Nucleotides Metabolism

Introduction

Nucleotides are organic molecules consisting of a nucleoside and a phosphate. They serve as monomeric units of the nucleic acid polymers – deoxyribonucleic acid (DNA) and ribonucleic acid (RNA), both of which are essential biomolecules within all life-forms on Earth. Nucleotides are obtained in the diet and are also synthesized from common nutrients by the liver.

Nucleotides are composed of three subunit molecules: a nucleobase, a five-carbon sugar (ribose or deoxyribose), and a phosphate group consisting of one to three phosphates. The four nucleobases in DNA are guanine, adenine, cytosine and thymine; in RNA, uracil is used in place of thymine. Nucleotides can be recycled through salvage pathways or synthesized de novo.

Nucleotide salvage

During salvage pathway a biological product is produced from intermediates in the degradative pathway of its own or similar substances. The term often refers to nucleotide salvage in particular, in which nucleotides are synthesized from intermediates in their degradative pathway.

Nucleotide salvage pathways are used to recover bases and nucleosides that are formed during degradation of RNA and DNA. This is important in some organs because some tissues cannot undergo de novo synthesis. The salvaged products can then be converted back into nucleotides.

Salvage Pathway of Purine Ribonucleotides

Phosphoribosyltransferases add activated ribose-5-phosphate (Phosphoribosyl pyrophosphate, PRPP) to bases, creating nucleoside monophosphates. There are two types of phosphoribosyltransferases: adenine phosphoribosyltransferase (APRT) and hypoxanthine-guanine phosphoribosyltransferase (HGPRT). HGPRT is an important enzyme in Purine pathway metabolism and its deficiency is implicated in Lesch–Nyhan syndrome. This disease is characterized by three major hallmarks:

1. Neurologic dysfunction
2. Cognitive deficits
3. Behavior abnormalities including self-mutilation
4. Uric acid overproduction (hyperuricemia).

Damage to the basal ganglia causes sufferers to adopt a characteristic fencing stance due to the nature of the lesion. Some may also be afflicted with macrocytic anemia due to the faulty DNA synthesis, most likely due to deficient purine synthesis that lead to a lag of cell division with respect to increases in cell mass. Virtually all patients are male; males suffer delayed growth and puberty, and most develop shrunken testicles or testicular atrophy. Female carriers are at an increased risk for gouty arthritis but are usually otherwise unaffected.

De novo Synthesis of Purine Ribonucleotides,

The atoms that are used to build the purine nucleotides come from a variety of sources.

The pathway starts with the formation of phosphoribosyl pyrophosphate (PRPP) from ribose-5'-phosophate (R5'P) which in turn formed primarily by the pentose phosphate pathway.

The enzyme PRPP synthetase converts ribose phosophate to PRPP by reacting it with ATP. The reaction is unusual in that a pyrophosphoryl group is directly transferred from ATP to C_1 of R5P and that the product has the α configuration about C1. During the following steps, other biomolecules contribute in IMP synthesis including glutamine, glycine, N-formyl tetrahydrofolate, bicarbonate, and aspartate.

The *de novo* synthesis of purine ribonucleotides proceeds by a 10-step pathway to the branch-point intermediate IMP, the nucleotide of the base hypoxanthine.

AMP and GMP are subsequently synthesized from this intermediate via separate, two-step pathways. Thus, purine moieties are initially formed as part of the ribonucleotides rather than as free bases.

Do novo Synthesis of Pyrimidine Ribonucleotides

The synthesis of the pyrimidines CTP and UTP occurs in the cytoplasm and starts with the formation of carbamoyl phosphate from glutamine and bicarbonate. Next, aspartate carbamoyltransferase catalyzes a condensation reaction between aspartate and carbamoyl phosphate to form carbamoyl aspartate, which is cyclized into dihydroorotate by dihydroorotase. The latter is converted to orotate by dihydroorotate dehydrogenase.

Orotate phosphoribosyltransferase (PRPP transferase) catalyzes the net reaction yielding orotidine-5'-phosphate (OMP).

Orotidine 5'-monophosphate is decarboxylated by orotidine-5'-phosphate decarboxylase to form uridine monophosphate (UMP). UMP is phosphorylated by two kinases to uridine triphosphate (UTP) via two sequential reactions with ATP.

CTP is subsequently formed by the amination of UTP by the catalytic activity of CTP synthetase. Glutamine is the NH_3 donor and the reaction is fueled by ATP hydrolysis, too.

