Inherited metabolic disorders / genetic basis

Introduction

- **Congenital metabolic disorders** = Human biochemical diseases; disease states in which a specific genetic enzyme defect causes a metabolic block with pathological consequences
- Most congenital metabolic errors are X-linked inheritance; some are AD inheritance – probably affecting regulators of metabolic processes (membrane receptors and enzymes that catalyze steps depending on the amount of product); their disorder leads to damage to feedback, mutations and subsequent changes in protein structure
- Mutations can manifest themselves as enzymopathy, but they can also affect other mechanism of regulation
- Most metabolic diseases are caused by an **enzyme defect** − the defective enzyme most often has **reduced enzyme activity** compared to its normal counterpart; sometimes the activity is completely absent - the decreased activity is eventually due to reduced affinity for the substrate or cofactor or instability of the enzyme molecule ; sometimes **increased protein activity**, prolonged or shortened biological half-life may be present; sometimes, some changes in the nucleotide sequence may lead to **excessive production of a fully functional protein** (impaired regulation of gene expression or translatio) - protein disorders are therefore both qualitative and quantitative in nature
- Metabolism takes place step by step through a series of reactions, each step being catalyzed by a different enzyme; mutation of one enzyme of the metabolic process leads to accumulation of the precursor and reduction of the amount of product; both can have pathological consequences
- Examples:

defect type	examples of disabilities
enzyme defect	PKU, galactosemia, adenosine deaminase deficiency
receptor defect	testicular ferminization, hypercholesterolemia
molecular transport defect	cystic fibrosis, hypertension
cell structure defect	Duchenne and Becker muscular dystrophy
homeostasis defect	antihemophilic globulin, immunoglobulins
growth and differentiation regulation defect	sex determination, X chromosome inactivation, tumor suppressors
intercellular communication defect	insulin, growth hormone, sex differentiation
mitochondrial defect	Leber's optic atrophy

Enzymopathy

- In total, more than 200 disorders of enzyme function have been described
- **Phenylketonuria** (PKU), **hyperphenylalaninemia** (HPA)
  - disorders of amino acid metabolism
  - PKU = AR inheritance disorder of phenylalnine metabolism with a frequency in the Czech Republic of about 1:6000
  - manifests itself in the gradual development of mental retardation epilepsy and low pigmentation
  - high levels of phenylalanine in the blood, manifested by phenylpyruvic acid in the urine
  - is caused by a mutation in the gene for phenylalanine hydroxylase (PAH), which catalyzes the conversion of phenylalanine to tyrosine
  - Phenylalanine is part of all dietary proteins and, if not metabolised by tyrosine in patients with PKU, accumulates in body fluids and impairs myelination of developing nerve fibers.
  - part of phenylalanine is converted by phenylalanine aminotransferase into phenylpyruvic acid, which is excreted to a greater extent in the urine and gives it a mouse odor; there is less tyrosine in body fluids and fewer products of its metabolism in the body
  - it manifests itself only after birth
  - in pregnacy, excess fetal phenylalanine is drained by the placenta; with the first doses of milk drunk, the level of phenylalanine in the newboen's blood rises
  - a diet with a very low content of phenylalanine and the addition of tyrosine can affect the level of phenylalanine in the blood and ensure almost normal psychomotor development of the child
  - the basis of successful treatment is early diagnosis
  - the diagnosis can be made by screening: on the 5th day of the life, blood is taken; if PKU is suspected, the newborn is hospitalized immediately
  - for women with PKU, another critical period of their mother's life is; during pregnancy, the placenta concetrates many times phenylalanine in the fetal's blood - if a woman does not follow a strict diet, the level of phenylalanine will impair the development of the fetus, regardless of its genotype; the result of

