Hereditary disorders of amino acid metabolism/Questions and case studies

Questions

1. **which amino acids are mostly 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 release into the bloodstream in the greatest amount?**
   - A – glycine
   - B – arginine
   - C – alanine
   - D – glutamic acid
   - E – glutamine
   - F – leucine
   - G – histidine
   - H – tyrosine
3. **which Enzyme defects in the cycle of urea formation lead to disorders of brain function. What is it caused by?**
   - A – Hyperamonemia
   - B – Formation of atypical amino acids
   - C – Increased formation of biogenic amines
   - D – Hyperuricemia
   - E – Hypeoglycemia (gluconeogenesis from amino acids is reduced)
4. **Which amino acids are not nutritionally essential?**
   - A – Methionine
   - B – Fenylalanine
   - C – Cysteine
   - D – Tyrosine
   - E – Leucine
   - F – Isoleucine
   - G – Valine
   - H – Threonine
5. **Which amino acids are not glucogenic?**
   - A – Isoleucine
   - B – Leucine
   - C – Histidine
   - D – Cystine
   - E – Lysine
   - F – Valine
   - G – Tryptophan
6. **Tyrosine is a precursor for the synthesis of:**
   - A – Noradrenalinu
   - B – Adrenalinu
   - C – Melaninu
   - D – DOPA
7. **The key intermediate metabolite for cysteine synthesis in the liver is::**
   - A – Argininosuccinate
   - B – Homoserine
   - C – Glutamic acid semialdehyde
   - D – Cystathionine
   - E – Xanthurenic acid
8. **The mechanism of creatinine excretion by the kidneys is:**
   - A – In glomerular filtration (no tubular secretion or tubular reabsorption)
   - B – In glomerular filtration and in a small proportion of tubular secretion
   - C – In glomerular filtration and tubular reabsorption
   - D – In tubular secretion
9. **In prerenal uremia it is**
   - A – Increased creatinine proportional to increased urea
   - B – Elevated urea and creatinine at the upper limit of normal
   - C – Elevated creatinine and urea at the upper limit of normal
   - D – Creatinine and urea only at the upper limit of normal.

Answers

Question 1.{| **Otázka 1.**

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

- E – Right. Glutamine is absorbed by the kidney, which is also formed 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 (with the participation of glycine aminotransferase, which catalyzes the transfer of an amino group from glutamate or alanine to glyoxalate)
- B – wrong - Arginine is formed mainly in the liver as part of the urea genetic cycle
- C – Correct. Alanine is excreted from the muscles into the circulation in a relatively large amount (50% of all amino acids). In the liver, it undergoes oxidative deamination and gives rise to pyruvate, which is the main substrate of gluconeogenesis.

- D – wrong.

- E – Right. Glutamine is also released by the muscle in relatively large quantities.
- F – Wrong. Branched-chain amino acids, which include 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 catalyzed by phenylalanine hydroxylase from Phe.

Question 3.

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

- B – Wrong. With a defect in ureagenesis, atypical amino acids are not formed; with a certain block, intermediates can accumulate in larger quantities (e.g. arginine succinate, etc., also glutamine as a result of efforts to remove excess NH4+).
- C – Wrong. Biogenic amines are not primarily formed in an increased amount in case of ureagenesis disorder.
- D – Wrong. An increase in the level of uric acid is not related to a ureagenesis disorder.
- E – Wrong. Hypoglycemia does not occur as a result of impaired ureagenesis. However, hypoglycemia can cause brain dysfunction (the brain is energy dependent on the supply of glucose).

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 S-adenosylmethionine, which gives rise to homocysteine; the latter 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. Valine is essential. Important especially for the activity of brain tissue like other branched chain amino acids.
- H – Wrong. Threonine is essential

Question 5.

- A – Wrong. Isoleucine is both ketogenic and glucogenic. One of its catabolites is propionyl CoA, which passes to succinyl-CoA, which then via other intermediate products to oxaloacetate; which enters the gluconeogenic 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. Via glutamate, it provides 2-oxoglutarate and thus enters the intermediate of the citrate cycle.
- D – Wrong. Cystine is a glucogenic amino acid. Conversion to pyruvate begins with oxidation or possibly transamination.
- E – Wrong. Lysine is a ketogenic, but also a glucogenic amino acid. Catabolism of lysine takes place via saccharopine to form đ-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 the precursor of all the listed metabolites. Tyrosine hydroxylase with the participation of biopterin first produces DOPA, by decarboxylation dopamine, oxidation of noradrenaline and from it adrenaline. The path to melanins leads through dopaquinone.

Question 7.

- A – Wrong. Argininosuccinate is an intermediate in the urea cycle.
- B – Wrong. Homoserine is a product that is formed simultaneously with cysteine when serine reacts 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 the synthesis of cysteine. It is formed by the reaction of serine with homocysteine. It is then split into homoserine and cysteine.
- E – Wrong. Xanthurenoic acid is a metabolite of tryptophan.

Question 8.

