# Hereditary disorders of amino acid metabolism / Questions and case reports

## Questions

1. **Which amino acids are mainly taken up by the kidneys?**
   - A – glycine
   - B – arginine
   - C – alanine
   - D – glutamic acid
   - E – glutamine
   - F – leucine
   - G – histidine
   - H – tyrosine
2. **Which amino acids does the muscle supply to the bloodstream in the largest amount?**
   - A – glycine
   - B – arginine
   - C – alanine
   - D – Glutamic acid
   - E – glutamine
   - F – leucine
   - G – histidine
   - H – tyrosine
3. **Enzyme defects in the urea cycle lead to brain disorders. What is the cause?**
   - A – Hyperammonemia
   - B – Formation of atypical amino acids
   - C – Increased formation of biogenic amines
   - D – Hyperuricemia
   - E – Hypoglycemia (glukoneogenesis from amino acids is reduced)
4. **Which amino acids are not nutritionally essential??**
   - A – Methionine
   - B – Phenylalanine
   - C – Cysteine
   - D – Tyrosine
   - E – Leucine
   - F – Isoleucine
   - G – Valin
   - H – Threonine
5. **Which amino acids are not glucogenic?**
   - A – Isoleucine
   - B – Leucine
   - C – Histidine
   - D – Cystine
   - E – Lysine
   - F – Valin
   - G – Tryptophan
6. **Tyrosine is a precursor for the synthesis of:**
   - A – Noradrenaline
   - B – Adrenaline
   - C – Melanin
   - D – DOPA
7. **The key intermediate metabolites for cysteine synthesis in the liver are:**
   - A – Argininosuccinate
   - B – Homoserine
   - C – Glutamic acid semialdehyde
   - D – Cystathionine
   - E – Xanthurenic acid
8. **The mechanism of renal creatinine exrecion is:**
   - A – In glomerular filtration (without tubular secretion or tubular reverse resorption)
   - B – In glomerular filtration and in a small proportion of tubular secretion
   - C – In glomerular filtration and tubular reverse resorption
   - D – In tubular secretion
9. **In prerenal uremia, it is**
   - A – Increased creatinine in proportion to increased urea
   - B – Increased urea and creatinine at the upper limit of normal
   - C – Increased creatinine and urea at the upper limit of normal
   - D – Creatinine and urea only at the upper limit of normal..

**Answers**

**Question 1.**

- A – wrong
- B – wrong
- C – wrong
- D – wrong

- E – Correct. Glutamine is taken up by the kidney, which also forms in the kidney from glutamate and NH4 +.

- F – wrong
- G – wrong
- H – wrong.

**Question 2.**

- A – Wrong. Glycine is formed in a number of tissues. Most in the liver (involving glycinaminotransferase, which catalyzes the transfer of amino groups from glutamate or alanine to glyoxalate)
- B – Wrong - Arginine is formed mainly in the liver as part of the ureagenetic cycle.

- C – Correct. Alanine is excreted from the muscles into the circulation in relatively large amounts (50% of all amino acids). It undergoes oxidative deamination in the liver and produces pyruvate, which is a major substrate of gluconeogenesis.

- D – Wrong.

- E – Correct. Glutamine is also released by the muscle in relatively large amounts.

- F – Wrong. Branched chain amino acids, including leucine, are taken up mainly by the liver and taken up by the muscles and especially the brain.
- G – Wrong.
- H – Wrong. Tyrosine is formed in the liver by catalysis of phenylalanine hydroxylase from Phe.

**Question 3.**

- A – Correct. Ammonia is very toxic to all cells. It is therefore detoxified by the formation of glutamine (NH4 + fixation by glutamate) and by the formation of urea. Ureagenesis, which takes place almost exclusively in the liver, captures both ammonia from the intestine and mainly ammonia formed by oxidative deamination of amino acids (via glutamate dehydrogenase from glutamate).

- B – Wrong. A defect in ureagenesis does not produce atypical amino acids; in a certain block, intermediates (eg arginine succinate, etc., also glutamine as a result of efforts to remove excess NH4 +) may accumulate in larger quantities.
- C – Wrong. Biogenic amines are not formed primarily to an increased extent in ureagenesis disorders
- D – Wrong. Elevated uric acid levels are not related to impaired ureagenesis.
- E – Wrong. Hypoglycaemia does not result from a disorder of ureagenesis. However, hypoglycemia can cause brain disorders (the brain is energy dependent on glucose supply).

