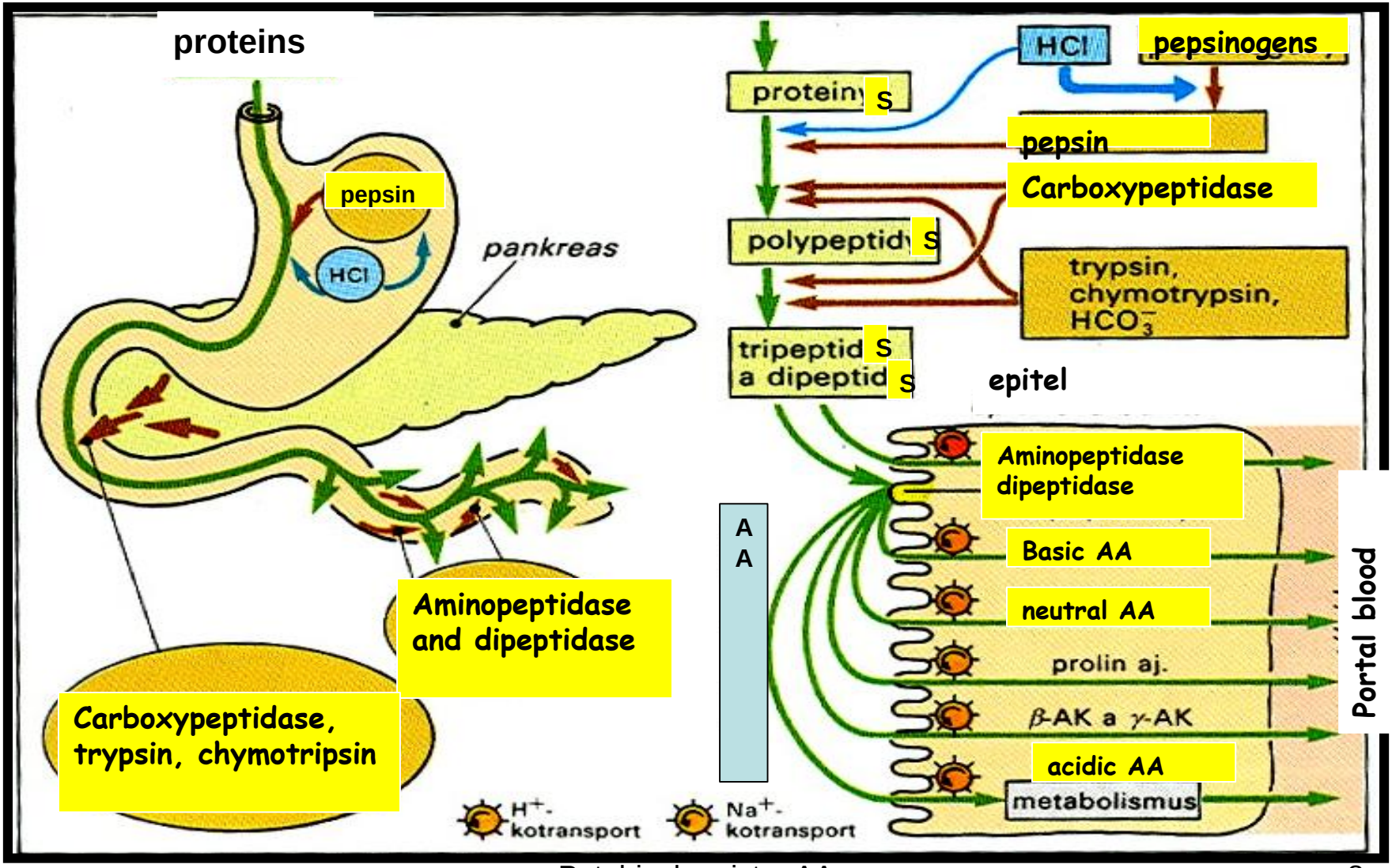
resorption whole proteins in diet

– limited potential

- through endocytosis
- and/or at the sites of epithelia

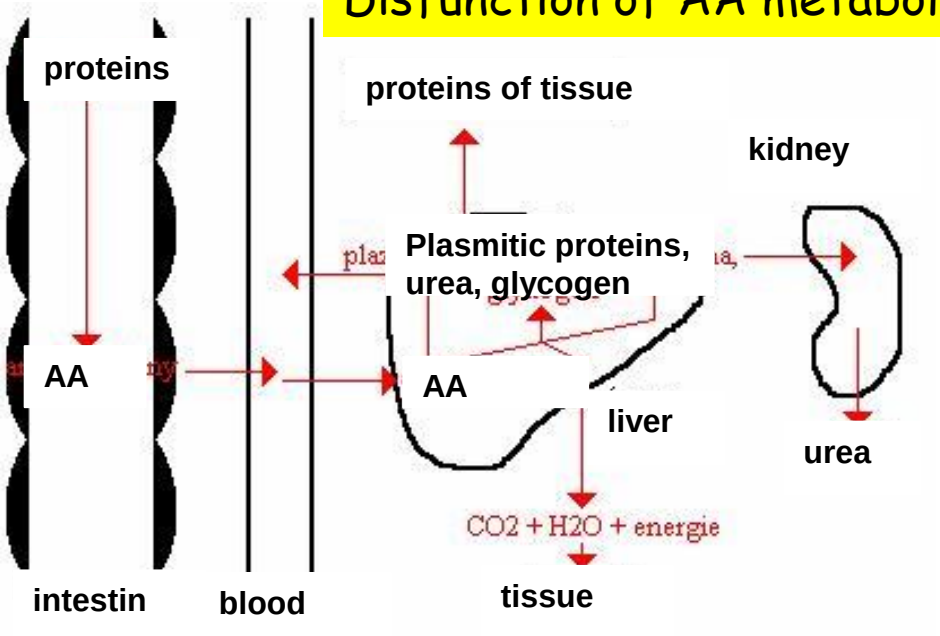
– it's used for **systemic enzyme therapy** (capsule resistant to the effect of HCl and pancreatic enzymes)

Digestion of Proteins



Disfunctions of protein´s metabolism

Disfunction of AA metabolisms or its transporters



AMINOACIDS

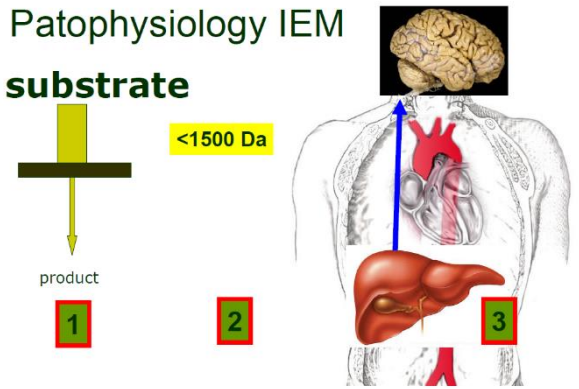
- basic structural components (structural proteins, enzymes,hormones, purines, ·plasma proteins, amines, heme)
- source of energy carbonaceous residues of the amino acids incorporated into Crebs cycle, by protein metabolism is produced ammonia→
urea → ornithin cycle

- proteins are not stored in stock

	incidence	affected enzyme
hyperphenylalaninemia	1:6500 (ČR), 1:13 000 (world)	phenylalaninhydroxylase(98 %) , tetrahydrobiopterin (2 %)
tyrosinemia I	1:100 000 (world)	fumarylacetoacetathydrolase
tyrosinemia II	rare	tyrosinaminotransferase
tyrosinemia III	rare	4-hydroxyphenylpyruvate dioxygenase
alkaptonuria	1:100 000 - 1:1 000 000 (world), 1:19 000 (Slovakia)	homogentisate-1,2-dioxygenase
homocystinuria	1-9:1 000 000 (world)	cystationin ß-syntase
cystinuria	1:7000 (USA)	defect of renal transport of certain amino acids
maple syrup disease	1:185 000	dehydrogenase of branched-chain alfaketoacids
izovaleric acidemia	1:230 000 (world)	isovaleryl-CoA dehydrogenase
glutaric aciduria	1:40 000 (whites)	glutaryl-CoA dehydrogenase
methylmaloni c aciduria	rare	metylmalonyl-CoA mutase
propionic acidemia	rare	propionyl-CoA carboxylase
urea cycle disorders	1:30 000 (world)	

Disorders of AA metabolism

- 1) Aminoacidopathy
- 2) Organic aciduria
- 3) Disorders of ammonia detoxification



Disorders of AA transport

Disorders of peptides metabolism

Table 17–2 Some human genetic disorders affecting amino acid catabolism

TEST

Medical condition	Approximate incidence (per 100,000 births)	Defective process	Defective enzyme	Symptoms and effects
Albinism	3	Melanin synthesis from tyrosine	Tyrosine 3-monooxygenase (tyrosinase)	Lack of pigmentation; white hair, pink skin
Alkaptonuria	0.4	Tyrosine degradation	Homogentisate 1,2-dioxygenase	Dark pigment in urine; late-developing arthritis
Argininemia	<0.5	Urea synthesis	Arginase	Mental retardation
Argininosuccinic acidemia	1.5	Urea synthesis	Argininosuccinate lyase	Vomiting, convulsions
Carbamoyl phosphate synthetase I deficiency	>0.5	Urea synthesis	Carbamoyl phosphate synthetase I	Lethargy, convulsions, early death
Homocystinuria	0.5	Methionine degradation	Cystathione β-synthase	Faulty bone development, mental retardation
Maple syrup urine disease (branched-chain ketoaciduria)	0.4	Isoleucine, leucine, and valine degradation	Branched-chain α-keto acid dehydrogenase complex	Vomiting, convulsions, mental retardation, early death
Methylmalonic acidemia	<0.5	Conversion of propionyl-CoA to succinyl-CoA	Methylmalonyl-CoA mutase	Vomiting, convulsions, mental retardation, early death
Phenylketonuria	8	Conversion of phenylalanine to tyrosine	Phenylalanine hydroxylase	Neonatal vomiting; mental retardation

TEST

	incidence	affected enzyme
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methylmalonic aciduria	rare	metylmalonyl-CoA mutase
propionic acidemia	rare	propionyl-CoA carboxylase
urea cycle disorders	1:30 000 (world)	

A). AMINOACIDOPATHY

- Accummulation of AA, variations in degradation of AA in the cytosol
- Ammonia accumulation
- Carbon skeleton accumulations of organic acids
- Product deficiency
- Deficiencies of mitochondrial enzymes (dehydrogenase of ketoacids with branched chain) *leucinesis*
- It doesn´t include CoA-activated metabolites
- Accummulation of toxic metabolites, phenylalanin, phenylpyruvate, phenylacetate –PHENYLKETONURIA (specific organ damage)
- Diagnosed by determination of metabolites level
- diets

B) ORGANIC ACIDURIAS

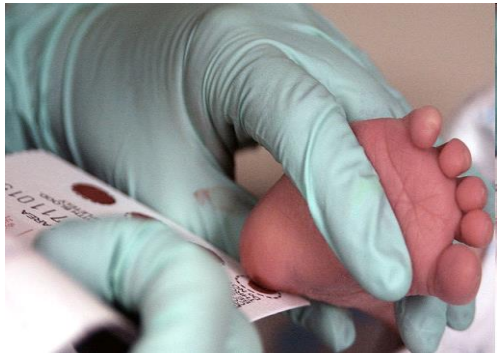
- *Deficiency of the enzyme in the mitochondrial metabolism, CoA-activated carboxylic acids*

- several dozens of diseases
- common feature: excretion of carboxylic acids (test-organic acids in urine)
- orginin usually from carbon skeleton degradation of AAs (or saccharides or lipids)
- usually acute presentation- „intoxication type“
- metabolic acidosis common (combination with hyperammonemia frequent)

Disorders of aromatic AA metabolism (Phenylalanin, Tyrosin)

PHENYLALANIN → TYROSIN (phenylalanine hydroxylase)

1) hyperphenylalaninemia



deficiency of ***phenylalaninehydroxylase*** – **classical phenylketonuria (PKU)**

defect dihydrobiopterinreductase – **hyperphenylalaninemia type II and III**

defect of dihydrobiopterin biosynthesis (cofactor) – **hyperphenylalaninemia type IV and V**

AR hereditary disease

accumulation of phenylalanine and metabolites (phenylpyruvic, phenyllactic, phenylacetate, o-hydroxyphenylacetate acid)

disbalance of plasmatic AA: damage brain development,

phenylalanine inhibits enteral resorption of tyrosine (compete together for a transporter)→

impaired catecholiamines and melanines synthesis (skin pigmentation and hair is reduced) →

irreversible mental retardation (high level of Phe harms brain), seizures, psychosis, eczema,

urine odor after mice, light pigmentation (blond hair and blue eyes even in the case that there is no genetic predisposition)

2) hypertyrosinemia

Tyrosinemia type 1 – *deficiency of fumaryl acetoacetate hydroxylase enzyme*

metabolite sukcynilaceton accumulates in the blood, which damages the liver, kidneys, CNS and PNS, particular manifestation of sick is self-harming

Tyrosinemia type 2- *deficiency of the enzyme tyrosine aminotransferase (disability eyes, skin and the CNS)*

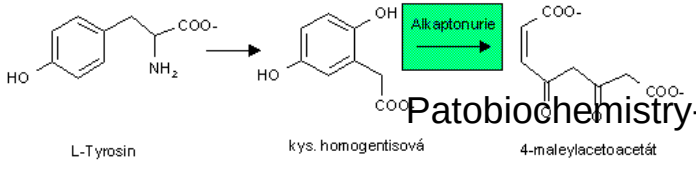
Transient tyrosinemia or hyperphenylalanemia in newborns- *Delaying the enzyme phenylalanine hydroxylase,*

A transient increase tyrosine in plasma in the first 2 weeks of life, given the delayed maturation enzymes of tyrosinaminetransferase or 4-hydroxyphenylpyruvatedioxygenase in liver

