Disorders of amino acid metabolism

http://plantandsoil.unl.edu/croptech2005/UserFiles/Image/siteImages/AminoAcidLG.gif
General comments on AA metabolism
Disorders of aromatic AA metabolism
Disorders of branched chain AA metabolism
Disorders of sulfur metabolism
Disorders of propionate, B12 and biotin metabolism
Urea cycle disorders
Other disorders of AA metabolism and defects in creatine synthesis
# Energy stores

<table>
<thead>
<tr>
<th>Energy store</th>
<th>tissue</th>
<th>amount (g)</th>
<th>energy (kj)</th>
<th>(kcal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycogen</td>
<td>liver</td>
<td>70</td>
<td>1176</td>
<td>280</td>
</tr>
<tr>
<td>Glycogen</td>
<td>muscle</td>
<td>120</td>
<td>2016</td>
<td>480</td>
</tr>
<tr>
<td>Glucose</td>
<td>blood</td>
<td>20</td>
<td>336</td>
<td>80</td>
</tr>
<tr>
<td>Triacylglycerols</td>
<td>fat</td>
<td>15 000</td>
<td>567 000</td>
<td>135 000</td>
</tr>
<tr>
<td>Proteins</td>
<td>muscle</td>
<td>6000</td>
<td>100 800</td>
<td>24 000</td>
</tr>
</tbody>
</table>

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

Phospho-enol pyruvate

Oxaloacetate

Fumarate

Succinyl-CoA

Pyruvate

Acetyl CoA ↔ Acetoacetyl CoA

α-Ketoglutarate

Asparagine
Aspartate
Phenylalanine
Tyrosine

Isoleucine
Methionine
Valine

Alanine
Cysteine
Glycine
Serine
Threonine
Tryptophan

Isoleucine
Leucine
Tryptophan

Leucine
Lysine
Phenylalanine
Tryptophan
Tyrosine

Arginine
Glutamate
Glutamine
Histidine
Proline

http://www.natuurlijkerwijs.com/english/b5e55bf0.gif
Protein requirements

Protein intake
Patients with disorders of AA metabolism

incidence of aminoaciopathies for ČR ~ 1:3000
  ~ 20 patients with HPA/PKU
  ~ 30 patients with other AA/OAU
Patophysiology IEM

substrate

1

<1500 Da

2

product

3

<1500 Da
Aminoacidopathies—most common mechanisms

- Accumulation of AA
- Ammonia accumulation
- Carbon skeleton accumulations—organic acids
- Product deficiency
Disorders of aromatic amino acid metabolism
PAH

Tyrosine

p-Hydroxyphenylpyruvate

Homogentisate

Acetoacetate

Fumarate

4-Fumarilacetoacetate

4-Maleylacetoacetate

Tyrosine-transaminase

p-Hydroxiphenoxyphenylpyruvate-dioxygenase

Homogentisate-dioxygenase

Maleylacetoacetate-cis-trans-isomerase

http://www.chemie.fu-berlin.de/chemistry/bio/aminoacid/gif/phe.gif
Phenylketonuria

http://www.chemie.fu-berlin.de/chemistry/bio/aminoacid/gif/phe.gif
Untreated HPA/PKU

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

http://www.dshs.state.tx.us/newborn/images/PKU_untreated.jpg
Classical dietary treatment of PKU

Prof. Horst Bickel


http://www.milupa-metabolics.com/produkte.php?sourceId=162&sysId=139
Dyfsunkce enzymu při nedostatku kofaktoru

Těžké mutace PAH
Lehké mutace PAH
Deficit BH4

*Error bars indicate 95% confidence interval.*
Tyrosinemia 2

PAH

Tyrosine → Tyrosine-transaminase → p-Hydroxyphenylpyruvate → p-Hydroxiphenylpyruvate-dioxygenase → Homogentisate

Homogentisate-dioxygenase → Homogentisate

Acetoacetate → 4-Fumaryl-acetoacetate → 4-Fumarylacetoacetate → Maleylacetoacetate