Nucleotide degradation

In humans, pyrimidine rings (C, T, U) can be degraded completely to CO_2 and NH_3 (urea excretion). That having been said, purine rings (G, A) cannot. Instead, they are degraded to the metabolically inert uric acid which is then excreted from the body. Uric acid is formed when GMP is split into the base guanine and ribose. Guanine is deaminated to xanthine which in turn is oxidized to uric acid. This last reaction is irreversible. Similarly, uric acid can be formed when AMP is deaminated to IMP from which the ribose unit is removed to form hypoxanthine. Hypoxanthine is oxidized to xanthine and finally to uric acid.

Instead of uric acid secretion, guanine and IMP can be used for recycling purposes and nucleic acid synthesis in the presence of PRPP and aspartate (NH_3 donor).

Uric acid was first isolated from kidney stones in 1776 by the Swedish chemist Carl Wilhelm Scheele. In 1882, the Ukrainian chemist Ivan Horbaczewski first synthesized uric acid by melting urea with glycine.

Uric acid

In general, the water solubility of uric acid and its alkali metal and alkaline earth salts is rather low. All these salts exhibit greater solubility in hot water than cold, allowing for easy recrystallization. This low solubility is significant for the etiology of gout.

Xanthine oxidase is an enzyme which catalyzes the formation of uric acid from xanthine and hypoxanthine, which in turn are produced from other purines. Xanthine oxidase is a large enzyme whose active site consists of the metal molybdenum bound to sulfur and oxygen.[10] Within cells, xanthine oxidase can exist as xanthine dehydrogenase and xanthine oxireductase.

Clinical significance of Uric Acid

In human blood plasma, the reference range of uric acid is typically 3.4–7.2 mg per dL (200–430 μmol/L) for men, and 2.4–6.1 mg per dL for women (140–360 μmol/L).

Uric acid concentrations in blood plasma above and below the normal range are known as, respectively, hyperuricemia and hypouricemia. Likewise, uric acid concentrations in urine above and below normal are known as hyperuricosuria and hypouricosuria, respectively. Uric acid levels in saliva may be associated with blood uric acid levels.

Hyperuricemia

High levels of uric acid or hyperuricemia, which induces gout, has various potential origins:

1. Diet may be a factor. High intake of dietary purine, high-fructose corn syrup, and table sugar can increase levels of uric acid.
2. Serum uric acid can be elevated by reduced excretion via the kidneys.
3. Fasting or rapid weight loss can temporarily elevate uric acid levels.
4. Certain drugs, such as thiazide diuretics, can increase blood uric acid levels by interfering with renal clearance.

Hyperuricemia also relates with:

1. Tumor lysis syndrome
2. Lesch–Nyhan syndrome
3. Cardiovascular diseases
4. Type 2 diabetes mellitus (T2DM)
5. Kidney stones

Genetics of Gout

Although foods such as meat and seafood can elevate serum urate levels, genetic variation is a much greater contributor to hyperuricemia. A proportion of people have mutations in the proteins responsible for the excretion of uric acid by the kidneys.

A 2011 survey in the United States indicated that 3.9% of the population had gout, whereas 21.4% had hyperuricemia without having symptoms.

Excess blood uric acid can induce gout, a painful condition resulting from needle-like crystals of uric acid precipitating in joints, capillaries, skin, and other tissues. Gout can occur where serum uric acid levels are as low as 6 mg per 100 mL (357 μmol/L), but an individual can have serum values as high as 9.6 mg per 100 mL (565 μmol/L) and not have gout.

Gout Treatment

Today, urate levels are managed with allopurinol. Allopurinol is an analog of hypoxanthine and weakly inhibits xanthine oxidase via a suicide mechanism.

Hypouricemia

Low uric acid or hypouricemia can have numerous causes.

1. Low dietary zinc intakes cause lower uric acid levels. This effect can be even more pronounced in women taking oral contraceptives.
2. Sevelamer, a drug indicated for prevention of hyperphosphataemia in people with chronic kidney failure, can significantly reduce serum uric acid.

Multiple sclerosis and Hypouricemia

Meta-analysis of 10 case-control studies found that the serum uric acid levels of patients with multiple sclerosis were significantly lower compared to those of healthy controls, possibly indicating a diagnostic biomarker for multiple sclerosis.