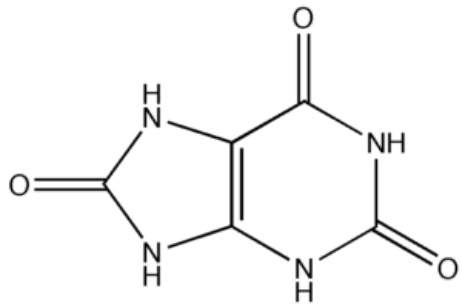
Disorders of uric acid metabolism

The importance of uric acid

In humans, monkeys, reptiles and birds, it is the end product of DNA and RNA metabolism as well as free nucleotides (ATP, GTP, cAMP, NAD^+, NADP and FAD). Uric acid has antioxidant effects and protects cells against oxygen radicals. It also inhibits the oxidation of ascorbic acid.

According to one theory (Ames, 1983), individuals with higher uricemia values have higher intelligence, a lower incidence of cancer, and live to an older age. However, this has the disadvantage that uric acid is very slightly soluble in water, at **pH 7.4** most of it is in the form of **monosodium urate**, which forms a saturated solution (at 37° C) in plasma already at a concentration of 420 µmol/l.



Uric acid

Metabolism

Urea acid biosynthesis is associated with **purine formation**. The key metabolite is **5-phosphoribosyl-1-pyrophosphate (=PRPP)**, which arises from ribose-5-phosphate and ATP. (PRPP is also an intermediate in the synthesis of NAD^+ and $NADP^+$ and pyrimidine nucleotides). PRPP then reacts with glutamine to form 5-phosphoribosyl-1-amine. This, through a number of intermediates, gradually forms the basis of the purine nucleus by adding C, N and H atoms from glycine, N5, N10-methylenetetrahydrofolate, aspartate and N10-formylfolate; this produces **inosine monophosphate (IMP)**. This "central" metabolite can now be converted via other intermediates to **adenosine monophosphate (AMP)** or **guanosine monophosphate (GMP)**, or it can be catabolized via inosine.

In mammals, the liver is the major site of purine nucleotide biosynthesis. In contrast, the brain partially needs exogenous purines, erythrocytes and polymorphonuclear cells cannot produce PRPP at all, lymphocytes produce them to a small extent. De novo IMP synthesis requires energy of 6 mol equivalent of ATP plus glycine, glutamine, methenyl-FH4 and aspartate. It is, therefore, advantageous for the organism that the nucleotide catabolism intermediates be reused for nucleotide and nucleic acid resynthesis (**salvage pathway**). This process consumes **phosphoribosyl pyrophosphate (PRPP)**, which reacts with free purine bases and catalyzes the corresponding nucleotide molecules under the catalysis of hypoxanthine-guanine **phosphoribosyltransferase (HGPRT)** and adenine phosphoribosyltransferase. PRPP is both a substrate and an activator of the PRPP-glutamyl-amidotransferase reaction, which initiates the synthesis of purine nucleotides. PRPP deficiency therefore causes a reduction in purine nucleotide production.

The biosynthesis of pyrimidine nucleotides takes place from similar precursors, the difference being that ribose-5-phosphate, which is at the beginning of the synthesis at purine bases, enters the molecule at pyrimidine bases in later reactions. **Pyrimidine ring formation** is based on carbamoyl phosphate through a number of metabolites such as orotic acid, orotidine monophosphate (OMP), and uridine monophosphate (UMP), which also provides uridine diphosphate (UDP) and uridine triphosphate (UTP) or cytidine triphosphate (TMP).

Purine and pyrimidine synthesis inhibitors

Inhibition of tetrahydrofolate compound formation

Two water-soluble vitamins are needed for nucleotide metabolism: **folic acid** and **vitamin B_{12}**. The metabolic function of folic acid is that it can transfer compounds of one carbon unit (methyl-, methylene-) to the compounds. However, for this purpose, it must be converted into tetrahydro derivatives (FH4) (N5-methyl- or N_5, N_{10}-methylene- or N5-methylidene-tetrahydrofolate). The latter passes its CH_3 group to homocysteine to form methionine. The reaction is catalyzed by homocysteine methyltransferase, which requires vitamin B_{12} as a cofactor. Methionine reacts with ATP to provide active S-adenosylmethionine, which is a methyl group donor.

The effect of **antifolates** (drugs that block the synthesis of tetrahydrofolates) is as follows:

Bacteria can make folic acid on their own. Therefore, administration of p-aminobenzoic acid (PABA) -based chemotherapeutics such as sulfonamides (sulfanilamide) results in the incorporation of the sulfonamide into the formed folate molecule in place of PABA. The resulting folate analogue does not have the effects of real folic acid and therefore the growth of bacteria is stopped. Sulphonamides do not harm a person who ingests folic acid as a vitamin (cannot synthesize it from PABA).

