Purine Metabolism

Purine nucleotides are essential cellular constituents; they intervene in energy transfer, metabolic regulation and the synthesis of DNA and RNA. Purine metabolism can be divided into three pathways:

1. The biosynthetic pathway, often termed de novo, starts with the formation of phosphoribosyl pyrophosphate and leads to the synthesis of inosine monophosphate (IMP). From IMP, adenosine monophosphate (AMP), guanosine monophosphate (GMP) and the other adenine and guanine nucleotides are formed. Deoxyribonucleotides are formed at the diphosphate level.

2. The catabolic pathway starts from GMP, IMP and AMP and produces uric acid, a poorly soluble compound which tends to crystallize once its plasma concentration surpasses 6.5–7 mg/dl (0.38–0.47 mmol/l).

3. The salvage pathway utilizes the purine bases, guanine, hypoxanthine and adenine (which are provided by food intake or the catabolic pathway) and reconverts them into GMP, IMP and AMP, respectively.

Fig. 31.1. Pathways of purine metabolism. ADP, adenosine diphosphate; AICAR, aminoimidazolecarboxamide ribotide; d, deoxy; GDP, guanosine diphosphate; GMP, guanosine monophosphate; GTP, guanosine triphosphate; IMP, inosine monophosphate; PRPP, phosphoribosyl pyrophosphate; S-AMP, adenylosuccinate; SAICAR, succinylaminoimidazolecarboxamide ribotide; XMP, xanthosine monophosphate; 1, PRPP synthetase; 2, adenylosuccinase; 3, AMP deaminase; 4, adenine deaminase; 5, purine nucleoside phosphorylase; 6, xanthine oxidase; 7, hypoxanthine-guanine phosphoribosyltransferase; 8, adenine phosphoribosyltransferase; 9, ribonucleotide reductase. Enzyme deficiencies are indicated by solid bars.
INBORN ERRORS OF PURINE METABOLISM

Inborn errors of purine metabolism comprise errors of:

- The synthesis of purine nucleotides: phosphoribosyl-pyrophosphate (PRPP)-synthetase superactivity and deficiency, adenylosuccinase (ADSL) deficiency
- Purine catabolism: the deficiencies of muscle AMP deaminase (AMP-DA, also termed myoadenylate deaminase), adenosine deaminase (ADA), purine nucleoside phosphorylase (PNP) and xanthine oxidase
- Purine salvage: the deficiencies of hypoxanthine-guanine-phosphoribosyl transferase (HGPRT) and adenine phosphoribosyl transferase (APRT)

With the exception of muscle AMP-DA deficiency, all these enzyme defects are very rare.

**Phosphoribosyl Pyrophosphate-Synthetase Superactivity**

**Clinical Presentation**

The disorder is mostly manifested by the appearance, in young adult males, of gouty arthritis and/or uric acid lithiasis, potentially leading to renal insufficiency [1, 2]. Uricemia can be very high, reaching 10-15 mg/dl (0.60-0.90 mmol/l) [normal adult values: 2.9-5.5 mg/dl (0.17-0.32 mmol/l)]. The urinary excretion of uric acid is also increased, reaching up to 2400 mg (14 mmol)/24 h [normal adult values: 500-800 mg (3-4.7 mmol)/24 h]. Determination of the ratio of uric acid to creatinine (mg/mg) can also be informative, as described in the section discussing diagnostic tests of HGPRT deficiency. A few patients have been reported in which clinical signs of uric acid overproduction already appeared in infancy and were accompanied by neurologic abnormalities – mainly sensorineural deafness (particularly for high tones) but also hypotonia, locomotor delay, ataxia and autistic features [2].

**Metabolic Derangement**

The enzyme forms PRPP from ribose-5-phosphate and ATP (Fig. 31.1). PRPP is the first intermediate of the de novo synthesis of purine nucleotides (not shown in detail in Fig. 31.1), which leads to the formation of inosine monophosphate (IMP), from which the other purine compounds are derived. PRPP synthetase is highly regulated. Various genetic regulatory and catalytic defects [1, 2] lead to superactivity, resulting in increased generation of PRPP. Because PRPP amidotransferase, the rate-limiting enzyme of the de novo pathway, is not physiologically saturated by PRPP, the synthesis of purine nucleotides (and hence the production of uric acid) increases. PRPP-synthetase superactivity is one of the few known examples of a hereditary anomaly that enhances the activity of the