- A – A – Wrong. Creatinine does not behave as a "thresholdless" substance like inulin.
- B – Correct. Creatinine is excreted by glomerular filtration and a small (about 10%) tubular secretion. The proportion of secretion increases in pathological hypercreatininemia.
- C – Wrong. Unlike urea, creatinine does not undergo tubular reabsorption
- D – Wrong. Creatinine is primarily filtered by the glomeruli.

Question 9.

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

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Case reports

Infant with psychomotor retardation

Infant, 3 and 1/2 months, normal delivery. After several weeks, the mother observed that the child (compared to his siblings) showed little interest in the surroundings and that he was not making progress. The urine in the diapers had a strange smell, like mice. The girl also developed tremors in her limbs. In the laboratory, a positive Guthrie's test for hyperphenylalaninemia was demonstrated, the urine gave a positive reaction with ferric chloride for phenylpyruvic acid. Phenylalanine concentration in plasma: 1089 mol/l (N: 109 mol/l). Examination of the biopsy specimen of the liver showed a significant reduction (to 1%) of phenylalanine hydroxylase. This indicates the presence of the "classic" form of phenylketonuria

Questions:

1. why can't the presence of phenylalanine in food be completely excluded in the dietary treatment of phenylketonuria?
2. What may be at risk for the fetus of a pregnant woman with phenylketonuria (who has not inherited this disorder)
3. Can the organism of a patient with phenylalanine hydroxylase deficiency form 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 a "phenylalanine-free" diet.
2. Possible hyperphenylalaninemia. Phenylalanine passes through the placental barrier from the circulation of the mother to the circulation of the fetus, whose central nervous system can be damaged by phenylalanine.
3. If it were complete, it cannot, but even 1% activity of phenylalanine hydroxylase is sufficient to synthesize tyrosine in the presence of a small amount of phenylalanine. Tyrosine actually becomes an essential amino acid in a patient with phenylketonuria. (such as phenylalanine)

A patient with dislocation of the eye lens and mild retardation with a convulsive

attack

A boy, 15 years old, had a sudden seizure resembling a "grand-mal". The doctor found muscle weakness on the left face and on the left upper and lower limbs, and therefore sent the boy to the hospital with a diagnosis of cerebrovascular accident (right hemisphere). Here he was examined in more detail and the history of surgery (iridectomy) of both eye lenses due to their large dislocation was found. 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: serum total homocyst(e)in – 965 µmol/l (N: < 30), cysteine unmeasurable, folate and B12 normal.

Questions:

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

Answers

1. In hereditary homocystinuria, cystathionine synthase is absent. cystathionase. The defect leads to an increase in methionine and homocysteine, while cysteine is low. Metabolism to cysteine is interrupted, the accumulated homocysteine is converted to methionine to an increased extent in the presence of tetrahydrofolate and vitamin B12.
2. Yes, with a lack of methyltetrahydrofolate, which is formed 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 a cerebrovascular event in a boy: formation of a thrombus, formation of an embolism, damage to the vessel wall). An increased concentration of methionine in the brain also absorbs adenosine (S-adenosylhomocysteine is formed). Adenosine suppresses brain activity and its deficiency in the brain lowers the threshold for convulsions.

A patient with renal colic

A boy, 16 years old, was hospitalized for severe pain in the left side radiating to the pubic area. He had red-brown urine and marked erythrocyturia in the urinary sediment, and after acidifying the urine with acetic acid, flat transparent hexagonal crystals were found in the sediment. Imaging techniques found stones in both kidneys.

Questions:

1. What urinary calculus comes into consideration here?
2. What disorder (deficiency) is the essence of hereditary cystinuria?
3. How can you prevent or at least reduce the formation of cystine stones?
4. What is the difference between cystinuria and cystinosis?

Answers

1. Hexagonal transparent crystals falling out of urine in an acidic environment are typical for 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 cells of the proximal renal tubule and cells of the mucosa of the small intestine. The impossibility of reabsorption of these diamino acids from the primary urine leads to marked cystine-lysine-arginine-ornithinuria. Cystine, which is very insoluble in urine below pH 6.5, falls out and forms stones.
3. Alkalization of urine by increased diuresis and further reduction of protein in the diet.
4. In these two syndromes, two different transport systems for cystine are deficient. In cystinuria, it is a transport protein specific for diamino acids, namely in the proximal tubule and intestinal mucosa; in cystinosis, it is a transport protein enabling the transfer of cystine across the lysosomal membrane of lysosomal vesicles into the cytosol. Thus, cystine accumulates in lysosomes, damages cells, forms crystals in some tissues and disrupts their function. Affected children die of renal failure usually between the ages of 6 and 12. There is no diaminoaciduria in cystinosis,

Links

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- Disorders of ureagenesis

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- MASOPUST, Jaroslav a Richard PRŮŠA. *Patobiochemie metabolických drah.* 1. vydání. Praha : Univerzita Karlova, 1999. 182 s. s. 50- 54. ISBN 80-238-4589-6.