In contrast, methotrexate, a dihydrofolate reductase inhibitor (converting FH_2 to FH_4), acts on this enzyme in both bacteria and humans. Therefore, *methotrexate cannot be used as an antibiotic*. However, it is used as an anticancer agent. They are most affected by cells with significant proliferative activity (when the maximum DNA synthesis is "de novo"), ie mainly tumour cells. Of course, non-tumour cells are also affected to a lesser extent,

especially those that have a rapid turnover (bone marrow cells). Therefore, in aggressive anticancer therapy, the level of methotrexate should be monitored and, if its elevated levels persist, an antidote, formyltetrahydrofolate (leucovorin), a product whose synthesis has been inhibited by methotrexate, should be given.

Synthetic analogues of purines and pyrimidines

Examples of analogues used in anticancer therapy. Template: Example Other than azathioprine, which is metabolized to 6-mercaptopurine, inhibits the proliferation of immunocompetent cells and is used to suppress transplant organ rejection.

5-Fluorouracil, 6-thioguanine, 6-mercaptopurine, 5- or 6-azauridine, azacytidine

Other than azathioprine, which is metabolized to 6-mercaptopurine, it suppresses the proliferation of immunocompetent cells and is used to suppress transplant organ rejection.

The purine analogue 4-hydroxypyrazolopyrimidine (*allopurinol*) inhibits not only de novo purine synthesis but also xanthine oxidase activity and thus the conversion of xanthine to uric acid and is therefore used in the treatment of hyperuricemia.

Disorders of purine and pyrimidine metabolism

Hyperuricemia

Hyperuricaemia means an increase in plasma urate:

- in men over 420 µmol / l,
- in women over 380 µmol / l.

The clinical symptoms are the **precipitation of monosodium urate crystals** from the solution and their deposition in the tissues (joints, kidneys), which can lead to an inflammatory reaction (entry of phagocytes) such as gouty arthritis or in the soft tissues of the urate sediment - tophy. Urea acid is the final metabolite of purines, not pyrimidines, which are degraded to relatively water-soluble derivatives.

Phagocytosis of monosodium urate crystals by granular leukocytes leads to an intracellular increase in lactate and the release of lysosomal enzymes. Proteolytic enzymes also induce kinin activation (the cause of the pain). Lysosomal enzymes in synovial cells cause the destruction of articular cartilage.

The tubules in the kidney may be damaged and urate nephropathy may develop. The formation of urinary stones from uric acid crystals (uricite) or ammonium urate is common (at a urine pH around 5, the solubility of urates is very low - 150 mg/l, alkalizing to 7.6 significantly increases: 1500-2000 mg/l).

The adult excretes 400-600 mg daily in the urine

Causes of hyperuricemia

Primarily caused by overproduction and increased uric acid excretion for disorders of phosphoribosyl pyrophosphate synthetase

either to increase Vmax or for resistance to feedback inhibition or at low Km to ribose-5-phosphate.

or partial or total (*Lesch-Nyhan syndrome*) hypoxanthine-guanine-phosphoribosyltransferase deficiency, which causes an increased concentration of intracellular PRPP due to the inability to use it for re-utilization in "de novo" nucleotide synthesis.

Allopurinol (a structural analogue of hypoxanthine) is converted by xanthine oxidase to oxypurinol (alloxanthine), which binds tightly to the enzyme and thus prevents its further catalytic activity. Thus, allopurinol is a "suicidal" xanthine oxidase inhibitor, reducing the concentration of uric acid in the blood and thus in other fluids (eg synovial). The amount of urate excreted decreases, and the excretion of slightly more soluble hypoxanthine and xanthine increases. In addition, the final metabolite is not one product but three, thus reducing the risk of exceeding the solubility constant that would be the case for one final product.

Secondary hyperuricaemia is caused by increased cell waste (eg in leukaemia) or by a re-transport disorder in the renal tubules (eg in lactate acidosis, lactate in the renal tubule competes with urate for resorption).

Hypouricemia

It can be caused by xanthine oxidase deficiency. It is associated with increased urinary xanthine excretion and the occurrence of xanthine urinary stones.

Immunological deficiency

Based on an adenosine deaminase defect. It is an inherited disease with clinical immunodeficiency (T and B cells) with increased deoxyadenosine secretion.

Immunological deficiency for hereditary purine-nucleoside phosphorylase deficiency is accompanied by T-cell deficiency, inosinuria, deoxyinosinuria, guanosinuria, deoxyguanosinuria, and hypouricaemia.

Orotic aciduria

Orotate phosphoribosyltransferase or orotidyldecarboxylase are missing. There is a lack of pyrimidine production and thus normal development is delayed. It is also associated with megaloblastic anaemia. Uridine administration bypasses the metabolic block. Uridine is formed into uridine monophosphate, from which other derivatives (pyrimidine nucleotides) are formed.

Literature

- MASOPUST, Jaroslav a Richard PRŮŠA. *Patobiochemie metabolických drah.* 2. vydání. Univerzita Karlova, 2004. 208 s. s. 110−114.