3) alkaptonuria

defect of homogentisate oxygenase

high concentration of homogentisic acid (oxidation homogentisate on benzochininacetate → generalized pigmentation binder, sclerae, ears, skin), arthritis (hips, ankles, spine), kidney damage (urolithiasis) and heart valves (aortic or mitral regurgitation valves), calcification of the aorta, urine darkens on light (brown pigment alkapton)



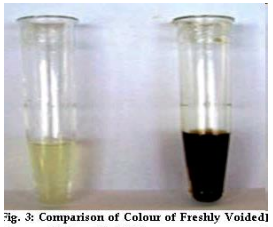
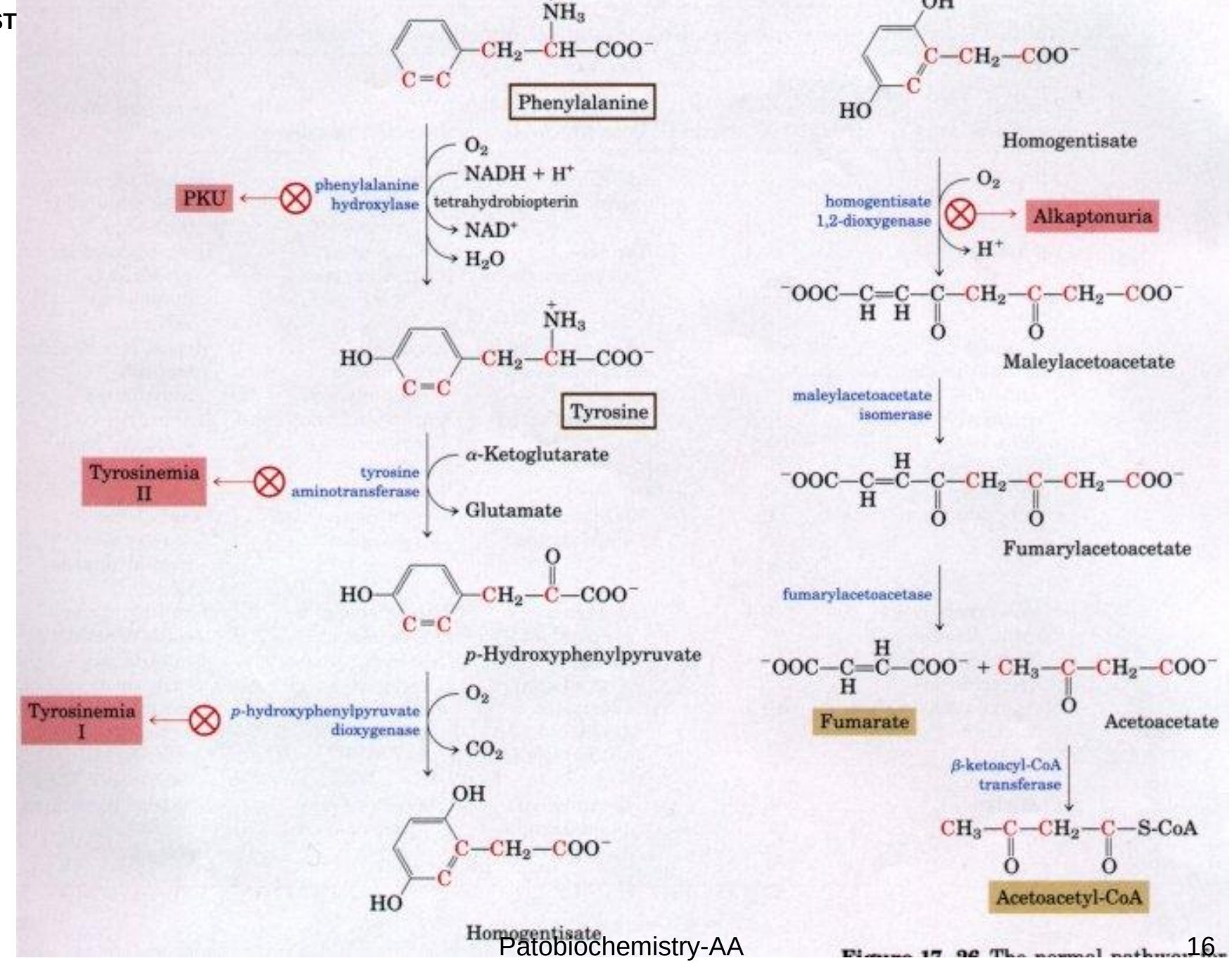


Fig. 3: Comparison of Colour of Freshly Voided Urine and Urine after 24 Hours

TEST


Phenylalanine
PKU
phenylalanine hydroxylase
O2
NADH + H+
tetrahydrobiopterin
NAD+
H2O
Tyrosine
Tyrosinemia II
tyrosine aminotransferase
α-Ketoglutarate
Glutamate
p-Hydroxyphenylpyruvate
Tyrosinemia I
p-hydroxyphenylpyruvate dioxygenase
O2
CO2
Homogentisate
Homogentisate
homogentisate 1,2-dioxygenase
O2
H+
Alkaptonuria
Maleylacetoacetate
maleylacetoacetate isomerase
Fumarylacetoacetate
fumarylacetoacetase
Fumarate
Acetoacetate
β-ketoacyl-CoA transferase
Acetoacetyl-CoA

Disorders of aromatic AA metabolism (Phenylalanin, Tyrosin)

PHENYLALANIN → TYROSIN (phenylalanine hydroxylase)

1) hyperphenylalaninemia

a) deficiency of ***phenylalaninehydroxylase*** – **classical phenylketonuria (PKU)**

b) defect dihydrobiopterinreductase – **hyperphenylalaninemia type II and III (HPA)**

c) defect of dihydrobiopterin biosynthesis (cofactor) – **hyperphenylalaninemia type IV and V**

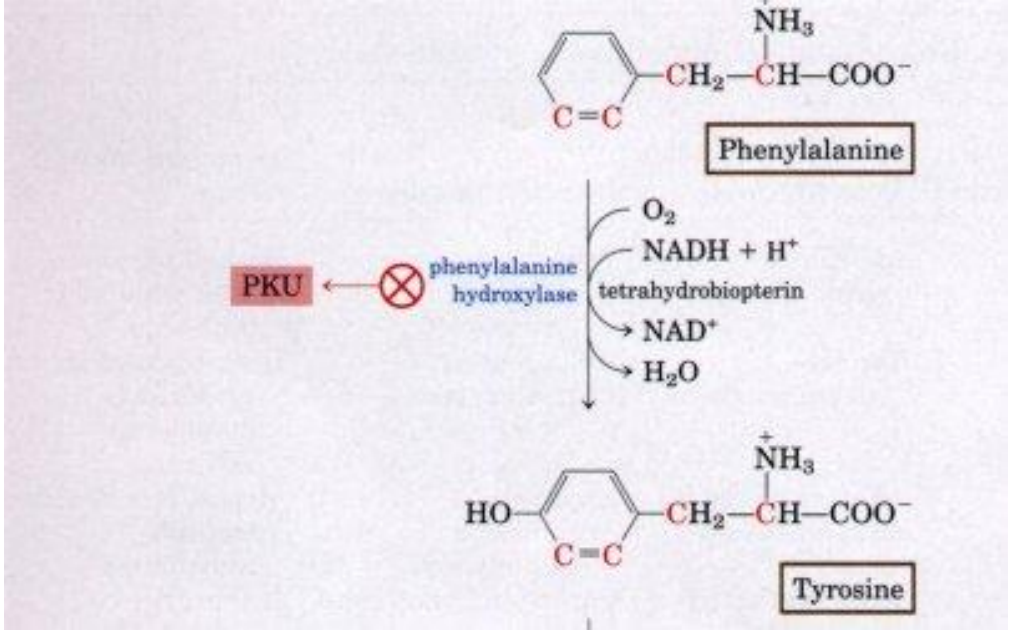
AR hereditary disease

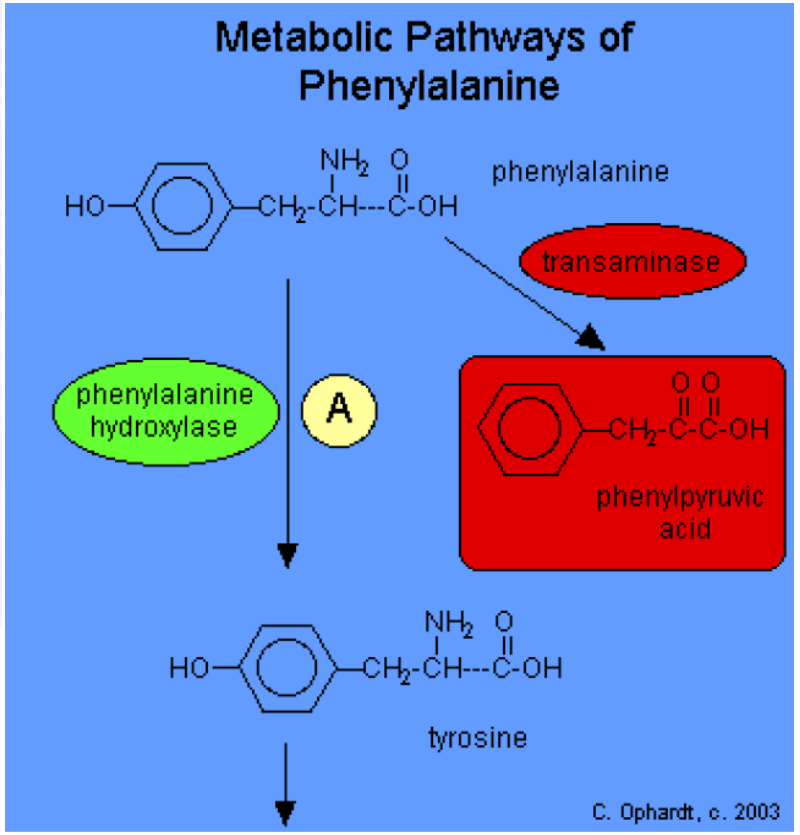
accumulation of phenylalanine and metabolites (phenylpyruvic, phenyllactic, phenylacetate, o-hydroxyphenylacetate acid)

The frequency of 1 / 10,000 individuals

- disbalance of plasmatic AA: damage brain development,
- phenylalanine inhibits enteral resorption of tyrosine (compete together for a transporter)→
- impaired catecholiamines and melanines synthesis (skin pigmentation and hair is reduced) →
- irreversible mental retardation (high level of Phe harms brain), seizures, psychosis, eczema,
- **urine odor after mice**,
- **light pigmentation** (blond hair and blue eyes even in the case that there is no genetic predisposition)

Diet therapy (until the end of the development of the CNS - i.e. up to about the 20th year of life), serving saptoterin (Kuvan) → synthetic versions of the natural THBP (increases the activity of phenylalanine hydroxylase, whether the problem is faulty enzyme or THBP), serving L-DOPA (substitution for the formation of catecholamines), LNAA trasporter (large neutral amino acids trasporter – blocking transfer of Phe at high levels through the blood brain barrier



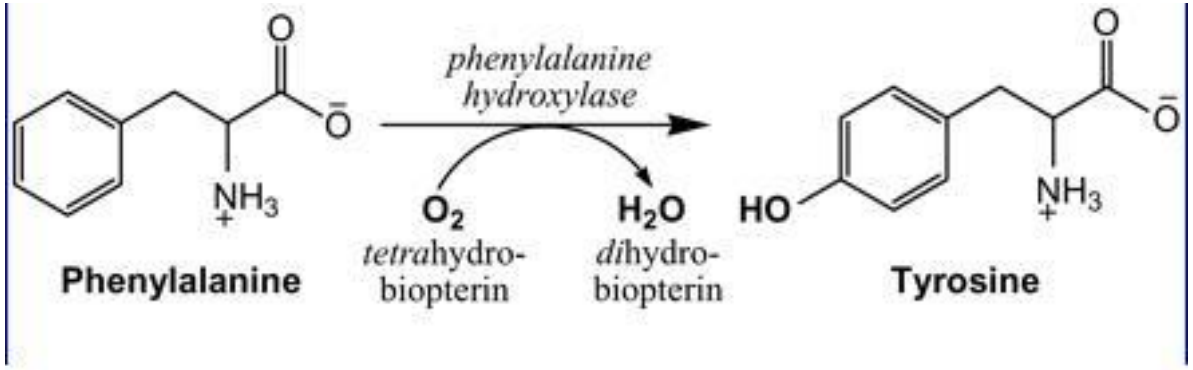


http://www.elmhurst.edu/~chm/vchembook/images/635pku.gif

Phenylalanine hydroxylase → monooxygenase = engages only one O, arises from the second water H2 donor for the formation of water is tetrahydrobiopteridin (THBP), after releasing H2 arises dihydrobiopteridin (DHBP), it is reduced DHBP reductase back to THBP