Maleylacetoacetate-cis-trans-isomerase → 4-Maleylacetoacetate

http://www.chemie.fu-berlin.de/chemistry/bio/aminoacid/gif/phe.gif
Tyrosine

Tyrosinemia type 2

hyperkeratosis

herpetiformic keratitis

http://www.ijo.in/articles/2007/55/1/images/IndianJOphthalmol_2007_55_1_57_29497_2.jpg
http://208.96.47.3/images/community/dermatlas/Tyrosinemia_type_2_2_041213.png
Tyrosinemia type 2

- very rare
- herpetiformic keratitis
- palmoplantar hyperkeratoses with ulcers
- PMR, growth retardation
- dietary treatment
Alkaptonuria

PAH

http://www.chemie.fu-berlin.de/chemistry/bio/aminoacid/gif/phe.gif
Coxarthrosis
Valvular
involvement
Urolithiasis

Harwa, 1500 př.n.l.
Alkaptonuria treatment - artificial block above the enzyme block

What are the possible therapy complications?

http://www.natuurlijkkerwijs.com/english/b4f4ca00.gif
PAH

Tyrosinemia 1

Tyrosine

\[ \text{Tyrosine} \xrightarrow{\text{Tyrosine-transaminase}} \text{p-Hydroxyphenylpyruvate} \]

\[ \text{p-Hydroxyphenylpyruvate} \xrightarrow{\text{p-Hydroxylphenylpyruvate-dioxygenase}} \text{Homogentisate} \]

\[ \text{Homogentisate} \xrightarrow{\text{Homogentisate-dioxygenase}} \]

\[ \text{Acetoacetate} \xrightarrow{4\text{-Fumarilacetoacetate}} \text{4-Fumarilacetoacetate} \]

\[ \text{Fumarate} \xrightarrow{4\text{-Maleylacetoacetate}} \text{4-Maleylacetoacetate} \]

http://www.chemie.fu-berlin.de/chemistry/bio/aminoacid/gif/phe.gif
Tyrosinemia type I

- Fumarylacetoacetase deficiency
- Acute manifestation in infancy
- Hepatorenal involvement with acute hepatic dysfunction and Fanconi syndrome
- Porphyric crises - abdominal cramps
- Chronic - ci heatis and ca in cirhosim
- Diet, nitisone, liver transplant
Tyrosinemia type I
Alkaptonuria a tyrosinemia 1 treatment

nitison (NTBC)
Disorders of branched chain amino acids
BCAA

Valine  
Leucine  
Isoleucine

http://www.agron.iastate.edu/courses/Agron317/Images/Branched_chain_aa.jpg
How To Achieve A Positive Nitrogen Balance And Why You Care

By Fitness Atlantic Writer: Mike Westerdal

http://www.fitnessatlantic.com/how_achieve_nitrogen_balance.htm
Leucinosis/maple syrup urine disease
MSUD

- Peracute presentation in newborns, intermittent variants
- Coma, dystonia-boxing, cycling
- Maple syrup odour
- Acute crisis prevention and management
- Long term treatment-diet

http://losyoruguas.com/archivos/0686.gif
Psychomotor development - MSUD

![Graph showing average IQ with standard deviation for different age groups with symptoms onset.](Image)
Isovaleric acidemia

Leucine Metabolism in Isovaleric Acidemia

1-Leucine → 2-Ketoglutarate Transaminase → 2-Ketoisocaproic Acid → Branched Chain Ketoacid Decarboxylase → Isovaleryl-CoA

Glycine-N-Acylase/Acetyltransferase

Isovaleryl-CoA → Oxidation/De-esterification

↓ 3-Methyl-Crotonyl-CoA

Isovaleryl-CoA → 3-Hydroxyisovaleric Acid, Isovaleric Acid

* Isovalerylglycine
* Isovaleryl carnitine

* Toxic metabolites
‡ Nontoxic and excreted in the urine

Source: South Med J © 2003 Lippincott Williams & Wilkins
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

