Nucleotide metabolism

Nucleotide metabolism deals with the digestion, biosynthesis and catabolism of purine and pyrimidine nucleotides and with specific diseases related to genetic defects of these processes.

Metabolism of purine nucleotides

Biosynthesis of purine nucleotides

Purines are not essential in diet and the human body can synthesize them. The nitrogenous base is not synthesized separately and is attached to the pentose phosphate, but entire nucleotides are always synthesized.

The synthesis of purine nucleotides starts from ribose-5'-phosphate, which is phosphorylated to 5'-phosphoribosyl-1'-diphosphate (PRPP). A series of reactions follow to form inosine monophosphate (IMP), a common precursor for both guanosine monophosphate (GMP) and adenosine monophosphate (AMP). See Fig. 1.

Formation of AMP from IMP

IMP reacts with aspartate in the presence of adenylosuccinate synthetase, consuming a molecule of GTP and releasing a molecule of water. The resulting adenylosuccinate cleaves the fumarate molecule by the action of adenylosuccinate (adenylosuccinate lyase) and AMP is produced. AMP is simply phosphorylated by non-specific kinases to ADP and then to ATP. See Fig. 1.

The emergence of GMP from IMP

IMP is oxidized to xanthosine monophosphate (XMP) by the action of IMP-dehydrogenase (the cofactor is NAD+). In the following reaction, XMP reacts with glutamine while consuming ATP. XMP forms GMP, glutamine forms glutamate. Simple phosphorylation of GMP produces GDP and GTP. See Fig. 1.

Regulation of purine biosynthesis

The main factor controlling the synthesis of purine nucleotides is the availability of PRPP.

File:Puriny1.png

Fig. 1 - regulation of the synthesis of purine bases

Also important for the rate of synthesis is a negative and positive feedback mechanism in some steps of biosynthesis that induce AMP, ADP, GMP and GDP (see Fig. 1). As a result of the mutual coordination, when there is enough GTP, the conversion of IMP to AMP is accelerated. If there is enough ATP, the conversion of XMP to GMP is accelerated. This relationship guarantees the synthesis of almost the same amount of GMP as AMP.

Salvage pathway

File:Puriny2.png

Fig. 2 - pathway sparing reaction

Metabolism constantly releases purine bases and nucleosides in the body. Their recycling has been proven, we are talking about a cost-saving route. Through it, hypoxanthine (and adenine) and guanine are enzymatically converted to monophosphates to triphosphates in the liver (see Fig. 2). These reactions are less energy intensive than de novo synthesis.

Synthesis of purine deoxyribonucleotides

Deoxyribonucleotides are formed from ribonucleotides. Reduction of D-ribose on the second carbon of ribonucleoside diphosphate (e.g., ADP) produces 2'-deoxyribonucleoside diphosphate (dADP). This reaction is catalyzed by ribonucleotide reductases using NADPH and thioredoxin (see Fig. 3). Similar to the cases above, dNTP is produced by phosphorylation of dNDP by non-specific kinases. Thioredoxin reductase contains selenocystein in the active center.

File:Puriny3.png

Fig. 3 - synthesis of purine dNTPs

Catabolism of purine nucleotides

Cleavage of nucleic acids produces free nucleotides. These are converted to nucleosides by the action of nucleotidases. Some purine base molecules are capable of reacting with PRPP and can regenerate the corresponding nucleoside monophosphates (AMP, GMP) in the already mentioned saving pathway.

File:Puriny4.png

Fig. 4 - degradation of purine nucleotides

The degradation scheme is shown in Fig. 4. In humans, the final product of purine metabolism is uric acid, which is excreted in the urine. In most mammals, uric acid is further broken down by uricase (urate oxidase) to form allantoin. In humans, however, its creation is insignificant.

Diseases associated with purine metabolism

Hypoxanthine-guanine phosphoribosyltransferase deficiency causes a genetic disease, **Lesch-Nyhanův syndrom**. In this disease, the operation of the sparing pathway is limited. This is manifested by increased urate formation (hyperuricemia) and increased intracellular PRPP.

Deficiency of adenosine deaminase causes severe combined immunodeficiency (SCID).

Hyperuricemia causes gout (arthritis uratica). This serious joint disease does not have a single cause, several deviations of purine metabolism have been demonstrated. The most common and common cause is a defect in PRPP synthesis. In patients, a large amount of uric acid accumulates in the soft tissues, resulting in the formation of so-called tophi. Nephrolithiasis is also a common consequence. The main symptom of gout is very painful acute attacks in the joints.

Metabolism of pyrimidine nucleotides

Biosynthesis of pyrimidines

File:Pyrimidiny1.png
Fig. 5 - synthesis of pyrimidine nucleotides

As with purines, here too, a finished nucleotide is synthesized, not a separate nitrogenous organic base with the subsequent addition of a pentose and a phosphate. Biosynthesis takes place in the cytosol and the first step is the synthesis of carbamoyl phosphate by cytosolic carbamoyl phosphate synthetase (mitochondrial carbamoyl phosphate synthetase functions in urea synthesis). Carbamoyl phosphate is produced by the reaction of glutamine with CO2 using ATP. Through several reactions, the cyclization of carbamoyl phosphate with aspartate splits off water, and subsequent dehydrogenation produces orotic acid (orotate). The subsequent reaction with PRPP produces orotidine-5'-phosphate (orotidine monophosphate, OMP), which changes to uridine-5'-phosphate (UMP) by decarboxylation. During the synthesis of pyrimidines, part of the enzymes is located on a single protein enzyme chain, which significantly speeds up the course of the reactions. UMP is a common precursor for TTP, CTP and UTP (see Fig. 5). CDP is formed by ribonucleotide reductase to form dCDP, followed by phosphorylation of dCTP.

Saving lane

The sparing pathway is also important in the metabolism of pyrimidines. Its principle is the same as for purine nucleotides.

Catabolism of pyrimidine nucleotides

Catabolism of pyrimidines takes place mainly in the liver. Individual pyrimidine bases are formed by the degradation of nucleic acids, similarly to purine ones (see Fig. 4). The degradation processes of individual pyrimidine bases are approximately the reverse synthesis. The end products of degradation are (in contrast to the degradation of purines) generally well soluble in water (see Fig. 6).

File:Pyrimidiny2.png
Fig. 6 - degradation products of pyrimidine nucleotides

Links

- ws:Metabolismus nukleotidů

Related articles

- Poruchy metabolismu purinů
- Poruchy metabolismu pyrimidinů
- Poruchy metabolismu kyseliny močové

References

-
-
-

Kategorie:Biochemie Kategorie:Genetika