Chapter 20

Human Purine Metabolism

O. Sperling, Department of Clinical Biochemistry, Beilinson Medical Center, Petah-Tikva, and Department of Chemical Pathology, Sackler School of Medicine, Tel-Aviv University, Ramat Aviv, Israel

The purpose of purine metabolism in man is to maintain an optimal level of the nucleotides in the tissues. The nucleotides play an important role in nearly all biochemical processes, including energy metabolism, DNA and RNA structure, and regulation of many metabolic pathways through allosteric effects on enzymes, or through the adenylate energy charge. The nucleotides regulate their de novo and salvage synthesis and the interconversions between AMP and GMP. Uric acid is the waste, degradation endproduct of purine nucleotides in man. Uric acid is hardly soluble in physiological fluids. Therefore, hyperuricemia and hyperuricosuria are associated with precipitation of tophi in joints and other tissues and calculi in the urinary tract. Inborn errors in purine metabolism include the x-linked superactivity of 5-phosphoribosyl-1-pyrophosphate synthetase (gout and uric acid lithiasis), the complete deficiency of hypoxanthine-guanine phosphoribosyltransferase (Lesch-Nyhan syndrome) and the partial deficiency of this enzyme (gout and uric acid lithiasis), and the autosomal recessive deficiency of the following enzymes: adenine phosphoribosyltransferase (2,8-dihydroxyadenine lithiasis), adenosine deaminase (combined immunodeficiency), purine nucleoside phosphorylase (T-cell immunodeficiency), xanthine oxidase (xanthinuria) and myoadenylate deaminase (muscle disease). A transport defect for urate in the renal tubules, manifested in hypouricemia, has also been reported.

Importance

Purine nucleotides play an important role in nearly all biochemical processes (14,24,31,49). Adenine nucleotides are active in the storage and transfer of metabolically available energy, ATP being the universal currency of energy in biological systems. Another important function of the nucleotides is the carrying of a wide variety of groups, and their transfer to appropriate acceptors (glycosyl group, alcohol phosphate, sulfate, hydrogen, hydride ion, electrons, and alkyl group). In addition, the purine nucleotides form structural units. They are the activated precursors of DNA and RNA, the bulk of cellular nucleotides being in the form of these polymers. Nucleotides also participate as structural units in low molecular weight compounds, such as histidine and certain vitamins (folic acid, thiamine and riboflavin). Adenine nucleotides are components of three major coenzymes: NAD+, FAD, and CoA, and of the important methyl donor, S'-adenosylmethionine. Other nucleotides, such as cAMP and cGMP, have physiological functions as mediators of hormone action (regulatory signals). The nucleoside adenosine is considered to have an hormonal-like "retaliatory metabolite" role in matching energy demands to the synthesis of ATP in the heart muscle (32) and probably in some other tissues. Last but not least is the role of the nucleotides in the regulation of many catabolic pathways through allosteric effect on the enzymes, and their effect on many pathways of intermediary metabolism through the energy charge, ([ATP] + 0.5 [ADP])/([ATP] + [ADP] + [AMP]), in the cells (2).
Metabolism

The pathways of purine nucleotide metabolism operate to maintain an optimal level of the various nucleotides in the tissues. The pathways of purine metabolism include (14,24,31,38,49,58,59): synthesis of nucleotides, either from small nonpurine molecules, by the energetically costly de novo pathway, or from preformed purines by the economical salvage pathways; interconversions between the nucleotides; and degradation of excess nucleotides. The degradation of nucleotides may furnish purine bases or nucleosides for salvage nucleotide synthesis in tissues in greater need for the nucleotides than the source tissue. Not all pathways operate in all tissues, and certainly not at the same intensity (see tissue characterization, below).

De Novo Biosynthesis of Purine Nucleotides

The purine ring is assembled from glycine (C-4, C-5, and N-7), from the amino nitrogen of aspartate (N-1), from the amide nitrogen of glutamine (N-3 and N-9), from activated derivatives of tetrahydrofolate (C-2 and C-8) and from CO₂ (C-6) (Fig. 1).

The purine ring structure is being assembled on a ribosyl moiety and when completed it is the nucleotide IMP. This is in contrast to the pyrimidine ring, which structure is completed before its attachment to the 5'-phosphoribosyl moiety to form OMP. The first-committed step in the de novo pathway is the formation of 5'-phosphoribosylamine from 5-phosphoribosyl-1-pyrophosphate (PRPP) and glutamine, catalyzed by glutamine-PRPP amidotransferase. The amide group of glutamine displaces the pyrophosphate group attached to the C-1 of PRPP. The other components of the purine skeleton are introduced in nine additional reactions, yielding finally IMP (Fig. 2; for full details, see refs. 14,19). IMP is the parent purine nucleotide molecule, but as a nucleotide it has no role in metabolism, except for being the precursor of AMP and GMP. AMP is synthesized from IMP in two steps. The first step is amination, accomplished through the attachment of aspartic acid to form the intermediate adenylosuccinate. This reaction is catalyzed by adenylosuccinate synthetase (EC 6.3.4.4). GTP is required in this reaction, providing a potential regulatory mechanism. Adenylosuccinate lyase (EC 4.3.2.2) cleaves fumaric acid from adenylosuccinate to form AMP. GMP is formed from IMP also in two steps. In the first step, IMP is oxidized to XMP, catalyzed by IMP dehydrogenase (EC 1.2.1.14) with NAD⁺ as hydrogen acceptor. XMP is aminated by the amide group of glutamine to form GMP. ATP is consumed in this reaction, being cleaved to AMP + Ï€Pi. The conversion of GMP and AMP to their respective di- and triphosphates

![Fig. 1. The sources of the carbon and nitrogen atoms of the purine ring.](image-url)