Disorders of sulfur amino acid metabolism
Remethylation

- S-AdoMet → MG
- S-AdoHcy
- Methionine
- THF
- DMG
- Betaine
- Cystathionine
- Cysteine
- L-gamma-glutamylcysteine
- Glutathione
- SO₃²⁻ → SO₄²⁻
- Taurine
- Hypotaurine
- Cysteinesulfinate
- H₂S
- Cysteine
- Methylenetetrahydrofolate (MTHF)
- Methyltetrahydrofolate (MTHF)
- Tetrahydrofolate (THF)
- Serine (Ser)
- Glycine (Gly)
Methylene-THF → THF → Methyl-THF → Methyl-THF

Ser → Gly

THF → DMG → S-AdoMet → MG

S-AdoHcy → Betaine

Methionine

Homocysteine → Cystathionine → Cysteine → L-gamma-glutamylcysteine

Cysteinesulfinimate

H₂S → Cysteine

Glutathione

SO₃²⁻ → SO₄²⁻

CysGly

Hypotaurine → Taurine
Vitamins and Hcy metabolism

- S-AdoMet
- S-AdoHcy
- Homocysteine
- Cystathionine
- Cysteine
- THF
- Methionine
- DMG
- Betaine
- Cysteinesulfinic acid
- Hypotaurine
- Taurine
- L-gamma-glutamylcysteine
- Glutathione
- CysGly
- Ser
- Gly
- Methylenethen
- Methyl-THF

Vitamins:
- Folates
- B12
- B2
- B6

Chemical reactions:
- $\text{SO}_3^2 \rightarrow \text{SO}_4^2$
CBS deficiency

- frequency 1:6,000-1:900,000
- classical and mild forms
- clinical triade
  - Connective tissue: marfanoid features, kyfoskoliosis, osteoporosis, lens luxation
  - hemokoagulation: thromboses
  - CNS: cognitive impairment, seizures

- therapy: low Met diet, pyridoxine as a chaperone, betaine to enhance remethylation

16L -antikoncepce
náhlá cefalea, trombóza mozkového splavu
Remethylation homocystinurias

- About 10 diseases
- Low Met a low SAM
- Severely impaired myelinization
- Neurological sequelae
- Thrombosis
- Therapy - betaine, Met, SAM
Cystine
1810 Wollaston- bladder stone (Greek cystos)- „cystic oxid“

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

merkaptopropionylglycine (thiopronine)

Cys-Cys

4-5 L fluids/day alkalinization
Adult cystinosis

Cystinosis

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

- defect of lysosomal transporter cystinosin
- infantile form: Fanconi syndrome-severe tubulopathy
- FTT
- adult forms: ocular involvement, myopathy, hypothyreosis
- Rx- cysteamine locally and systematically
Disorders of propionate, cobalamin, folate and biotin metabolism
Folic acid and derivatives

6-Methylpteridin

p-Aminobenzoic acid (PABA)

Glutamic acid

Pteroylglutamic acid (Folic acid)

Folic acid

5-Methyltetrahydrofolate

5, 10-Methyltetrahydrofolate

7-Methyltetrahydrofolate

10-Formyltetrahydrofolate

Tetrahydrofolate
Origin and daily requirements

Daily folate requirements (µg/d, FAO)

- Infants 60
- Children 160-300
- Adults 400
- Pregnancy 600

Plant synthesis
Transport and metabolism of folates

- Folate monoglutamate
- Folate polyglutamate
- Folate deconjugase
- Folate carriers

Stomach

Proximal small intestine

Pancreas

Mid small intestine

Distal small intestine

Membrane

GGH

FPGS

One-carbon transfer reactions

: RFC1

: Folate

: FOLR1

: Glutamate

www.nature.com/.../v98/n9/thumbs/6604346f5th.jpg
http://www.ivis.org/images/advances/rc/chap03/fig4_xl.jpg
http://www.down-syndrome.org/updates/2051/updates-2051-Fig1-600w.jpg
Transport and metabolism of folates
Primary defects

- **Rare conditions**
  - FolR1 deficiency
    - Autoantibodies against FolR1 (nongenetic)
  - PCFT deficiency (=hereditary folate malabsorption)
  - MTHFR deficiency
- **Clinical findings**
  - Neurological impairment: psychomotor retardation, seizures, hypomyelination, brain atrophy
  - Hematological findings: PCFT- megaloblastic anemia
  - Laboratory tests: normal S-folates in FolR1, hypogamaglobulinemia in PCFT, low csf folates in all defects
Folates and complex diseases