the so-called maternal PKU are metnal retardation, microcephaly, congenital heart defects
- gene of PAH located on chromosome 12q24.1 using mRNA probes isolated from the liver cells; is 90 kb long and has 13 exons
- more than 170 different mutations in the PAH gene have been described; 4 prevail in the Czech Republic, the most common is R408W (60%); the mutation changed codon 408 in exon 12 so that instead of arginine (R) ir encodes tryptophan (W)
  - the highest frequency of mutations is in Belarus - it is therefore considered a Slavic mutation; the other most common in the Mediterranean and R261Q in exon 5 and 7
  - another type is the second most common IVS12ny1 mutation; affects the 12th intron and changes the splice site; the mutation is most abundant in Denmark
- most people with PKU are composed of heterozygotes; the severity of clinical manifestation is related to the combination of mutagenic alleles in the genome; for example, mutations R408W, IVS12nt1 and R158Q condition classical PKU with virtually zero PAH activity, but mutation R261Q conditions benign hyperphenylalaninemia (HPA); PAH activity is partially maintained and blood phenylalanine levels are significantly lower than in classical PKU (less than 1mM); The psychological development of children with HPA is adequate even without a diet treatment, but the fetus of women with HPA without a diet treatment during pregnancy is as damaged as the fetus of women with classic PKU
- DNA analysis aloows the detection of heterozygotes and prenatal examination of the fetus of heterozygous parents, the examination of the fetus is performed from trophoblast cells or amniotic fluid; DNA analysis can presymptomatically diagnose PKU, but also determine the severity of the disease and the method of treatment
- PKU is one of the candidates for gene therapy; the PAH gene was successfully transferred into mouse hepatocytes
- in some newborns with a higher level of phenylalanine in the blood, the condition is later adjusted and they do not need a diet treatment = so-called transient form of PKU with delayed expression of the PAH gene in liver cells
- diet treatment is not effective in 1-3% of children; PKU caused by mutation of genes for PAH cofactor synthesis - tetrahydrobiopterin (BH1) - for dihydrobiopterin synthetase and dihydropteridine reductase was demonstrated - more complicated treatment

Recepotors and their disorders

- receptor dysfunction - proven to be one of the causes of familial hyperlipidemias (**familial hypercholesterolemia**, FH) = zelevated plasma cholesterol. triglycerides or both; hyperlipidemias are significantly involved in the development of atherosclerosis and subsequently MI
- dietary fats are absorbed in the small intestine; much more cholesterol is synthesized de novo in the liver
- fats are insoluble in water and blood and are therefore transmitted and distributed in the body in binding with proteins
- lipoproteins = spherical formations composed of apolipoproteins that solubilize fats and bind specifically to fat cell receptors; There are 9 types of apolipoproteins: fats are transferred from the gut by chylomicrons (CM) to liver cells and tissues
- CMs ncontain mainly apolipoprotein B-48; in tissues lipase breaks down triacylglycerols into glycerol and fatty acids, which cells use as an energy source
- in liver cells, CM fats are metabolized and, together with de novo-synthesized cholesterol, incorporated into VLDL with apolipoprotein B-100 and E and transported to tissues
- in tissues, lipases cleave triacylglycerols from VLDL and convert them to LDL, mainly cholesterol
- LDL can penetrate cells through LDL receptors on the cell surface
- cells use cholesterol as a precursor of other metabolites; LDL uptake by liver cell LDL - receptors inhibits cholesterol neosynthesis; in excess, cholesterol is transferred from the tissues to the liver as HDL
- bound to HDL liver cell receptors and metabolized

- Familial hypercholesterolemia; FH = nincompletely dominant inherited disease with elevated plasma cholesterol levels, heterozygotes have 7 –15 mmol/l (normally about 5 mmol/l); incidence 1: 500; homozygotes have more than 20 mmol/l and may be affected by MI as early as childhood and adolescence; **LDL receptor** (LDLr) mutations are the most common cause of FH
- the LDLr gene is located on chromosome 19q13.3 (it has 45 kb, 18 exons and 5.3 kb mRNA transcript), mutations in different exons differ in their phenotypic expression; mutations can completely block LDLr, disrupt mRNA splicing, disrupt receptor binding in the membrane or transport of the complex into the cytoplasm and its processing in lysosomes
- another type of FH - conditioned by mutation of **APOB** gene for **apoB-100** (chromosome 2p23, gene is 43 kb long, has 29 exons, 14 kb mRNA – very long transcript due to gene length) • changes in apoB-100 affinity to LDLr due to mutation
- special expression of the APOB gene is so-called mRNA editing • apoB-100 is produced in the liver • 6666 bases of the APOB gene transcript are deaminated in intestinal cells • by changing the codon from CAA to UAA (stop codon) apoB-48 typical of chylomicrons is created
- another example of an APOB mutation is a codon 2488 mutation, causing a change in AMK causing low blood cholesterol
- another hereditary change in fat metabolism is caused by, for example, AR inherited cholesterol transferase deficiency - it transports cholesterol betwen different carriers (apolipoproteins) • decreased HDL levels and increased LDL and VLDL levels• greater risk of atherosclerosis