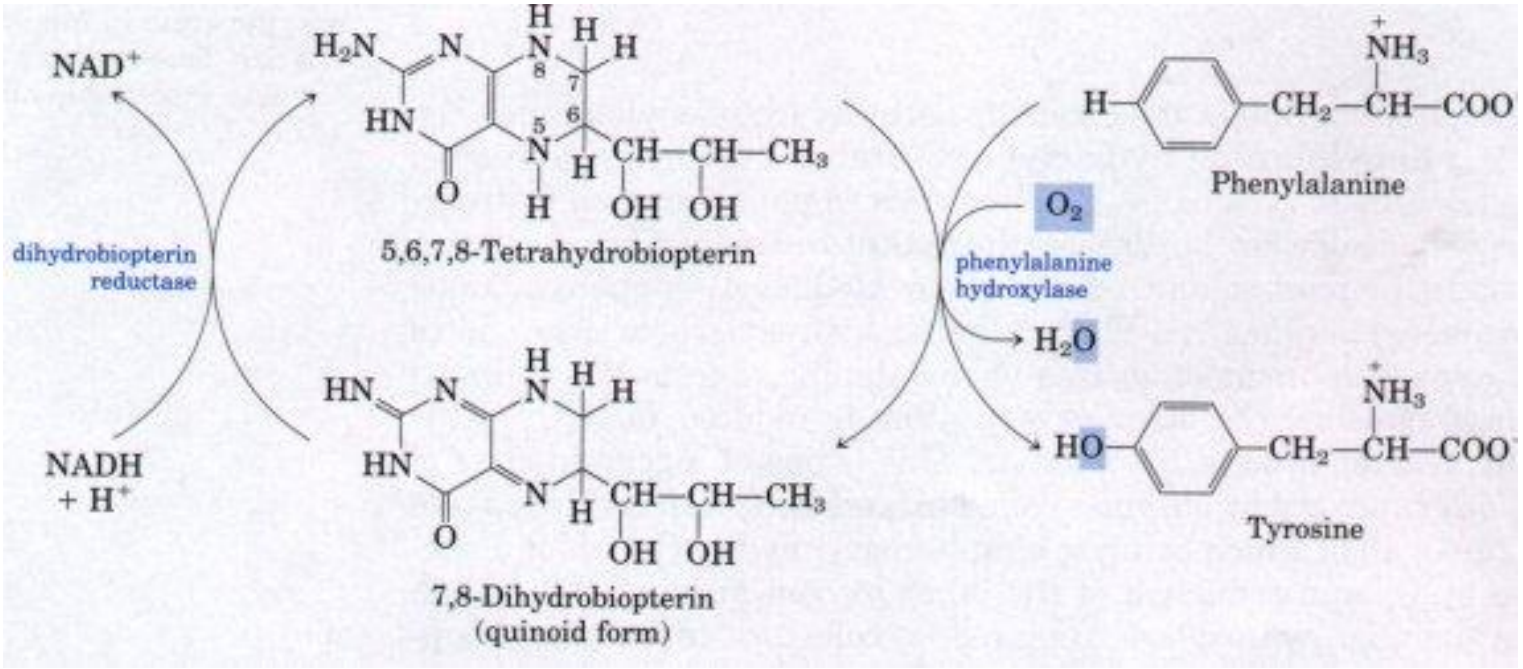
Phe is accumulated (hyperphenylalaninemia - up to 150-630mg /l plasma) and is converted to phenylpyruvate and phenyllactate and excreted in the urine, often is excreted as phenylacetylglutamine

defect **phenylalanine hydroxylase** – classical phenylketonuria (PKU)

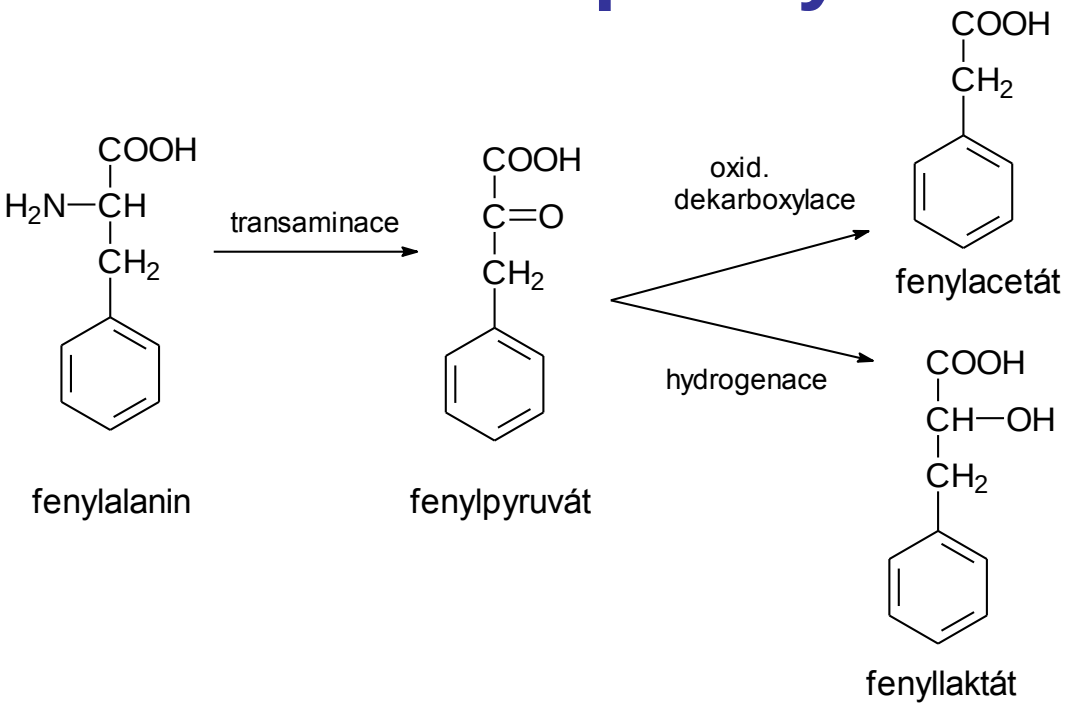


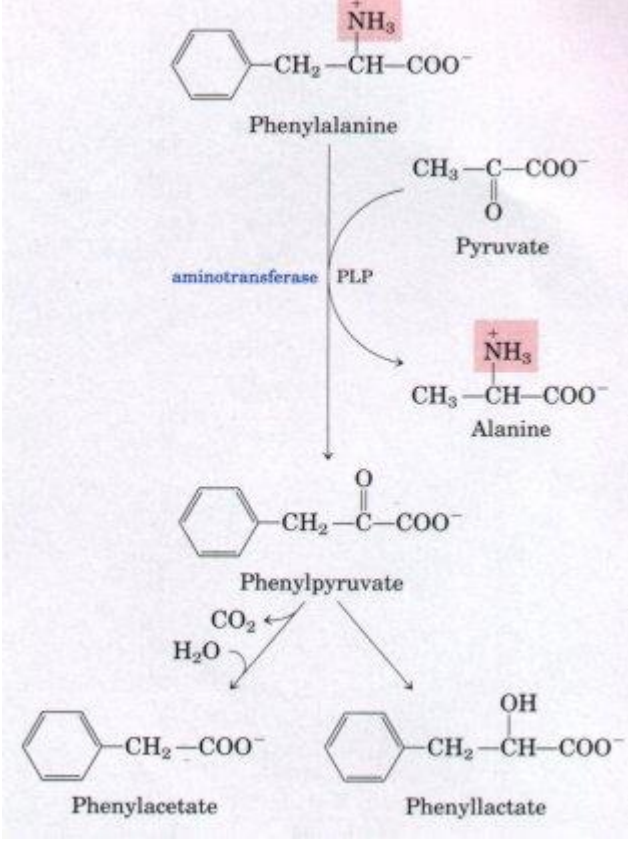
- The first enzyme in the catabolic pathway for phenylalanine (Fig. 17-26), **phenylalanine hydroxylase**, catalyzes the hydroxylation of phenylalanine to tyrosine. A genetic defect in phenylalanine hydroxylase is responsible for the **disease phenylketonuria (PKU)**. Phenylketonuria is the most common cause of elevated levels of phenylalanine (hyperphenylalaninemia). Phenylalanine hydroxylase inserts one of the two oxygen atoms of O2 into phenylalanine to form the hydroxyl group of tyrosine; the other oxygen atom is reduced to H2O by the NADH also required in the reaction. This is one of a general class of reactions catalyzed by enzymes called mixed-function oxidases (see Box 20-1), all of which catalyze simultaneous hydroxylation of a substrate by O2 and reduction of the other oxygen atom of O2 to H2O. Phenylalanine hydroxylase requires a cofactor**, tetrahydrobiopterin**, which carries electrons from NADH to O2 in the hydroxylation of phenylalanine. During the hydroxylation reaction the coenzyme is oxidized to dihydrobiopterin (Fig. 17-27). It is subsequently reduced again by the enzyme dihydrobiopterin reductase in a reaction that requires NADH.

defect dihydrobiopterinreductase –
hyperfenylalaninemia type II and III
defect of dihydrobiopterin biosynthesis (cofactor) –
hyperphenylalaninamia type IV and V



Metabolites of phenylalanine





When phenylalanine hydroxylase is genetically defective, a secondary pathway of phenylalanine metabolism, normally little used, comes into play. In this minor pathway phenylalanine undergoes transamination with pyruvate to yield phenylpyruvate (Fig. 17-28). Phenylalanine and phenylpyruvate accumulate in the blood and tissues and are excreted in the urine: hence the name of the condition, phenylketonuria. Much of the phenylpyruvate is either decarboxylated to produce phenylacetate or reduced to form phenyllactate. Phenylacetate imparts a characteristic odor to the urine that has been used by nurses to detect PKU in infants. The accumulation of phenylalanine or its metabolites in early life impairs the normal development of the brain, causing severe mental retardation. Excess phenylalanine may compete with other amino acids for transport across the blood-brain barrier, resulting in a depletion of some required metabolites.

Alternative pathways for catabolism of phenylalanine in phenylketonurics. Phenylpyruvate accumulates in the tissues, blood, and urine. Phenylacetate and phenyllactate can also be found in the urine.

Untreated HPA/PKU

Boy with untreated PKU
http://www.dshs.state.tx.us/newborn/images/PKU_untreated.jpg

- CZ 1:6,500, Turkey 1:3,000, very rare Finland, N Europe 1:15,000
- 1-2% HPA secondary due to primary pterine defectsl
- 30% patients BH4 sensitive
- newborn screening
- untreated HPA- mental retardation, typical mouse odour, light complexions, eczema, epilepsy
- maternal HPA-VCC, microcephaly a PMR

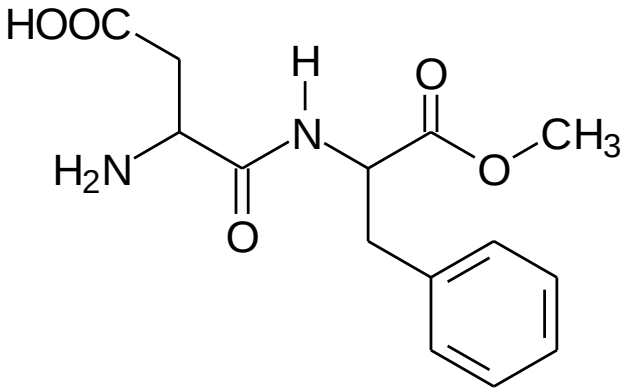
disease is included in the newborn screening (method of tandem mass spectrometry (from 1. 10. 2009); earlier Guthrieho test – collected blood of a child /4.–5.day after childbirth/ is added to colony of *Bacillus subtilis*, bacillus survives just in the blood rich in Phe)

PKU- 3rd d **PKU- 12the mo**

http://www.pahdb.mcgill.ca/images/pku.gif&imgrefurl

Hyperphenylalaninemia + Phenylketonuria

- consequence of untreated disorders - mental retardation
- treatment - strict diet with low intake of Phe to about 15 years of age
- later less strict diet
- many products contains sweetener **aspartame**, unsuitable for phenylketonurics, hydrolysis releases phenylalanine



L-aspartyl-L-fenylalanine methyl ester (180× more sweeter than sucrose)

Function of Phe in org.

- Phenylalanine occurs in 3 forms: L-phenylalanine, What is the natural form of which is found in proteins, D-phenylalanine, which is a mirror image of L-phenylalanine produced in the laboratory, and DL-phenylalanine, a combination of D- and L-forms . L-Phe form is part of the protein, while the D-form acts as a painkiller.
- The amino acid – **Phe** is the immediate precursor of **tyrosine** (**Tyr**), is converted primarily to that amino acid which is used in the biosynthesis of the dopamine and norepinephrine neurotransmitters

Treatment - dietary measures

- For a whole life
- The high content of Phe have these foods :
- eggs, milk, cheese, meat, poultry, fish, dried beans and legumes, high content of protein - excluded from food
- Treatment with BH4 -tetrahydrobiopterin, some patients don´t respond
- responsive to BH4 therapy depending on their **PAH gene mutation**. Sapropterin dihydrochloride (Kuvan, BioMarin Pharma) is an orally active synthetic form of BH4.
- Note: the same symptoms showed similar disease (**hyperphenylalaninemia**), which, however, has a different basis. The cause of this disease is a deficiency of one of four enzymes that are involved in the formation and metabolism of tetrahydrobiopterin BH4 - see herein above
- Another possibility is therapy with enzyme replacement

Content of Phe in food

Average content of phenylalanine (PHE) in various types of foods

Food	Average content of PHE in 1g of protein (mg)
Fresh fruits	27
Fresh vegetables	35
Fresh mushrooms	29
Potatoes and products made from it	49
Milk and dairy products	51
Bakery products	58
Pork meat	44
Beef meat	48
Smoked meat	46
Fish	43
Nuts	51
Corn	55
Yolk	49
Egg white	69
Candies, chocolate, cookies	50

LNAA v léčbě PKU

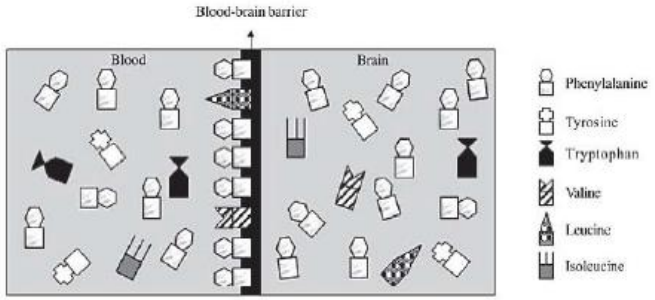
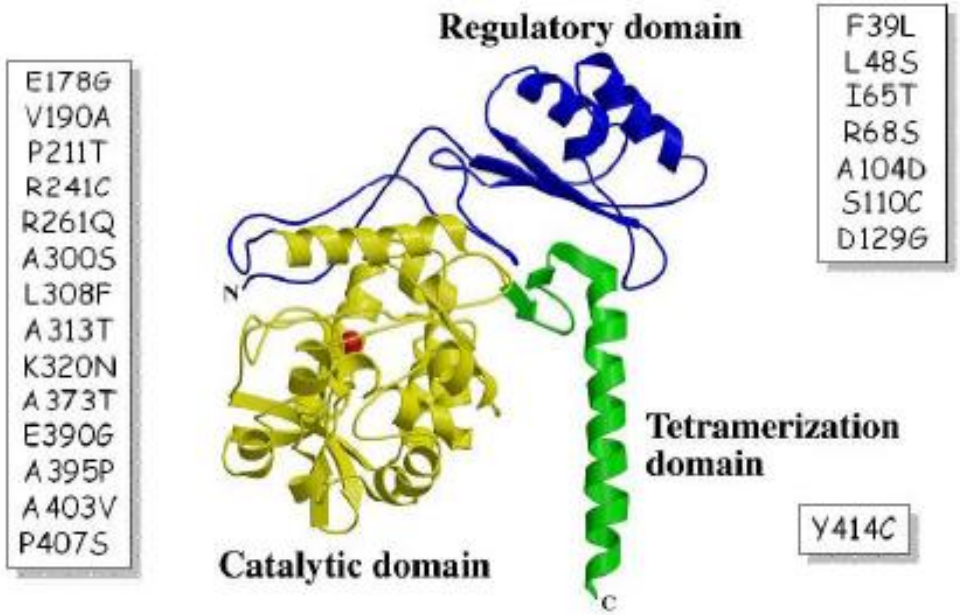