- Epidemiological evidence
  - Case control/prospective studies
  - Folate intake and/or folate concentration
  - Range of effects: OR/RR between ~0.3 and 1.0

- Diseases studied
  - NTD
  - Cancer
  - Atherosclerosis
  - Cognitive impairment/dementia

- Etiology of low folate status
  - Diet/ gastrointestinal problems
  - Genetics largely unknown
Vitamin B12

- complicated synthesis
- exogenous intake needed
- implied in only 2 reactions
- nutritional or endogenous deficiency is common
  - pregnancy and lactation
  - advanced age
  - GIT disorders
- long latent course
  - anemia
  - demyelinization
  - psychiatric manifestation
- treatment efficient and cheap
Resorpce kobalaminu
Intracellular B12 mtbl

http://www.biochem.med.umich.edu/files/2008-student-photos/cracan.figure.jpg
Amino acids (~50%)
Odd-chained fatty acids (~30%)
Propionate (gut-flora derived) (~20%)
Other (small)

Minor pathways of catabolism

Propionyl-CoA Carboxylase

Biotin, ATP, HCO₃⁻

D-Methylmalonyl-CoA Racemase
D-Methylmalonyl-CoA Hydrolase

L-Methylmalonyl-CoA
Adenosylcobalamin
Methylmalonyl-CoA Mutase

Succinyl-CoA

Krebs (TCA) Cycle

Energy
Amino acids
Glucose
Biosynthesis

Peritoneal dialysis in PA

http://www.metagene.de/program/d.prg?id_d=18
Propionic acidemia

- newborn variant: episodes of ketoacidosis/hyperammonemia, coma, pancytopenia
- milder forms: repeated encephalopathic crises, FTT
- chronic problems: FTT, infections, variable CNS involvement
- therapy: IMTV restriction, gut sterilization, biotin in some patients, aggressive treatment of crises, gastrostomy, liver transplant

http://www.uchsc.edu/cbs/images/fig2.JPG
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 patients B12, aggressive treatment of acute episodes

Biotinidase deficiency

Biotinidase deficiency

- Various degree of BTD deficiency
- Impaired breakdown of biocytin and thus biotin incorporation
- Multiple carboxylase deficiency
- Eczema, seizures, PMR
- Miraculous response to biotin administration

http://www.rug.nl/umcg/faculteit/disciplinegroepen/kindergeneeskunde/liverdigestivemetabolicdiseases/enzyme/images/biotinidase-grafiek.jpg
Urea cycle disorders
Ammonia

- ammonia cation normal level 50-70 µmol/l
- somnolence above cca 150 µmol/l
- coma above 300-400 µmol/l
Hyperammononemia is a medical emergency.
# Urinary nitrogen excretion

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>g 24 h*</th>
<th>% total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea</td>
<td>30</td>
<td>86</td>
</tr>
<tr>
<td>Ammonia ion</td>
<td>0.7</td>
<td>2.8</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.0-1.8</td>
<td>4-5</td>
</tr>
<tr>
<td>Uric acid</td>
<td>0.5-1.0</td>
<td>2-3</td>
</tr>
</tbody>
</table>
### Table 85-5  Estimation of the Incidence of Each Urea Cycle Disorder Based on Its Incidence Relative to Argininosuccinase Deficiency

<table>
<thead>
<tr>
<th>Enzyme Deficiency</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamyl phosphate synthetase</td>
<td>1 per 62,000</td>
</tr>
<tr>
<td>Ornithine transcarbamylase</td>
<td>1 per 14,000</td>
</tr>
<tr>
<td>Argininosuccinate synthetase</td>
<td>1 per 57,000</td>
</tr>
<tr>
<td>Argininosuccinase</td>
<td>1 per 70,000</td>
</tr>
<tr>
<td>Arginase</td>
<td>1 per 363,000</td>
</tr>
<tr>
<td>All urea cycle disorders</td>
<td>1 per 8200</td>
</tr>
</tbody>
</table>