**Question 4.**

- A – Wrong. Methionine is an essential amino acid
- B – Wrong. Phenylalanine is an essential amino acid

- C – Correct. Cysteine is not an essential amino acid. It is formed from methionine and serine via the S-adenosylmethionine pathway, which gives homocysteine; it reacts with serine to form cystathionine.
- D – Right. Tyrosine is not essential. It is formed from essential phenylalanine by hydroxylation at C-4 using phenylalanine hydroxylase and biopterin as a cofactor.

- E – Wrong. Leucine is essential.
- F – Wrong. Isoleucine is essential.
- G – Wrong. Valin is essential. Important especially for the activity of brain tissue like other branched chain amino acids.
- H – Wrong. Threonine is essential

**Question 5.**

- A – A - Wrong. Isoleucine is both ketogenic and glucogenic. One of its catabolites is propionyl CoA, which is converted to succinyl-CoA, which then crosses to other oxaloacetate intermediates; which enters the gluconeogenetic pathway via phosphoenolpyruvate (catalyzed by phosphoenolpyruvate carboxykinase).

- B – Correct. Leucine is the only ketogenic amino acid that gives acetoacetate and acetyl-CoA via β-methylcrotonyl CoA and β-hydroxy-β-methylglutaryl CoA.

- C – Wrong. Histidine is a glucogenic amino acid. Through glutamate, it provides 2-oxoglutarate and thus enters the citrate cycle mediator.
- D – Wrong. Cystine is a glucogenic amino acid. Conversion to pyruvate begins with oxidation or transamination.
- E – Wrong. Lysine is a ketogenic but also a glucogenic amino acid. Lysine catabolism occurs via saccharopine to form β-ketoadipate and glutaryl-CoA.

- F – Wrong. Valine is a glucogenic amino acid. It enters the citrate cycle via succinyl-CoA.
- G – Wrong. Tryptophan is a ketogenic but also a glucogenic amino acid.

**Question 6.**

- Everything right. Tyrosine is a precursor of all these metabolites. Tyrosine hydroxylase with the participation of biopterin first produces DOPA, decarboxylation of dopamine, oxidation of norepinephrine and adrenaline from it. The path to the melanins leads through dopaquinone.

**Question 7.**

- A – Wrong. Argininosuccinate is an intermediate in the urea cycle.
- B – Wrong. Homoserine is a product that is co-formed with cysteine in the reaction of serine with homocysteine, which is formed from methionine.
- C – Wrong. Glutamate semialdehyde is an intermediate in the synthesis of proline, not cysteine.
- D – Right. Cystathionine is a key metabolite in cysteine synthesis. It is formed by the reaction of serine with homocysteine. It is then cleaved to homoserine and cysteine.
- E – Wrong. Xanthurenic acid is a metabolite of tryptophan.

**Question 8.**

- A – Wrong. Creatinine does not behave like a "threshold" substance as inulin.
- B – Correct. Creatinine is excreted by glomerular filtration and small (about 10%) tubular secretion. The rate of secretion increases in pathological hypercreatininemia.
- C – Wrong. Creatinine is not subject to tubular resorption unlike urea.
- D – Wrong. Creatinine is primarily filtered by the glomeruli.

**Question 9.**

- A – Wrong. Proportional increase in both is in renal failure
- B – Correct. Urea is increased much more than creatinine. The reason is increased antidiuresis, which leads to increased water resorption together with electrolytes and urea (isoosmolar back diffusion).
- C - Wrong. An increase in creatinine is not characteristic of prerenal uremia.
- D – Wrong. In prerenal uremia, urea is always increased.

# Case reports

## Infant with psychomotor retardation

Infant, 3 and 1/2 months, normal birth. After a few weeks, the mother observed that the child (compared to siblings) showed little interest in the surroundings and that it was not doing well. The urine in the diapers had a strange smell, like a mouse. The girl also had tremors in her limbs. Guthrie's positive test for hyperphenylalaninemia was demonstrated in the laboratory, urine reacted positively with ferrochloride to phenylpyruvic acid. Plasma phenylalanine concentration: 1089 olmol / l (N:  109 mol / l). Examination of the liver biopsy showed a significant reduction (to 1%) in phenylalanine hydroxylase. This suggests the presence of a "classical" form of phenylketonuria

**Questions:**

1. Why can't the presence of phenylalanine in the diet be completely ruled out in the dietary treatment of phenylketonuria?
2. What might be the risk of a fetus of a pregnant woman with phenylketonuria (who did not inherit this disorder)?
3. Can the body of a patient with phenylalanine hydroxylase deficiency produce tyrosine?