Figure 1. Phenylalanine competes with other LNAAs for the same carrier to pass the blood-brain barrier. High phenylalanine levels, as seen in PKU patients, reduce the brain uptake of other LNAAs and their availability in the brain.

http://www.funpecrp.com.br/gmr/year2006/vol1-5/gmr0182_full_text.htm

PAH Mutations Associated with BH4-Responsive HPA



Source: Nenad Blau (personal comm., Sept 2002) displayed on Erlandsen H and Stevens RC, The Structural Basis of Phenylketonuria. *Mol Genet Metab.* 1999 Oct; 68(2): 103-125

Large Neutral Amino Acid Supplementation

Other novel therapeutic approaches can be categorized by the site of action or target organ (Figure 2) [17]. These categories include enteral, systemic, liver-directed approaches. Dietary restriction of Phe intake is an example of enteral approach. Alternatively Large Neutral Amino Acid (LNAA) can be used. LNAA can compete with the same transporter of Phe across the gastrointestinal and blood brain barrier to reduce Phe absorption and entry into the brain [18]. A double blind, placebo-controlled study indicated a significant decline in blood Phe concentration in patients with PKU treated with LNAA for 2 weeks suggesting that LNAA compete with the transport of Phe in the gastrointestinal trac [19]. These studies suggest that adding LNAA to the diet of patients with PKU could reduce blood Phe concentrations.

Disorders in metabolism of aromatic AA (Phenylalanine, Tyrosine)

PHENYLALANINE → TYROSINE (phenylalanine hydroxylase)

2.hypertyrosinemia

Tyrosinemia type 1 – *deficiency of enzyme fumarylacetoacetate hydroxylase*

Metabolite succinylacetone accumulated in blood, damaging liver, kidneys, PNS a CNS. Particular manifestation is is self-harming of the pacient

Tyrosinemia type 2- *deficiency of enzyme* ***tyrosine-aminotransferase*** (impairment of eyes, skind and CNS)

Transient tyrosinemia or hyperphenylalaninemia of the newborn – *delayed activation of enzyme* ***phenylalanine hydroxylase***,

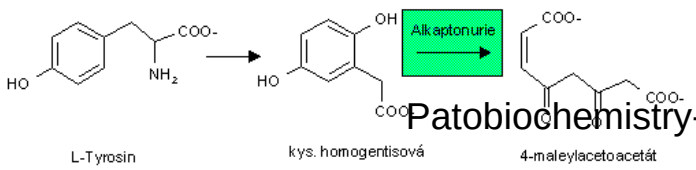
Transient increase of tyrosin levels in plasma in first 2 weeks of life, caused by delayed maturation maturation of enzyme tyrosine aminotransferase or 4-hydroxyfenylpyruvate dioxygenase in liver

3. alkaptonuria

Defect of ***homogentisate oxygenase***

High concentration of homogentisic acid (oxidation of homogentisate to benzoquinone acetate → generalised pigmentation of connective tissue, sclera,

auricles, skin), arthritis (hip, ankle, spine), kidney damage (urolithiasis) and heart valves (regurgitation of aortal or mitral heart valve), calcification of aorta, urine darkens on light **(brown pigment alkapton)**



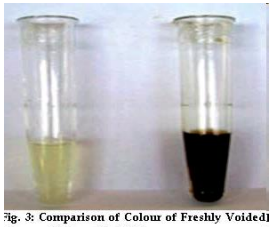


Fig. 3: Comparison of Colour of Freshly Voided Urine and Urine after 24 Hours

2. hypertyrosinemia

Tyrosinemia type 1 - *deficit of enzyme fumaryl acetoacetate hydroxylase*

- **sukcynilaceton metabolite is accumulated in the blood** and damages the liver, kidneys, CNS and PNS particular manifestation is a self-harm of sick person

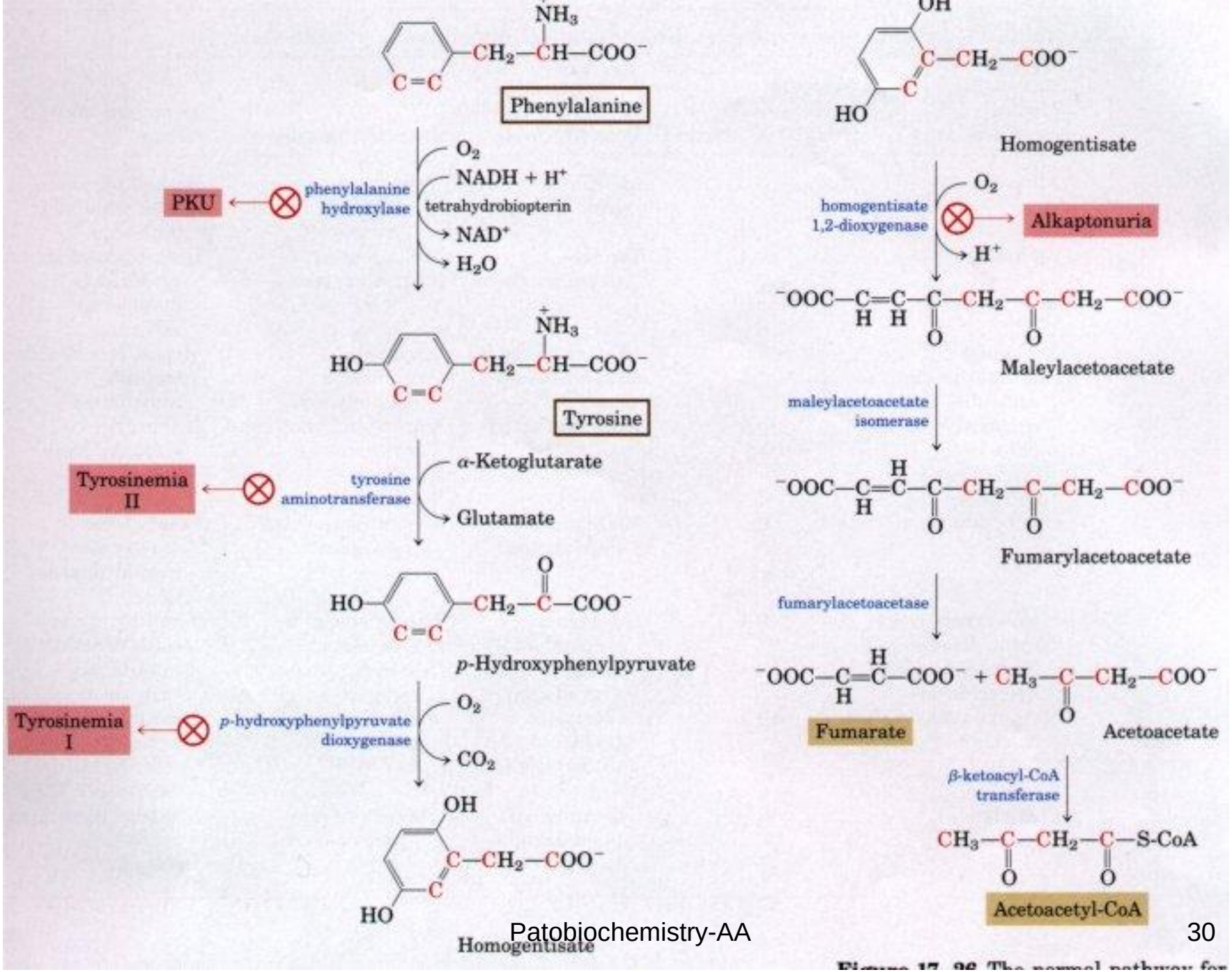
Tyrosinemia type 2- *deficiency of the enzyme tyrosine aminotransferase (disability eyes, skin and the CNS)*

Transient tyrosinemia or hyperphenylalanemia in newborns

- *Delayed activation of enzyme phenylalanine hydroxylase,*

A transient increase of tyrosine in plasma in the first 2 weeks of life, given the delayed maturation of enzymes tyrozinaminotransferázy or

4-hydroxyfenylpyruvátdioxygenázy in liver


Phenylalanine
PKU
phenylalanine hydroxylase
O2
NADH + H+
tetrahydrobiopterin
NAD+
H2O
Tyrosine
Tyrosinemia II
tyrosine aminotransferase
α-Ketoglutarate
Glutamate
p-Hydroxyphenylpyruvate
Tyrosinemia I
p-hydroxyphenylpyruvate dioxygenase
O2
CO2
Homogentisate
Homogentisate
homogentisate 1,2-dioxygenase
O2
H+
Alkaptonuria
Maleylacetoacetate
maleylacetoacetate isomerase
Fumarylacetoacetate
fumarylacetoacetase
Fumarate
Acetoacetate
β-ketoacyl-CoA transferase
Acetoacetyl-CoA

Tyrosinemia type 1

- *deficit of enzyme fumaryl acetoacetate hydroxylase (liver)*
- **sukcynilaceton metabolite is accumulated in the blood** and damages the liver, kidneys, CNS and PNS particular manifestation is a self-harm of sick person

Tyrosinemia type I

defect in **fumarylacetoacetate hydrolase** (expressed mainly in the liver and kidneys) and probably also in maleinylacetacetatehydrolase,

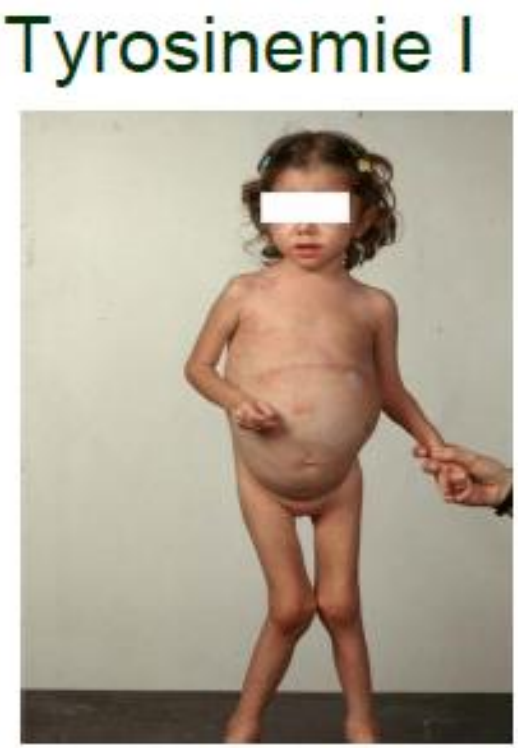
AR hereditary

high level Tyr (60-120mg / l plasma) and Met, the high level of metabolites affect activity of other enzymes and transport systems - severe pathology - **hepatorenal failure** (cirrhosis of the liver, hepatomegaly, coagulopathy, **Fanconi syndrome** - a disease of the proximal tubules of the kidneys, excretion of phosphate → hypophosphatemic

infliction of CNS (cramps, hyperextension, self-injury, respiratory arrest),

ascites, accumulated metabolites (maleylacetoacetate, fumarylacetoacetate) and their derivatives (succinylacetone and succinylacetoacetate) make glutathione derivatives (removal of function of one antioxidant) - tissue damage caused by radicals

•**acute tyrosinosis** without treatment → diarrhea, vomiting
•smell of cabbages, die within 6-8 months (liver failure)
• **chronic tyrosinemia** → symptoms are the same, but weaker individuals die within 10 years
• sooner treatment diet without Phe, Tyr; Today NTBC → p-blocker of hydroxyfenylpyruvathydroxylase



•the drug NTCB inhibits *p*-hydroxyphenylpyruvate dioxygenase, intercepting the degradative pathway upstream of the toxic metabolites
•dietary restriction of tyrosine required to prevent neurological deficit

<u>Treatment</u>:

Metabolic defect is treated by diet with low-income of tyrosine (Tyr) and (Phe) into adulthood, in serious cases → failure of liver functions, liver transplantation

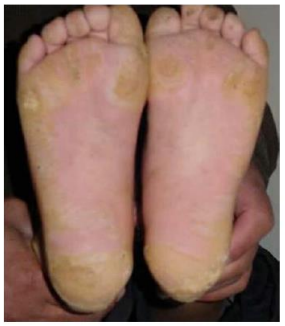
Treatment

Nitisone - known as NTBC, substance originally developed as a herbicide.
Now - substance used for slowing the effects of **tyrosinemia type I**.
For the first time for this indication was used in 1991 - **averted the need of using transplantation of liver damaged by this disease such as the treatment of first choice. It is studied in connection with alkaptonuria.**
Commercial name of the drug - **Orfadin**.

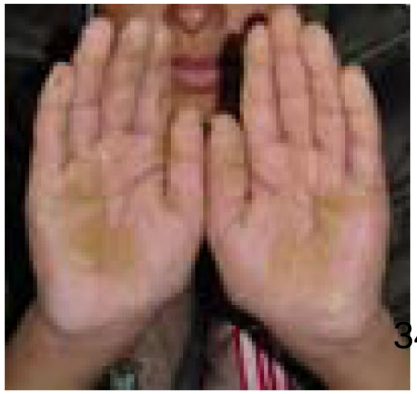
The mechanism of action of nitisinon involves **reversible inhibition** of **4-hydroxyphenylpyruvate oxidase** and performs preventive forming of maleylacetoacetic acid and fumarylacetoacetic acid.