Disorders of molecular transport

- **cystic fibrosis** (CF) = AR inherited disease and incidence in neonates 1:1600 –1: 2500
- CF affects the function of exocrine glands; insufficient secretion of the digestive enzymes of the pancreas causes thickening of the stool and obstruction of the intestines (meconium ileus) in newborns and digestive disorders in children; there is a higher concentration of chlorides in the sweat; mucus in the respiratory tract is viscous, difficult to cough and this is the cause of recurrent chronic infections of the respiratory tract and lungs; men tend to be sterile and women have reduced fertility
- death in 20-30 years due to changes in lung tissue after repeated infections and heart failure due to increased resistance to the pulmonary bloodstream
- CF gene – CFTR – bwas located on chromosome 7q31, is expressed in epithelial cells
- the product is a 1480 AMK protein with all domains doubled; CF is a real candidate for gene therapy
- 50–80 % of CFTR gene mutations are due to deletion of 3 bases in exon 10, encoding the 1st ATP-binding domain, mutation causes phenylalanine deletion = deltaF508 mutation causes severe CF
- CFTR is already degraded in the ER and is not incorporated into the plasma membrane at all
- CF patients are often heterozygous
- symptomatic treatment is focused on the substitution of exocrine secretion of the pancreas, on the liquefaction of the secretions of the respiratory glands, on the prevention and treatment of respiratory tract infections

Cell structure defect

- **Duchenne muscular dystrophy** (DMD) and **Becker muscular dystrophy** (BMD) – X-linked recessive inherited diseases; affecting skeletal muscles and, to a lesser extent, cardiac and smooth muscle.
- patients with DMD after childbirth without problems, during childhood there is weakness of the muscles of the lower limbs, **the calves are hypertrophic** (fat pseudohypertrophy),CNS involvement is manifested by a decrease in IQ by an average of 20 points, muscle weakness gradually worsens, so in adolescence there are patients confined to a wheelchair and dying under the age of 20 from heart failure or breathing; serum creatine kinase levels are elevated in those affected; in a muscle biopsy, color changes in muscle fibers
- in female carriors, the manifestation is affected by X chromosome inactivation – they may have mild muscle problems, elevated serum creatine kinase and histologically demonstrable involvement of some muscle fibers
- DMD in women is rare, affecting women with karyotypes 45,X (Turner syndrome) event. 46,XY (testicular ferminization) or with deletion of the short arms of the X –chromosome
- BMD is milder, with later onset of clinical manifestations, slower progression, and allows survival into old age; the population frequency is around 1:3500, of which 10-15% is maintained by a high frequency of new mutations; one third of cases are due to new mutations
- DMD gene is the largest known gene in humans - located on Xp21 - has 2.3 kb, more than 75 short exons, introns make up))% of the gene's length
- most mutations are due to deletions of one or more exons - most of these deletions accumulate at the 5´ end of the gene and in the 44-50 region. Exon; DMD and BMD do not differ in the location of mutations; more severe cource of DMD is conditioned by the shift of the reading frame, in BMD the deletion affects whole exons or triplets and there is no shift of the reading frame
- the transcription gene which is mRNA longer than 11 kb and the translation product is dystrophin with 3685 AMK, dystrophin is localized in the cytoplamic membrane of muscle cells, stabilizes the membrane and anchors actin molecules in the cytoskeleton