# OTC-clinical variability

## Table 85-6 Distribution of Cases of Ornithine Transcarbamylase Deficiency

<table>
<thead>
<tr>
<th>Distribution</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal onset</td>
<td>134</td>
</tr>
<tr>
<td>Late onset</td>
<td>200</td>
</tr>
<tr>
<td>Males</td>
<td></td>
</tr>
<tr>
<td>&lt; 18 yr</td>
<td>61</td>
</tr>
<tr>
<td>&gt; 18 yr</td>
<td>5</td>
</tr>
<tr>
<td>Females</td>
<td></td>
</tr>
<tr>
<td>&lt; 18 yr</td>
<td>102</td>
</tr>
<tr>
<td>&gt; 18 yr</td>
<td>21</td>
</tr>
<tr>
<td>Unknown age</td>
<td>11</td>
</tr>
<tr>
<td>Total cases</td>
<td>334</td>
</tr>
</tbody>
</table>

Lethality of OTC

Fig. 85-31 Long-term survival of 40 infants who survived their neonatal hyperammonemnic episode. Each small square represents length of time surviving patients were monitored (time until they were censored). Patients were censored at their age of orthotopic liver transplantation, when they were lost to follow-up, or when this study ended.
Scylla and Charibda
Other disorders of amino acid metabolism and creatine synthesis disorders
Glutaric aciduria type 1
Prolidase deficiency

- abnormal recycling of Pro into collagen-
  urinary loss of iminodipeptides
- secondary immune defects
- ulcers and typical facial appearance
- PMR, splenomegaly, bone changes, mikrocytic anemia
- therapy local, systemic proline administration

http://dermatology.cdlib.org/127/case_presentations/prolidase/2.jpg
Hyperornithinemia

- OAT deficiency
- late onset 3rd-4th decade-night blindness
- gyrate atrophy of retina
- treatment with pyridoxine and dietary restriction of Orn

The retina of a patient with gyrate atrophy of the choroid and retina of the eye caused by ornithine aminotransferase (OAT) deficiency. [Image credit: Muriel Kaiser-Kupfer, NEI, NIH, Bethesda, MD, USA and David Valle, Johns Hopkins University, Baltimore, MD, USA.]

Creatine metabolism
Enzymes:
AGAT = L-Arginine:glycine amidinotransferase
GAMT = S-adenosyl-L-methionine:N-guanidinoacetate methyltransferase
IEMs in creatine biosynthesis and transport

- GAMT deficiency (MIM 601240) ~ 60 Pt * 2008
  1994 (Stöckler et al)

- AGAT deficiency (MIM 602360) 7 Pt *
  2001 (Item et al)

- CRTR deficiency (MIM 300036) > 150 Pt *
  2001 (Salomons et al)
In vivo metabolite determination

Creatine deficiency in brain (MRS)

Před léčbou

Po léčbě
## Biochemical and clinical findings

<table>
<thead>
<tr>
<th></th>
<th>H-MRS</th>
<th>GAA U,P,CSF</th>
<th>CR U,P</th>
<th>CR/CRN U</th>
</tr>
</thead>
<tbody>
<tr>
<td>GAMT</td>
<td>↓↓</td>
<td>↑↑</td>
<td>↓</td>
<td>—</td>
</tr>
<tr>
<td>AGAT</td>
<td>↓↓</td>
<td>↓↓</td>
<td>(↓) n(U)</td>
<td>—</td>
</tr>
<tr>
<td>CRTR</td>
<td>↓↓</td>
<td>n</td>
<td>(↑)</td>
<td>↑*</td>
</tr>
</tbody>
</table>

- Clinical findings: developmental delay, various neurological problems, delayed speech, seizures
## Therapy

<table>
<thead>
<tr>
<th></th>
<th>deficiency correction</th>
<th>correction of accumulation</th>
<th>alternatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>GAMT</td>
<td>supplement CR</td>
<td>restriction ARG</td>
<td>supplement ORN</td>
</tr>
<tr>
<td>AGAT</td>
<td>Supplement CR</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CRTR</td>
<td>supplement CR, ARG GLY*</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Aminoacidopathies-mechanisms

- Amino acid accumulation
- Ammonia accumulation
- Carbon skeleton accumulation - organic acids
- Product deficiency