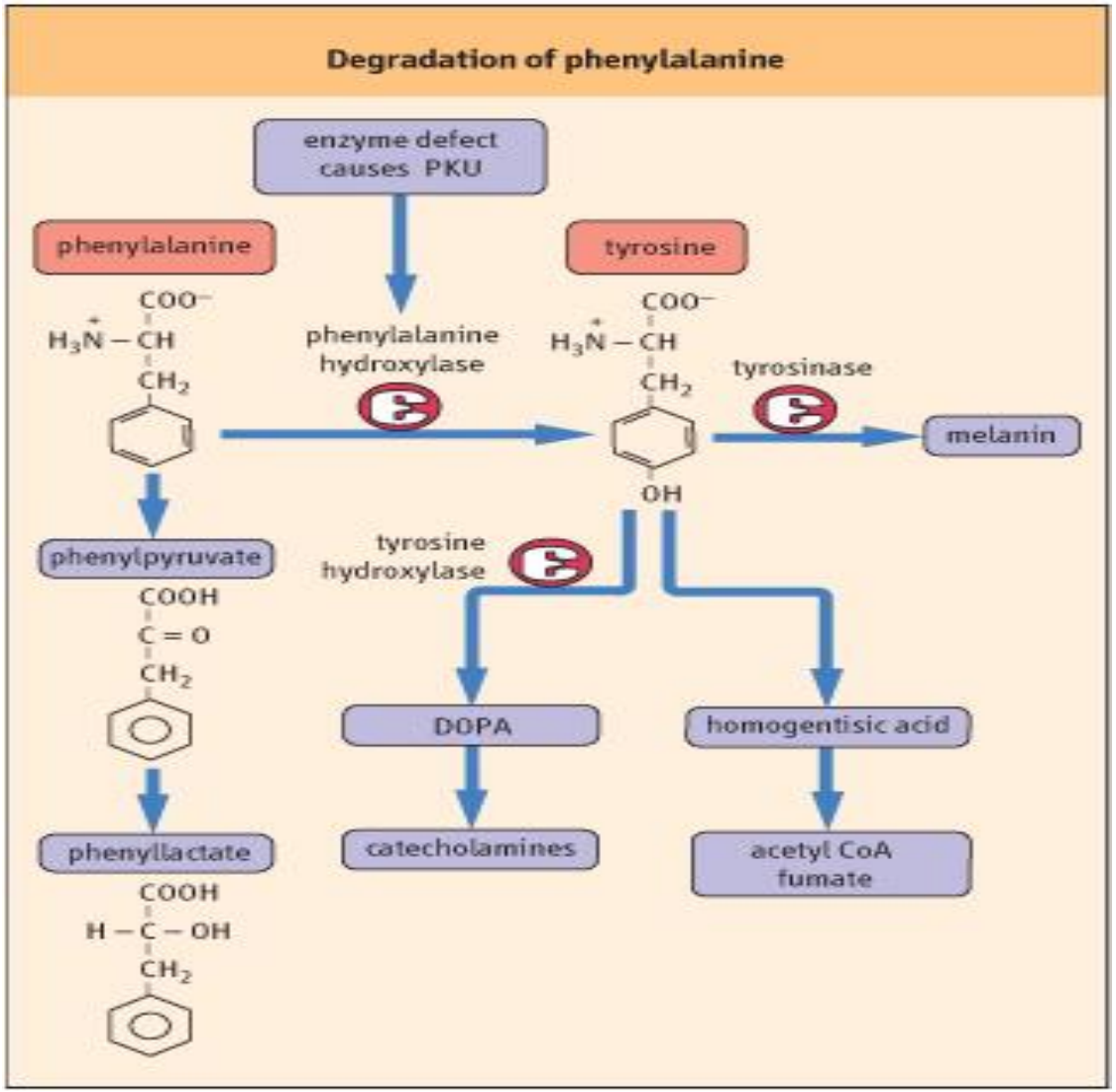
Tyrosinemia type II. (Richter-Hanhart syndrome)

- defect in liver tyrosintransaminase
- **Conversion of tyrosine to acetate - manifested by disease called keratosis**
- very rare disease, AR hereditary
- elevated levels of tyrosine (40-50mg / l plasma)
- mild mental retardation, hyperkeratosis (on the palms and soles feet), inflammation of the conjunctiva, corneal ulceration, nystagmus, glaucoma (turbidity by tyrosine crystals), tyrosine and its metabolites are present in urine
- treatment by diet
-

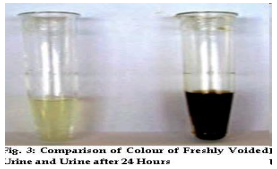


hyperkeratosis




Degradation of phenylalanine
enzyme defect causes PKU
phenylalanine
tyrosine
phenylalanine hydroxylase
tyrosinase
melanin
phenylpyruvate
tyrosine hydroxylase
DOPA
homogentisic acid
catecholamines
acetyl CoA fumate
phenyllactate

Metabolic disorders of aromatic AAs (phenylalanine, tyrosine)



FENYLALANINE → TYROSINE

3). alkaptonuria

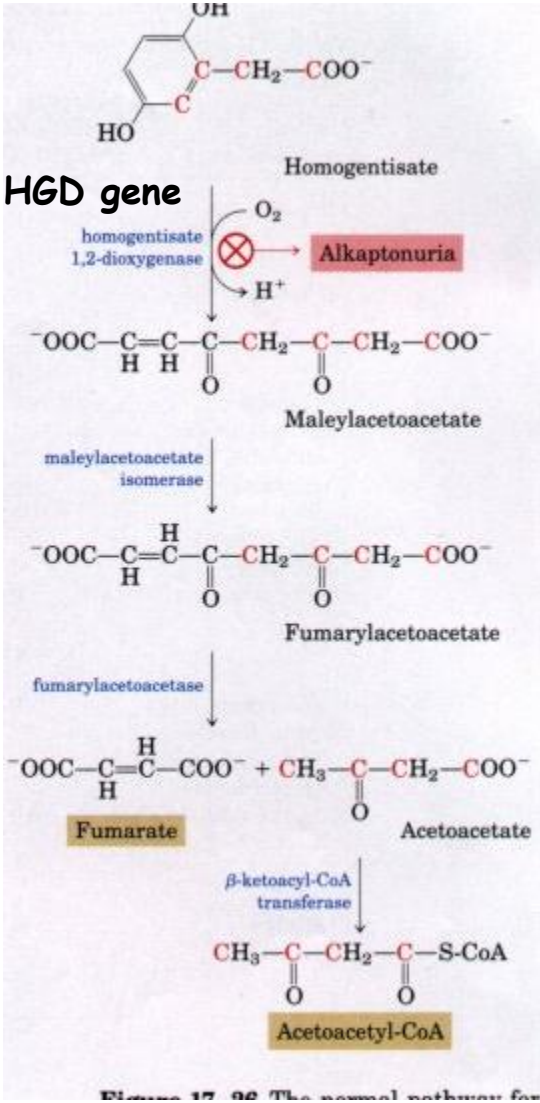
mutation in the HGD gene

defect of *homogentisateoxygenase*

high homogentisic acid concentration

(oxidation of homogentisate to benzochininacetate → generalized binder pigmentation, sclera, ears, skin), arthritis (hips, ankles, spine), kidney damage (urolithiasis) and heart valves (regurgitation of the aortic or mitral valve), calcification of the aorta, urine darkens on light (**brown pigment alkapton**)

- **Treatment** – diet, ascorbic acid (vit. C) prevents the binding of homogentisicacid. to binder, administration of NTBC



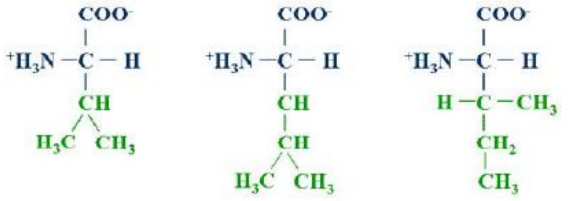
Metabolic disorders of **branched AMK (Val, Leu, Isoleucine)**

- BCAA (branched chain amino acids)
- all three are essential
- the first reactions of catabolism are similar (transamination oxide. decarboxylation dehydrogenation) final products are different
- leucine - ketogenic AA
- after eating, their representation in blood is high (about 70% of all AA), because the liver do not use them (lack of aminotransferases)
- most utilized by muscle and CNS
- favorably affect the catabolic states (infusion)

Metabolism of branched AMK overview

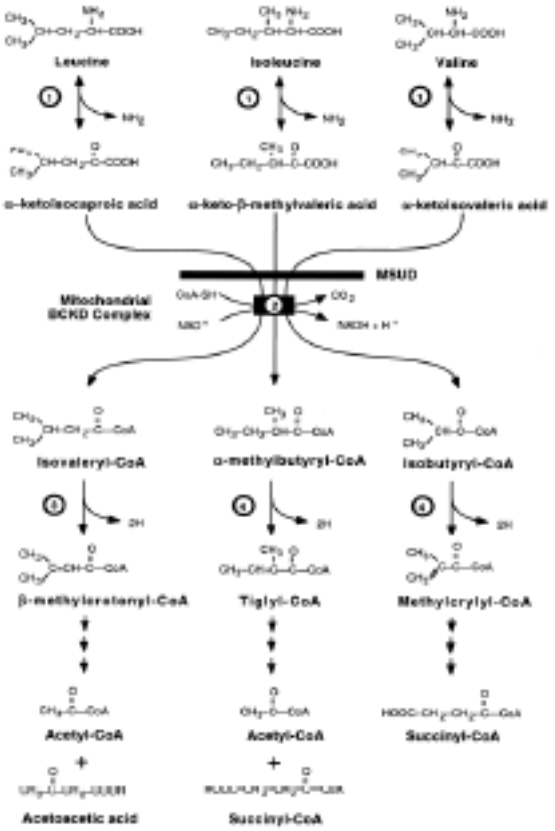
1. **transamination (transaminase)→ 2-oxoacids (val → 2-oxoisovalerate, leu → 2-oxokapronate, ile → 2-oxometylvalerate**
2. **dekarboxylation**
3. **dehydrogenation (specific multienzyme dehydrogenase)**

- the first three reactions common to all these AMK, AMK are going through liver
- **Common reactions**
  transamination (first reaction) by common transaminase (highest activity in myocardium and skeletal muscle, low in the liver) – corresponding 2-oxo acids are formed (2-val → oxoisovalerate, leu-oxokapronate → 2, 2 → ile-oxometylvalerate); **hypervalinemic block**
- **decarboxylation** (the second reaction) and **dehydrogenation** (the third reaction) - takes place in the mitochondria → specific multienzyme dehydrogenase → acyl-CoA which is one carbon shorter than the original oxoacids is formed; **block (2 – dekarboxylation) at the maple syrup disease; block (3 – dehydrogenace) at isovaleric acidemia**
- result:
- Val → methylakryoloyl-CoA
- Leu → β-metylkrotonoyl-CoA
- Ile → tigloyl-CoA



Compare the final products

Leucine	acetyl-CoA + acetoacetate	ketogenic AA
Isoleucine B_{12}	acetyl-CoA + sukcinyl-CoA	mixed AA
Valine B_{12}	sukcinyl-CoA	glukogenic AA



Metabolic disorders of branched AMK (Val, Leu, Isoleucine)

1. transamination (transaminase)→ 2-oxoacids (val → 2-oxoisovalerate, leu → 2-oxokapronate, ile → 2-oxometylvalerate
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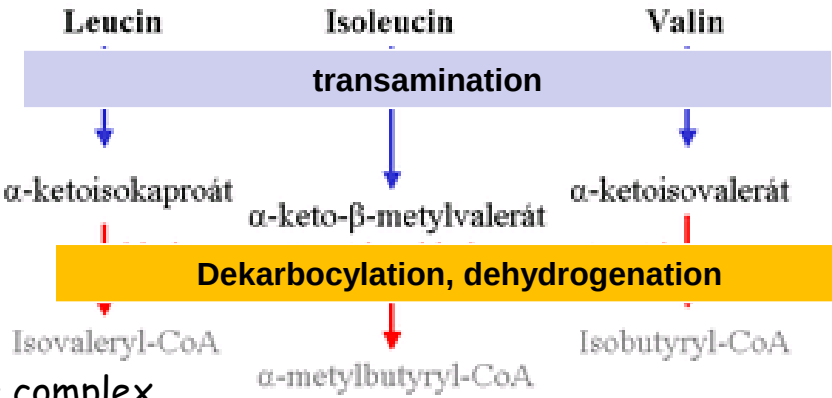


Hypervalinemia

low activity of transaminase common for valine,

a very rare disease,

Maple syrup disease (leucinosis)

deficit or insufficient activity decarboxylase/dehydrogenase complex
increased levels of Val, Leu and Ile, and 2-oxoacids
brain damage, failure to thrive, drowsiness, coma and later vegetative nerve problems (abnormal heart activity - bradycardia, hypothermia), severe dehydration

Intermittent forms of leucinosis

less severe modification of decarboxylase, metabolism of Val, Ile, and Leu is reduced but maintained, symptoms of leucinosis appear later and occasionally, (after ingestion of large amounts of AMK)

Isovaleric acidemia

deficit of *isovaleryl-CoA-dehydrogenase*

metabolic acidemia (pH 7,3), ketonuria, hyperammonemia, hypocalcemia, hyperlactémie, odor of breath, body fluids, coma after ingestion of large amounts of protein, Generalized pancytopenia

methylmalonic aciduria

Caused by avitaminosis B12. B12 is a cofactor of the enzyme which converts methylmalonyl-CoA to succinyl-CoA (radical isomerization) metabolic acidosis