Differentiation regualtion

- the male sex is determined by a combination of XY heterochromosomes
- in the presence of more than one X choromosome, the other and another X chromosome in the nucleus are 15-16. After fertilization, it is spiralized (creates a sex-chromatin mark) and most of its genes are inactivated, thus compensating for the imbalance in the number of X-chromosomes in women and men
- in women with translocation of part of the X-chromosome to autosomes , only onr part of its parts is inactivated - studies have shown an X inactivation center on the X chromosome
- the gene is located in the region Xq13.2 = so-called XIST - is 17 kb long; the transcription can be detected in the nuclei of cells with more than one X chromosome; the transcription never penetrates the cytoplasm and thus never translates
- in male determination: SRY gene was located in close proximity to the pseudoautosomal part of the Y chromosome, the gene is 2.1 kb and is highly conserved; its translocation to the X chromosome conditions findings 46, XX in men with the Klienefelter syndrome phenotype
- SRY is homologous to non-histone nuclear proteins, it binds to the promoter of the cytochrome-P450-aromatase gene, which converts testosterone to the female hormone estradiol.
- inactivation of the SRY gene in the embryo determines the male sex
- SRY protein binds to the promoter of the Muller inhibitory substance gene, its inactivation of the male embryo causes differentiation of testes and regression of female organs
- the SRY gene product acts as a transcriptional regulator, it contains no introns and ends with a sequence for the polyadenil end of the mRNA

Mitochondrial diseases

- mitochondria contain free nucleosome and free nuclear membrane -free circular DNA (mtDNA); they obtain energy by oxidative phosphorylation of sugars and fats and transfer it to cellular metabolism in the form of macroergic phosphate bonds ATP
- each mitochondria contains multiple copies of DNA
- it is actually the 24th chromosome of the human genome

- they arise by autoreplication and break down into daughter cells during mitosis; the zygote is equipped only with maternal mitochondria; sperm has one mitochondria, but it is destroyed after fertilization
- mtDNA mutations are inherited matroline and their manifestations are accentuated by age
- mtDNA mutations affect oxidative phosphorylation and therefore manifest themselves primarily in energy-sensitive tissues
- **Leber's atrophy optics**, bilateral blindness in adulthood
- defects in the structure and fuction of mitochondria can also be caused by mutations in nuclear DNA and inherited in the classical Mendelian law

Genes with an unknown mechanism of action

- **fragile X syndrome** (fra-X),
  - mental retardation of various degrees; frequency in men 1:1250, characteristic facial appearance - protruding long ear lobes, elongated rough face and large testes,
  - fragile site on the X chromosome in the Xp27.3 localization - FMR1 gene; inherited recessively in connection with the X chromosome, 30% of female carriers are mildly mentally retarded but without somatic changes, 20% of men with cytogenetically proven fra-X are carriers without clinical symtoms, daughters of these carriers are healthy, but sons and grandchildren of these daughters they may be mentally handicapped =so-called Sherman paradox

- in healthy men; carriers with cytognetically demonstrable fra-X, the number of CGG triplets is 52 - 200 =so-called premutation, if triplets have increased (premutation), it is very probable that triplets will increase and full mutation with clinical manifestations will occur;

- during mutation transmission by women, formation of full mutation, multiplication of CGG triplets up to 4000

- another sequence of CGG triplets was discovered near the described fragile site with the possibility of multiplication and manifestations of X chromosome fragility and oligophrenia =so-called FRAXE – is 600 kb away from FRAXA (FMR1)

- in the gene for myotonic dystrophy (19q13.2-3) a polymorphism of the number of GCT triplets was found,in Kennedy's disease (spinal and bulbar muscular atrophy) and in spinocerebellar ataxia a polymorphism of CAG triplets; the number of CAG triplets determines who will be affected by Huntington's disease (HD) – AD (4p16.3), nat the beginning of the gene for HD (IT15) we find 40 or more than 100 CAG triplets (normal 11 – 34)

- for all these diseases there are deviations from the basic rules of monogenic inheritance, when transmitted from the generation there is anticipation on the generation
- in subsequent generations the trait manifests earlier and genomic imprinting
- when transmitted from a parent of one sex the manifestation is earlier than when transmitted from a parent of the other sex

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