**Answers**

1. Other very important metabolites such as DOPA, catecholamines, etc. are formed from phenylalanine. Therefore, there is always a small amount (250-300 mg per day) of phenylalanine in the "phenylalanine" diet.
2. Possible hyperphenylalaninemia. Phenylalanine crosses the placental barrier from the mother's circulation to the circulation of the fetus, whose central nervous system may be damaged by phenylalanine.
3. If it is not complete, but even 1% phenylalanine hydroxylase activity is sufficient to synthesize tyrosine in the presence of a small amount of phenylalanine. Tyrosine in a patient with phenylketonuria actually becomes an essential amino acid. (such as phenylalanine)

## Patient with ocular lens dislocation and mild retardation with a seizure

The boy, 15 years old, suddenly had a seizure resembling a "grand-mal". The doctor found muscle weakness in his left cheek and left upper and lower limbs, so he sent the boy to hospital with a diagnosis of a cerebrovascular accident (right hemisphere). Here he underwent a more detailed examination and a history of surgery (iridectomy) of both eye lenses due to their large dislocation. The boy was slightly mentally retarded. These data led to a more detailed examination of sulfur-containing amino acids. The findings confirmed the diagnosis of homocystinuria: total serum homocystest (s) in - 965 µmol / l (N: <30), cysteine not measurable, folate and B12 normal.

**Questions:**

1. Which enzyme is deficient in this disease and what changes does it lead to in amino acid metabolism?
2. Can increased levels of homocyst (s) and homocystinuria also be caused by diet?
3. Elevated homocysteine levels are a risk factor. For which conditions?

**Answers**

1. Inherited homocystinuria lacks cystathionine synthase ev. cystathionase. The defect leads to an increase in methionine and homocysteine, while cysteine is low. Cysteine metabolism is interrupted, and the accumulated homocysteine is increasingly converted to methionine in the presence of tetrahydrofolate and vitamin B12.
2. Yes, in the absence of methyl tetrahydrofolate, which arises from dihydrofolate and vitamin B12. A diet low in folic acid and a lack of vitamin B12 can cause this
3. Premature occurrence of atherosclerosis (this may explain the cerebrovascular event in the boy: thrombus formation, embolism, vascular wall damage). Increased concentrations of methionine in the brain also take up adenosine (S-adenosylhomocysteine is formed). Adenosine suppresses brain activity and its deficiency in the brain lowers the threshold for convulsions.

### Patient with renal colic

The boy, 16 years old, was hospitalized for severe pain in his left hip shooting into the pubic area. He had reddish-brown urine and marked erythrocyturia in the urine, and flat acidic hexagonal crystals were found in the sediment after acidification of the urine with acetic acid. Imaging techniques found stones in both kidneys.

**Questions:**

1. What urinary calculus is possible here?
2. What disorder is the essence of hereditary cystinuria?
3. How can the formation of cystine stones be prevented or at least reduced?
4. What is the difference between cystinuria and cystinosis?

**Answers**

1. Hexagonal transparent crystals falling out of urine in an acidic environment are typical of cystine.
2. In cystinuria, there is a deficient transport protein that transports dibasic amino acids (cystine, lysine, arginine and ornithine) across the cell membrane of proximal renal tubule cells and small intestinal mucosal cells. The inability to reabsorb these diamino acids from primary urine leads to marked cystine-lysine-arginine-ornithinuria. Cystine, which is very insoluble in urine below pH 6.5, precipitates and forms stones.
3. By alkalinizing urine increased diuresis and further reducing protein diet.
4. Two different cystine transport systems are deficient in these two syndromes. Cystinuria is a diamino acid-specific transport protein in the proximal tubule and intestinal mucosa; in cystinosis, it is a transport protein that allows cystine to cross the lysosomal membrane of lysosomal vesicles into the cytosol. Cystine thus accumulates in lysosomes, damages cells, forms crystals in some tissues and disrupts their function. Affected children usually die of renal failure at the age of 6-12. There is no diaminoaciduria in cystinosis,

## Links

### Related articles

- Hereditary disorders of aino acid metabolism
- Disorders of ureagenesis

Other chapters from the book MASOPUST, Jaroslav – PRŮŠA, Richard. *Pathobiochemistry of metabolic pathways.* 1st edition. Praha : Univerzita Karlova, 1999. 182 pp. pp. 50- 54. ISBN 80-238-4589-6.

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