TEST

Metabolic disorders of branched AMK (Val, Leu, Isoleucine)

maple syrup disease	1:185 000	dehydrogenase of branched alfaketoacids
izovaleric acidemia	1:230 000 (worldwide)	isovaleryl-CoA dehydrogenase
glutaric aciduria	1:40 000 (white people)	glutaryl-CoA dehydrogenase
metylmalonic aciduria	rare	metylmalonyl-CoA mutase
propionic acidemia	rare	propionyl-CoA karboxylase

Maple syrup disease

- Disorder in Leu, Ile, Val mtb - branched amino acids – deficiency of dehydrogenase/decarboxylase complex of branched AA,
- organic acids are accumulated (alpha -ketoacids derivatives) – severe toxicity, increased levels of Val, Leu and Ile, and 2-oxoacids
- deficit or insufficient activity **decarboxylase**
- Excess of toxic metabolites - always after increased amount of branched AA, eg. an infant postpartum weight loss, protein degradation -fever, starvation, diet, disease
- clinical manifestation: (sweat, urine – breath odour after maple syrup, caramel, dried fruit)
- Newborn - soon after birth, lethargy, or does not accept breastfeeding - weak suck, irritability, a milder form - mental retardace.Hyperacidosa, hyperammonemia → convulsions, coma - death without treatment !!!

brain damage, failure to thrive, drowsiness, coma and later vegetative nerve problems (abnormal heart activity - bradycardia, hypothermia, ažapnoe), severe dehydration

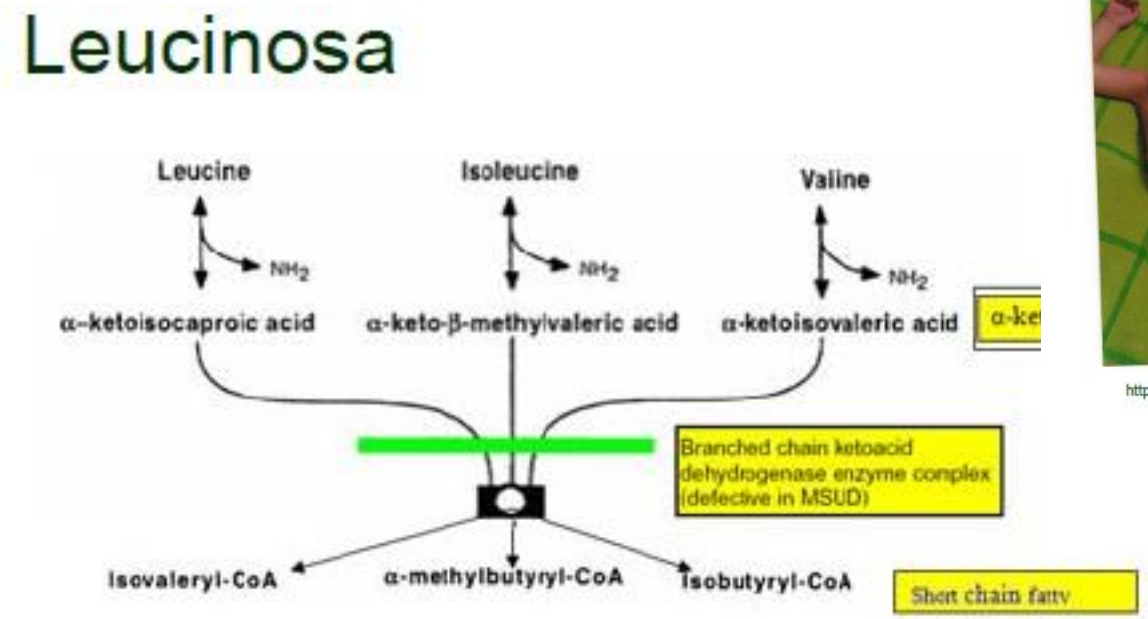
Treatment:
Diet with limited leucine and valine and izoleucine intake, additions spec. Nutrition with AA important for growth (contribution of health insurance company)
Precautions: avoid starvation, limiting protein intake - substituting for. Glucose / in sickness etc.).
Start treatment as soon as possible!!! after 14.days of starting the treatment – impairment of intellect, rarely - normal intellect

Leucinosis

Intermittent forms of **minor modifications of decarboxylase**

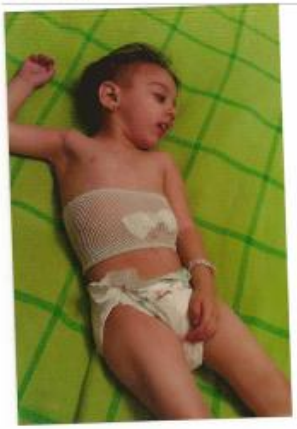
metabolism of Val, Ile, and Leu is reduced but maintained. Leucinosis symptoms appear later and occasionally

(after ingestion of large amounts of AMK)



http://www.childrenshospital.org/newenglandconsortium/NBS/MSUD/MSUD1.jpg

MSUD



http://losyoruguas.com/archivos/0686.gif

- Peracute presentation in newborns, intermittent variants
- Coma, dystonia-boxing, cycling
- maple syrup odour
- acute crisis prevention and management
- long term treatment-diet

Metylmalonic aciduria

Caused by **avitaminosis B12**. B12 is a cofactor of the enzyme which converts methylmalonyl-CoA to succinyl-CoA (radical isomerization)

Metabolic acidosis belongs to the group of organic acidurias.

- methylmalonyl-CoA mutse disorder (converts isoleucine, valine, methionine and threonine, involved in the synthesis of CHOL and MK).
- AR hereditary.
- **Clinical picture**
- Short symptomless period after birth; then vomiting; lethargy; progressive impairment of consciousness; brain edema; liver and kidney failure; children die of sepsis, bleeding or shock state
- **in the acute stage** - ketoacidosis and laboratory evidence of liver and renal failure
- There is higher level of glycine, valine, methionine and some organic acids (especially methylmalonic acid) in urine and blood.

- **Diagnosis**
- examination of organic acids and AAs in urine and blood;
- exact type of defect is determined by enzymatic examination of cultured fibroblasts
- **Therapy:** with suspicion, the supply of protein should be stopped and must avoid catabolism - glc concentrated infusion; prognosis is good if treated early
- critically ill patients must undergo elimination methods to detox
- with the recessionary effect: hemodialysis, hemodiafiltration, peritoneal dialysis and exchange transfusion; a lifelong diet is needed with low intake of natural protein with the addition of a mixture of essential AAs without isoleucine, valine, methionine and threonine.

Methylmalonic acidemia

- newborn variant: acute crisis with ketoacidosis, hyperammonemia and coma
- milder forms-repeated encephalopatic episodes
- chronic problems: nephropathy progressing in renal failure, variable CNS involvement (pacin picture partially deaf and mute), infections Candida sp.
- treatment: IMTV restriction, gut sterilization, in some pateints B12, aggresivní treatment of acute episodes

http://images.google.com/imgres?imgurl=http://www.toby-churchill.com/files/images/lynn5.jpg

Isovaleric acidemia

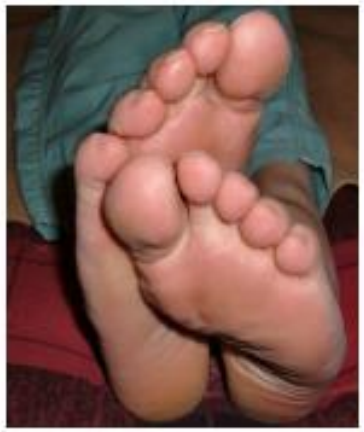
isovaleryl-CoA-dehydrogenase deficiency

metabolic acidemia (pH 7,3), ketonuria, hyperamonemia, hypocalcemia, hyperlactemia, odour of breath, body fluids, coma after ingestion oflarge amounts of proteins, generalized pancytopenia

Isovaleric acidemia

http://images.google.com/imgres?imgurl=http://www.ivasupport.org/images/

Isovaleric aciduria



- IVA-CoA DH deficiency
- Peracute/intermittent course
- Coma with acidosis/ketonuria, sweaty feet odour
- Acute crisis-elimination
- Long term-diet, karnitine, glycine
- Newborn screening

http://www.arxmanstyle.com/wp-content/uploads/2009/01/sweaty-feet.jpg

Hypervalinemia

low activity of common transaminase for valine, very rare disease,

Intermittent forms of leucinosis

minor modifications of decarboxylase
metabolism of Val, Ile, and Leu is reduced but maintained. Leucinosis symptoms appear later and occasionally
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Disorders of metabolism of sulfur AAs

Homocystinuria

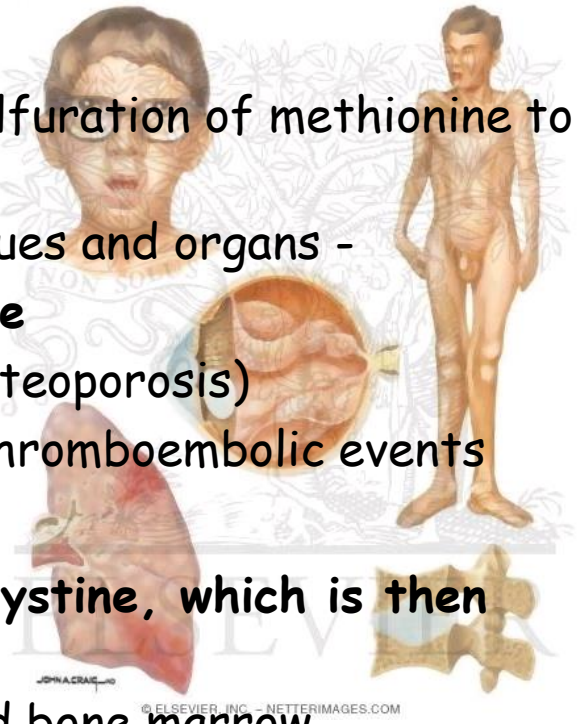
disorder in *β-cystathionine* synthetase activity (transsulfuration of methionine to cystine)

manifestations are quite diverse and affect various tissues and organs -

impairment of mental development, **marfanoid phenotype**

(tall slender figure, arachnodactyly, kyfosa, scoliosis, osteoporosis)

ectopia of lenses, glaucoma and central and peripheral thromboembolic events



Cystinosis

is a consequence of deficiency of lysosomes to release **cystine, which is then accumulated therein**,

accumulation affects RES (spleen, liver, lymph nodes and bone marrow

renal impairment - glycosuria, phosphaturia, albuminuria, hyperaminoacidurie,

chronic acidosis and uremia

Cystinuria

AR disorder *of AAs transport* – cystine, lysine, ornithine and arginine

in the kidney and the gut, renal and intestinal problems, cystine crystallizes in the urine

Homocystinuria

disorder in **β-cystathionine synthetase activity** (causes transsulfuration of methionine to cystine)

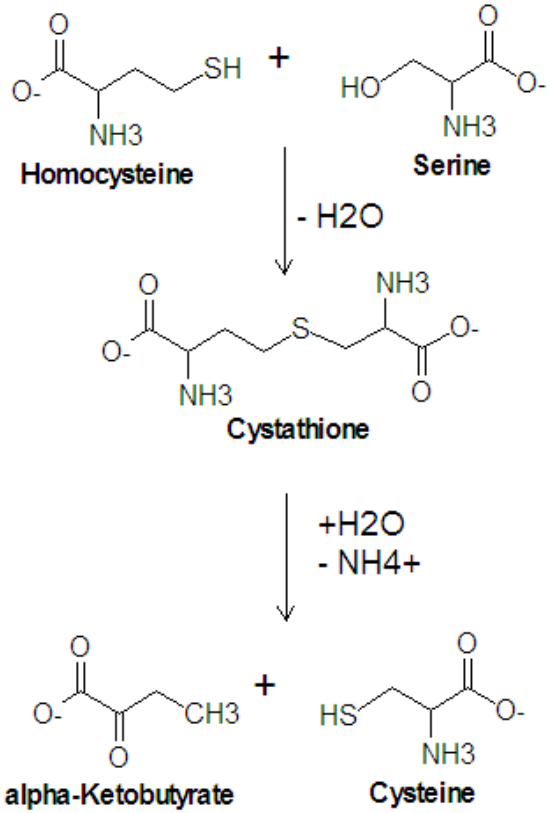
AR hereditary frequency 1 : 200 000[3]

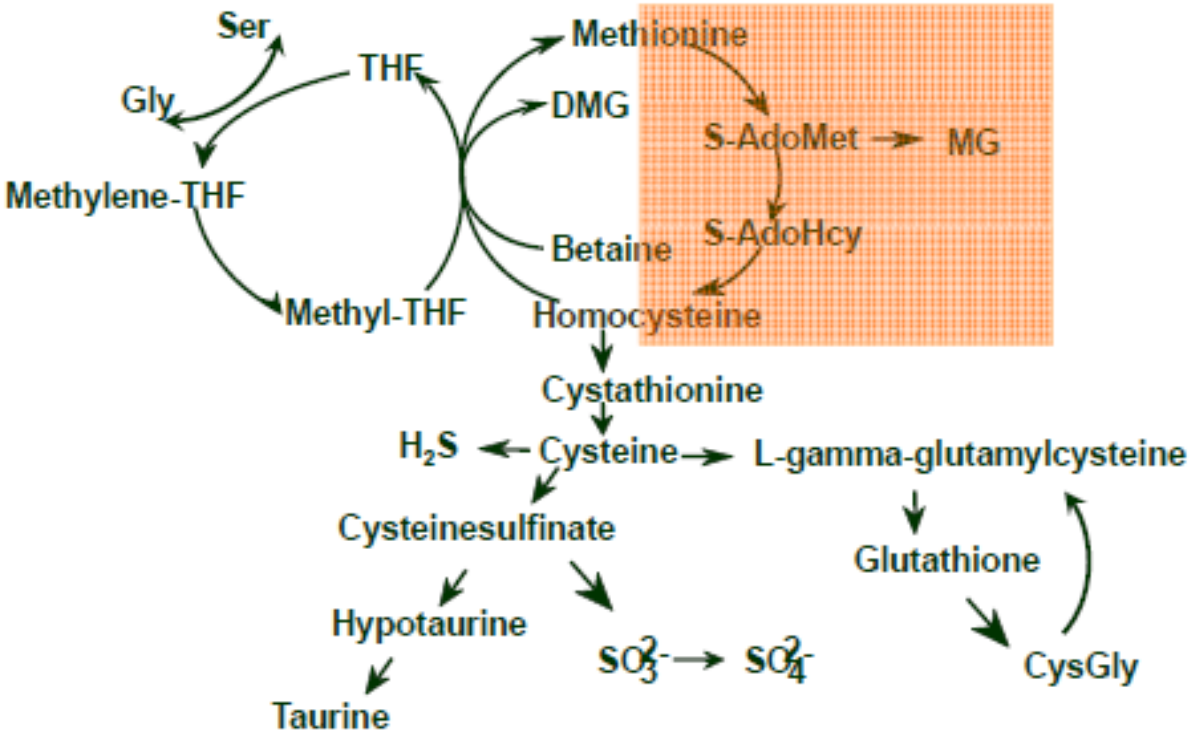
clinical picture: symptoms are not apparent at birth, but in the further development leads to symptoms affecting various tissues and organs

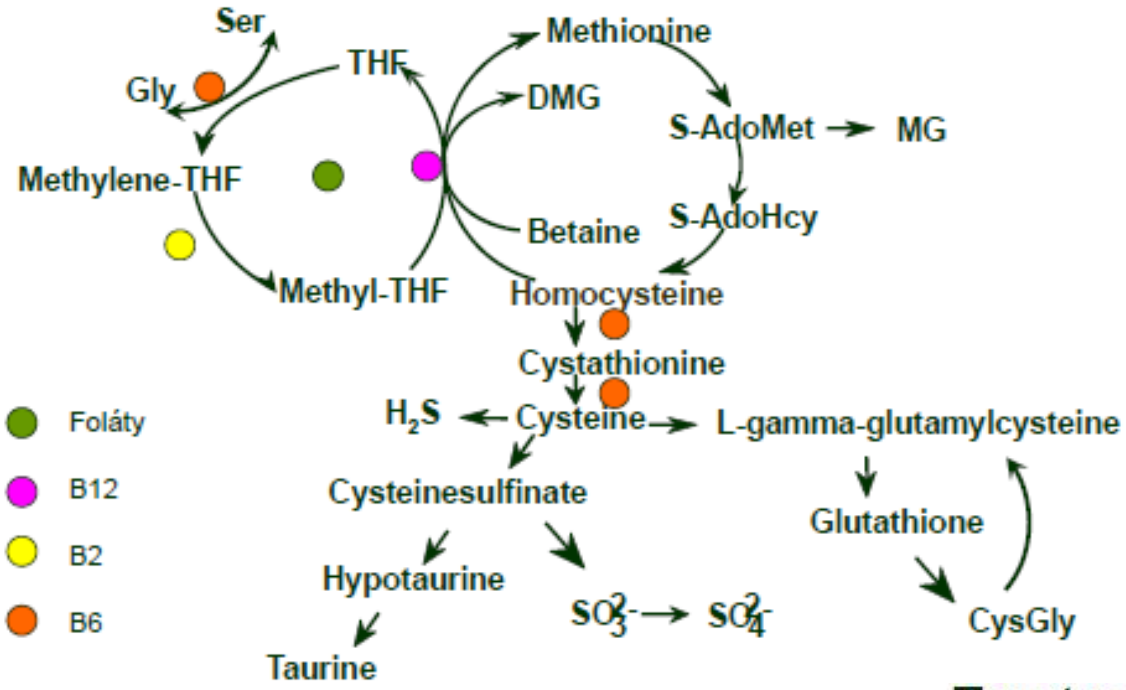
- appear in the toddler or preschool age - impaired mental development (psychomotor retardation in 60% of cases [4]), marfanoid phenotype (tall slender figure, arachnodactyly, kyfosa, scoliosis, osteoporosis) and ectopic lenses, glaucoma and central and peripheral thromboembolic events
- dislocation of the lens causing strong myopia, thromboses occur most frequently at the base of the skull and life-threatening, gangrena of organs occurs, which usually ends the patient's life in 20 to 30 year
- optic nerve atrophy, cor pulmonale, hypertension
- **laboratory**: increase of homocysteine in blood, frequent metabolic osteopathy
  - necessary to confirm at the enzymatic and molecular level
- **dif.dg**: homocysteinemia occurs also at methylmalonic acid metabolism impairment, cobalamin or B12 deficiency
- **therapy**: proportion of patients (approximately 50% [4]) responds favorably to high doses of pyridoxine (vitamin B6) (in an amount of 300-900 mg / d [4]), which regulates the activity of cystathionine β-synthetase
  - it is necessary to initiate dietary treatment with a limited supply of methionine
  - prenatal diagnosis is available

Homocysteine

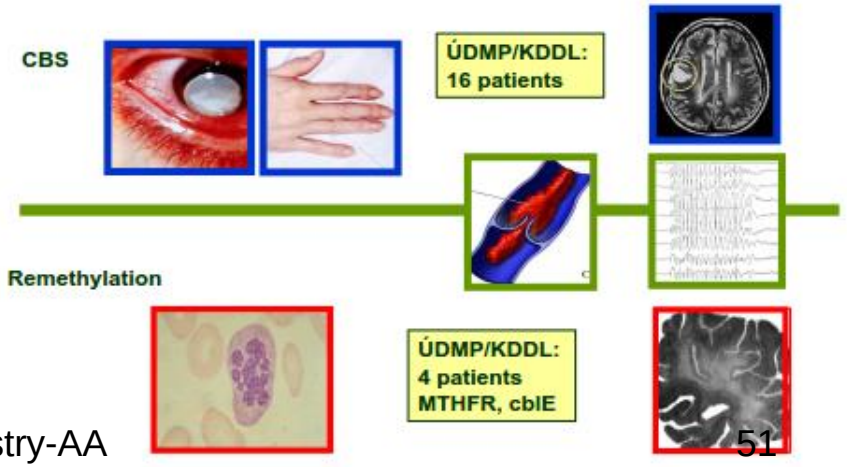
- Homocysteine (systematic name **2-amino-4-sulfanylbutanic acid**) is an amino acid that is produced during normal metabolism in humans and other mammals from the amino acid methionine. Normally is degraded to form amino acid called cysteine under the influence of B vitamins (especially B6, B12, folic acid).
- The lack of these vitamins, e.g. in vegetarian diets, or a rare hereditary disease **"homozygous homocystinuria"** [1] may lead to elevated levels of homocysteine in the blood.







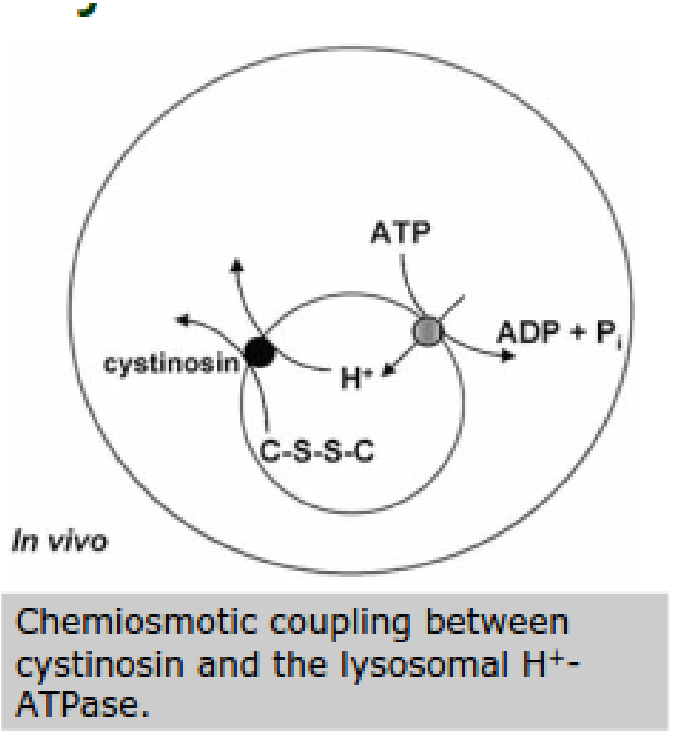
Two types of homocystinuria



2) Neuropathic cystinosis

- AR hereditary
- frequency 1 : 50 000 - 1 : 1 000 000[4]
- This is a **defect of lysosomal cystine transport**, which leads to its deposition
- accumulation affects RES (spleen, liver, lymph nodes and bone marrow), deposits can be proved even in the cells of the kidney tubules and conjunctiva
- clinical manifestations are evident only in the kidney, where there is a serious breach of their function
- **laboratory**: signs of kidney damage - glycosuria, phosphaturia, albuminuria, hyperaminoacidurie, chronic acidosis and uremia
  - generalized aminoaciduria is due to a decrease in GF, which will soon result in kidney failure
- **therapy**: symptomatic treatment tubular dysfunction, usually high doses of vitamin D are required [4]
  - **Supplementation with cysteamine** which acts in two ways
    - binding to cystine results in cysteine formation that can be secreted from the lysosome via cysteintransporter[4]
    - binding to cystine results in cysteine-cysteamine formation, which can be secreted from the lysosome via lysinetransporterudisulfide[4]

cystinosis

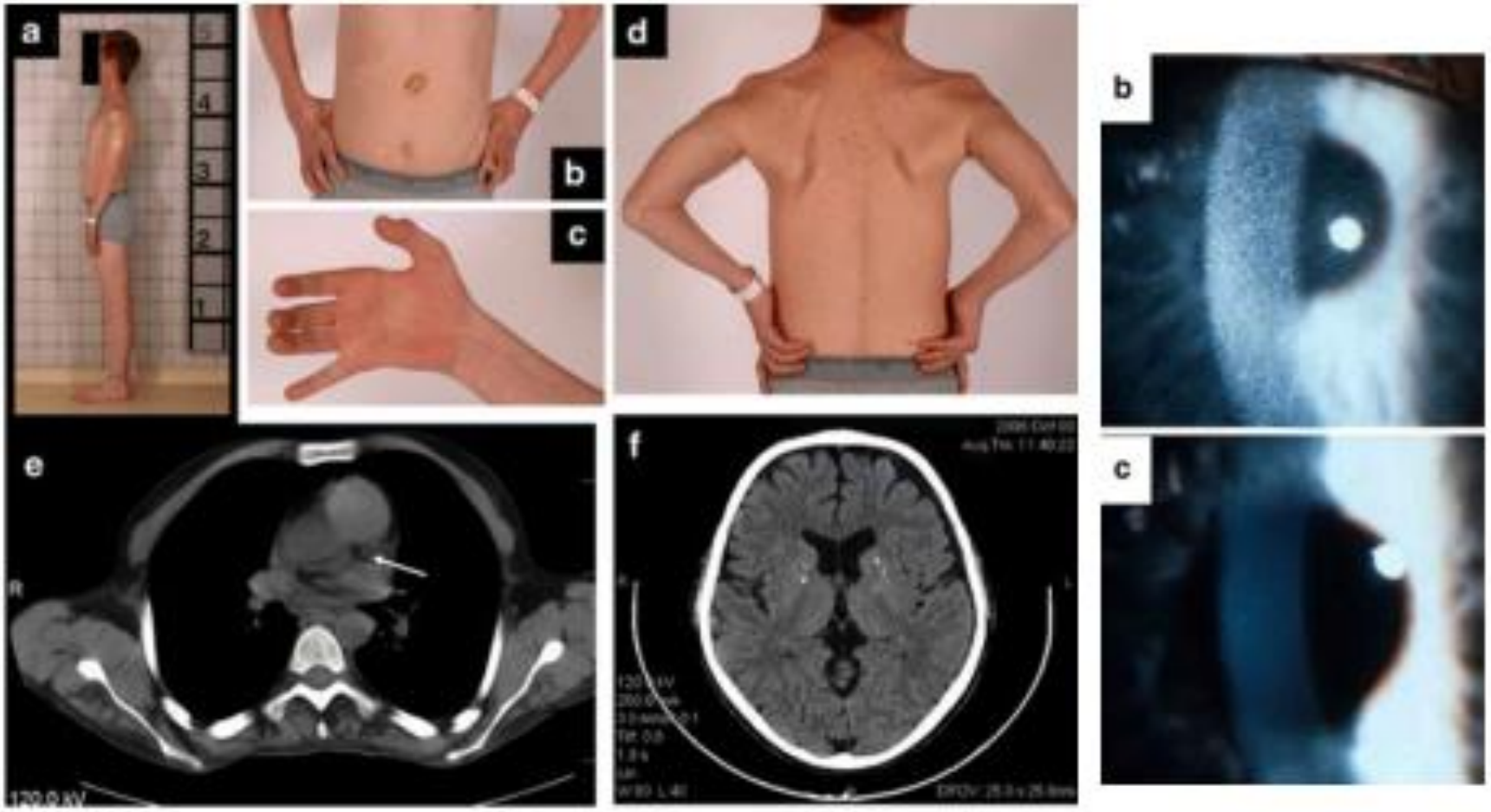


Chemiosmotic coupling between cystinosin and the lysosomal H^+-ATPase.

- defect of lysosomal transporter cystinosin
- infantile form: Fanconiho syndrome-severe tubulopathy
- FTT
- adultní forms: ocular involvement myopathy, hypothyreosis
- Rx- cysteamine locally and systematically

- Cystinosis - inborn disorder of metabolism of cystine with autosomal-recessive inheritance; free cystine accumulates in the lysosomes of cells of the whole organism, esp. in the **reticuloendothelial system**, bone, kidney and retina.
- In the foreground is renal tubular atrophy and variously extensive bone disease, if there is also an accumulation of ferritin in lysosomes, retinopathia retinitis pigmentosa is developped. Infantile c. - severe form of renal rickets resistant to vitamin D with a dwarf in stature, renal imairment is manifested by tubular acidosis with hypokalemia and aminoaciduria, further retinopathy. Juvenile c. - In the foreground is especially renal impairment. Glomerular proteinuria and progressive renal failure, retinopathy. C. adults - benign form, the disorder can be proved in the laboratory and histological crystals of cystine, kidney function is not significantly impaired. Syn. Abderhald-Kaufmann-Lignac syndrome, Fanconi-Lignac syndrome, Fanconi-Abderhalden sydrome specially type I

Adult cystinosis



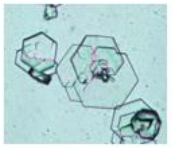
http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=ctns

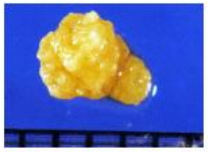
3) Cystinuria

disorder of *AAs transport* – cystine, lysine, ornithine and arginine **in the kidney and the intestine**, renal and intestinal problems, cystine crystallizes in the urine

AR hereditary

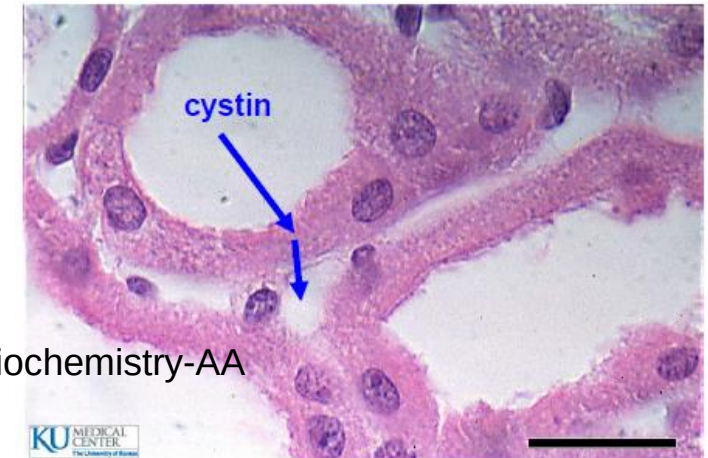
- frequency 1 : 2000 - 1 : 7000[4]
- congenital disorder transport dibasic AMK - cystine, lysine, ornithine and arginine in renal tubules and in the gut
- **clinical picture:** cystine nephrolithiasis, which is caused by poor solubility of cystine in water, and its crystallization in an acidic environment
- **Diagnosis:** elevated levels of cystine, ornithine, arginine, lysine in the urine; sono kidney and urinary system[4]
- **therapy**: the goal is to prevent the formation of nefrolitiasis; fluid intake coupled with a night drinking is recommended
- In severe cases it is possible to consider medical therapy **by D-penicillamine or mercaptopropionylglycine** which cause the formation of more soluble bisulfites with cystine[4]





1810 Wollaston- bladder stone (Greek cystos)- „cystic oxid"

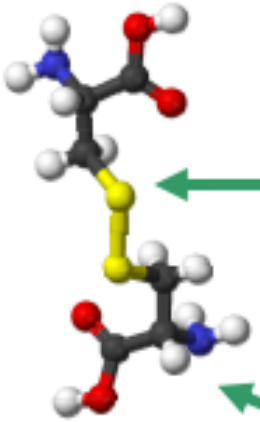
1817 Marcet- the same compound also found in kidney stones, family occurence (2 sibpairs)



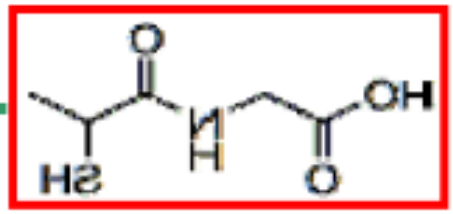
History of cystinuria

- **1908 Garrod- one of 5 IEMs**
- incidence cca 1: 10 000
- 1994 *SLCA1* gene, 1999 *SLC7A9*
- hundreds of mutations
- treatment: fluid intake, penicillamine, thiopronine

Aim of treatment= increased solubility



Cys-Cys



merkaptopropionylglycine
(thiopronine)

4-5 L fluids/day
alkalinization

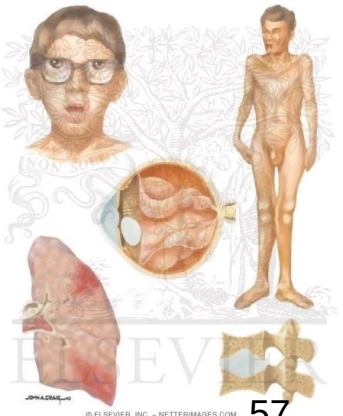
Disorders of metabolism of Tryptophan and Tyrosine

essential AAs, among others. formation of nicotinic acid and serotonin.

Hartnup disease -AR disorder of transporters of neutral AAs in kidney tubules and small intestine

tryptophan deficiency - skin changes

- AR hereditary.
- substrate is abnormal resorption of neutral AAs in the intestine and kidneys.
- usually does not cause any clinical symptoms.
- eventually. photosensitivity of skin is at the forefront



Organic acidurias

Organic acidurias are a group of several tens of diseases with common characteristics: **carboxylic acid excretion in urine.**

Organic acids accumulate in the body during metabolism disorder in particular **amino acids**, as well as fatty acids and carbohydrates, rarely other substances.

Heredity:

- AR

Pathogenesis:

- impairment of cytosolic, mitochondrial or peroxisomal pathway (deficiency of the enzyme, cofactor deficiency)
- accumulation of the substrate before failure

Symptoms:

- are different depending on the type aciduria, often nonspecific
- highly suspicious is strange odor
- often metabolic acidosis
- often hyperammonemia

•**Forms:**

1.Acute neonatal

- •serious impairment of the intermediary metabolism
- •manifests in the first days or weeks of life

2. Running intermittently

- •partial enzyme deficiencies that suffices for the intermediate metabolism under normal conditions
- •stimulus is increased catabolism (eg. operations), increased protein intake, long starvation
- •manifest themselves by attacks of acute encephalopathy, acidosis, hypoglycemia

3.Chronically ongoing

- •less common, progressive, difficult to influence
- •CNS disorders

Organic aciduria investigations within the nationwide newborn screening in the Czech Republic include:

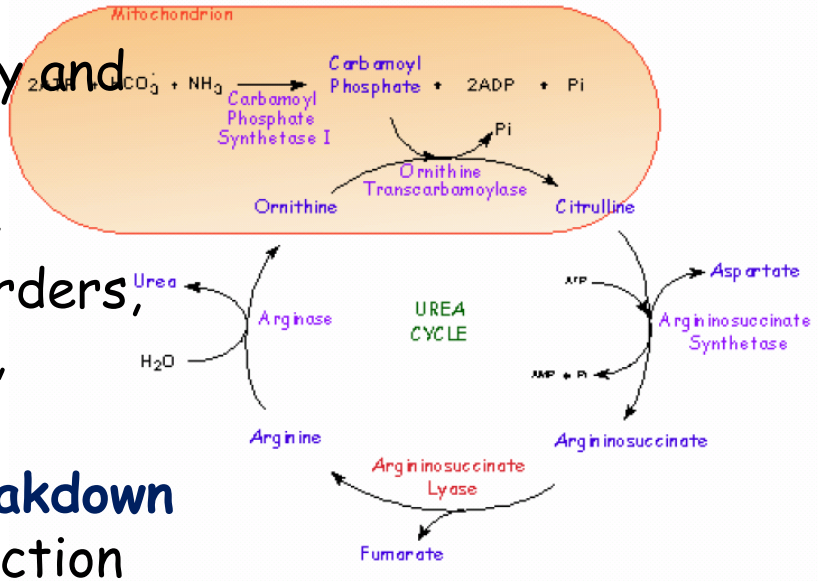
- •glutaric aciduria type I (GA I)
- •isovaleric acidemia (IVA)
- •leucinosis (MSUD)

Glutaric aciduria typ I (GA I)

- belongs among organic acidurias, is caused by the inability of the body to process the amino acids lysine and tryptophan due to deficiency of glutaryl-CoA dehydrogenase. The enzyme glutaryl-coenzymeA dehydrogenase is stored in mitochondria. In the liver, kidney, fibroblasts and leukocytes catalyzes the oxidative decarboxylation of glutaryl-CoA to crotonyl-CoA. Deficiency of this enzyme leads to increased levels of glutaric acid and toxic metabolites.[1]
- Flooding the body with toxic metabolites occurs after increased amount of lysine and tryptophan (eg. In the normal weight loss in the neonatal period, when the breakdown of body protein, child with fever and starvation, when common infections after surgery and in similar stressful situations) .[1]
- GA 1 is AR hereditary disease (gene GCDH- at 19p13.2, OMIM #231670). Since 1. 10. 2009 is part of a nationwide newborn screening in the Czech Republic. Increased C5-DC acylcarnitine testifies for GA I incidence. When GA I is suspected, analysis of organic acids in urine is immediately carried out. Elevated levels of glutaric acid and 3-hydroxyglutaric to confirm the diagnosis. If the analysis does not confirm a diagnosis, specialist DMP considers the analysis of glutarylkarnitine in urine and 3-hydroxyglutaric acid in the blood and cerebrospinal fluid, analysis of enzymes in fibroblasts and molecular analysis of GCDH gene.[1]
- Incidence of GA I: 1:40 000 in white populations and 1:30 000 in Sweden.[1]
http://www.wikiskripta.eu/index.php/Glutarov%C3%A1_acidurie

Urea cycle disorders

group of enzymatic disorders that result in the **accumulation** of **nitrogen in the form of ammonia**, which is **very toxic** for the body and **causes irreversible brain damage**



Hyperamonemia - cramps, vomiting, coma, psychomotor retardation, behavioral disorders, repetitive cerebellar ataxia, headache, metabolic acidosis

Gout (arthritis urika) **defect in the breakdown of purines (uricase)** - excessive production of uric acid. High levels of uric acid in the blood causes crystallisation of this compound in joints and other tissues (inflammation) may cause gout attacks of the joints, kidney stones blockade of urinary tract. The crystals of uric acid may also block tubules of the kidney and cause the kidney insufficiency.

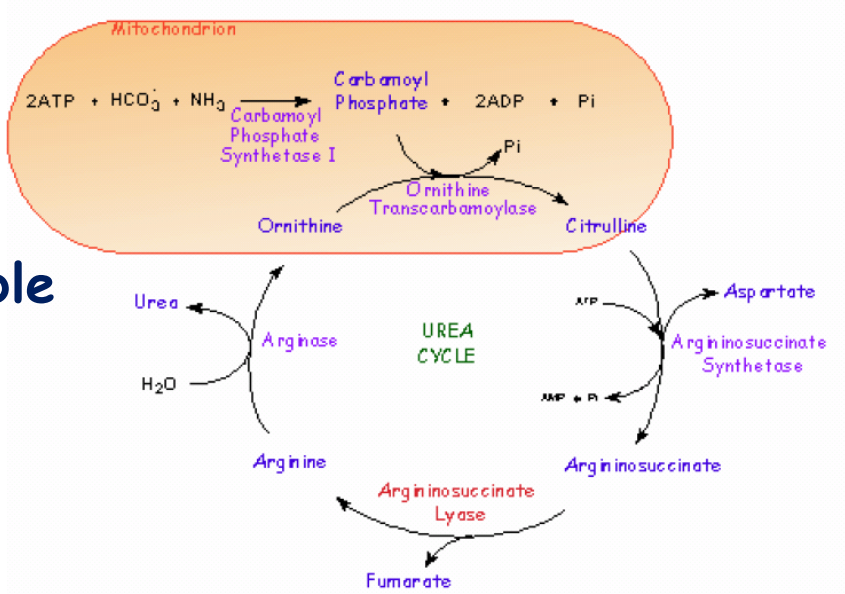
Hyperuricemia - industrialized countries (high intake of purines in the diet, alcohol, obesity, lead in food)

Hyperammonemia I
Hyperammonemia II
Citrulinemia
Argininsukcinateuria
Argininemia

TEST

Urea cycle disorders

group of enzymatic disorders that result in the **accumulation of nitrogen in the form of ammonia**, which is **very toxic** for the body and **causes irreversible brain damage**



Hyperamonemia - cramps, vomiting, coma, psychomotor retardation, behavioral disorders, repetitive cerebellar ataxia, headache, metabolic acidosis

	damaged enzyme	location	heredity type
Hyperammonemia I	**karbamoylphosphatesynthetase (CPS1)**	**mitochondria**	**AR hereditary**
Hyperammonemia II	**ornitinkarbamoyltransferase (OTC)**	**mitochondria**	**X conjugated representation in heterozygous girls**
Citrulinemia	**argininsukcinatesyntetase (ASS)**	**cytosol**	**AR hereditary**
Argininsukcinateuria	**argininsukcinase (ASL)**	**cytosol**	**AR hereditary**
Argininemia	**arginase (ARG1)**	**cytosol**	**AR hereditary**

- **Diagnostics**
- hyperamonemia; hyperamonemia; ABR – first respiratory alkalosis, metabolic acidosis later
- chromatography of amino acids in plasma: increased concentration of glutamine and glutamic acid, decreased level of arginine; increased concentration of amino acids before enzymatic defect and decreased concentrations of the amino acids after defect
- orotic acid in the urine, increased when disorders of all enzymes except CPS1 occurs
- Liver biopsy: determination of the enzymatic activity of liver tissue
- mutations analysis[2]
- **Therapy**
- First aid: **catabolism to anabolism conversion** (even high doses of glucose with insulin, high caloric parenteral nutrition) and detoxification (sodium benzoate, sodium phenylbutyrate, ev. hemodialysis, hemofiltration)
- substitution of the missing amino acids (usually arginine and citrulline)
- lifelong reduction of protein intake and their substitution by a mixture of essential amino acids
- severe impairment leads to **liver transplantation**[2]

Hyperlysinemia - (hyperammonemia) -high conc. Lys in blood, serum -block of enzym **arginase** (in ornithine, urea cycle) - high concentration of NH3 and arginine - illness, mental disability. Related to protein intake, difficulties decrease when restricting the proteins intake.

Hyperprolinaemia I -high values of Pro (low activity of Pro-dehydrogenase) - causes renal malformation, hematuria, renál insuficience = renal failure, decreased hearing, deafness - these disorders = so called Alport syndrome

Hyperprolinaemia II - does not affect the kidneys, slowing growth and mental development