Metabolism of nucleotides

Nucleotides consist of a nitrogenous base, a pentose sugar and a phosphate. Nucleotides participate in almost all the biochemical processes, either directly or indirectly. They are the structural components of nucleic acids (DNA, RNA), coenzymes, and are involved in the regulation of several metabolic reactions. On the basis of nitrogenous base, these are two types:

1. Purine nucleotides
2. Pyrimidine Nucleotides

In this section of course we will cover the biosyhtesis and catabolism of purine and pyrimidine nucleotides.

Biosythesis of purine ribonucleotides

Liver is the major site for purine nucleotide synthesis. Erythrocytes, polymorphonuclear leukocytes and brain cannot produce purines.

Many compounds contribute to the purine ring of the nucleotides (**Figure 1**).

1. N1 of purine is derived from amino group of aspartate.
2. C2 and C8 arise from formate of N10-formyl THF.
3. N3 and N9 are obtained from amide group of glutamine.
4. C4, C5 and N7 are contributed by glycine.
5. C6 directly comes from CO2.

It should be remembered that purine bases are not synthesized as such, but they are formed as ribonucleotides. **The purines are built upon a pre-existing ribose 5-phosphate**.

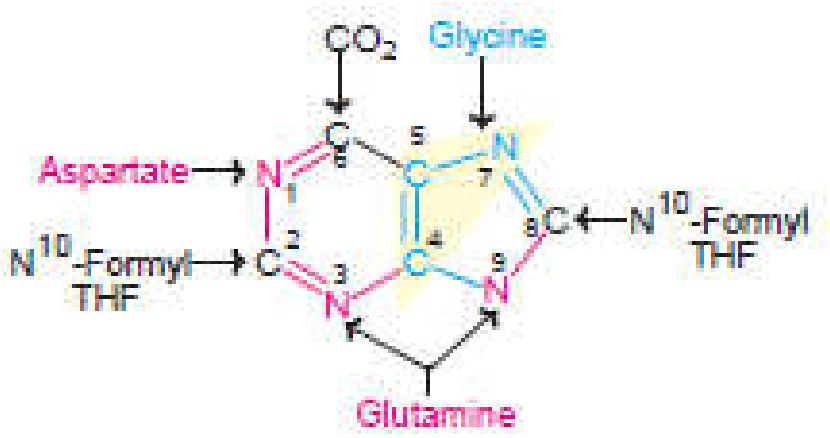

Figure 1: Sources of individual atoms in purine ring

The pathway for the synthesis of **inosine monophosphate** (IMP or inosinic acid), the 'parent' purine nucleotide is given in **Figure2**. The reactions are briefly described below:

1. Ribose 5-phosphate, produced in the hexose monophosphate shunt of carbohydrate metabolism is the starting material for purine nucleotide synthesis. It reacts with ATP to form phosphoribosyl pyrophosphate (PRPP).

2. Glutamine transfers its amide nitrogen to PRPP to replace pyrophosphate and produce 5-phosphoribosylamine. The enzyme **PRPP glutamyl amidotransferase** is controlled by **feedback inhibition** of nucleotides (IMP, AMP and GMP). This reaction is the '**committed step**' in purine nucleotide biosynthesis.

3. Phosphoribosylamine reacts with glycine in the presence of ATP to form glycinamide ribosyl 5-phosphate or glycinamide ribotide (GAR).

4. N10-Formyl tetrahydrofolate donates the formyl group and the product formed is formylglycinamide ribosyl 5-phosphate.

5. Glutamine transfers the second amido amino group to produce formylglycinamidine ribosyl 5-phosphate.

6. The imidazole ring of the purine is closed in an ATP dependent reaction to yield 5-aminoimidazole ribosyl 5-phosphate.

7. Incorporation of CO2 (carboxylation) occurs to yield aminoimidazole carboxylate ribosyl 5-phosphate. This reaction **does not require** the vitamin **biotin** and/or ATP which is the case with most of the **carboxylation** reactions.

8. Aspartate condenses with the product in reaction 7 to form aminoimidazole 4-succinyl carboxamide ribosyl 5-phosphate.

9. Adenosuccinate lyase cleaves off fumarate and only the amino group of aspartate is retained to yield aminoimidazole 4-carboxamide ribosyl 5-phosphate.

10. N10-Formyl tetrahydrofolate donates a one-carbon moiety to produce formaminoimidazole 4- carboxamide ribosyl 5-phosphate. With this reaction, all the carbon and nitrogen atoms of purine ring are contributed by the respective sources.

11. The final reaction catalysed by cyclohydrolase leads to ring closure with an elimination of water molecule. The product obtained is inosine monophosphate (IMP), the parent purine nucleotide from which other purine nucleotides can be synthesized.

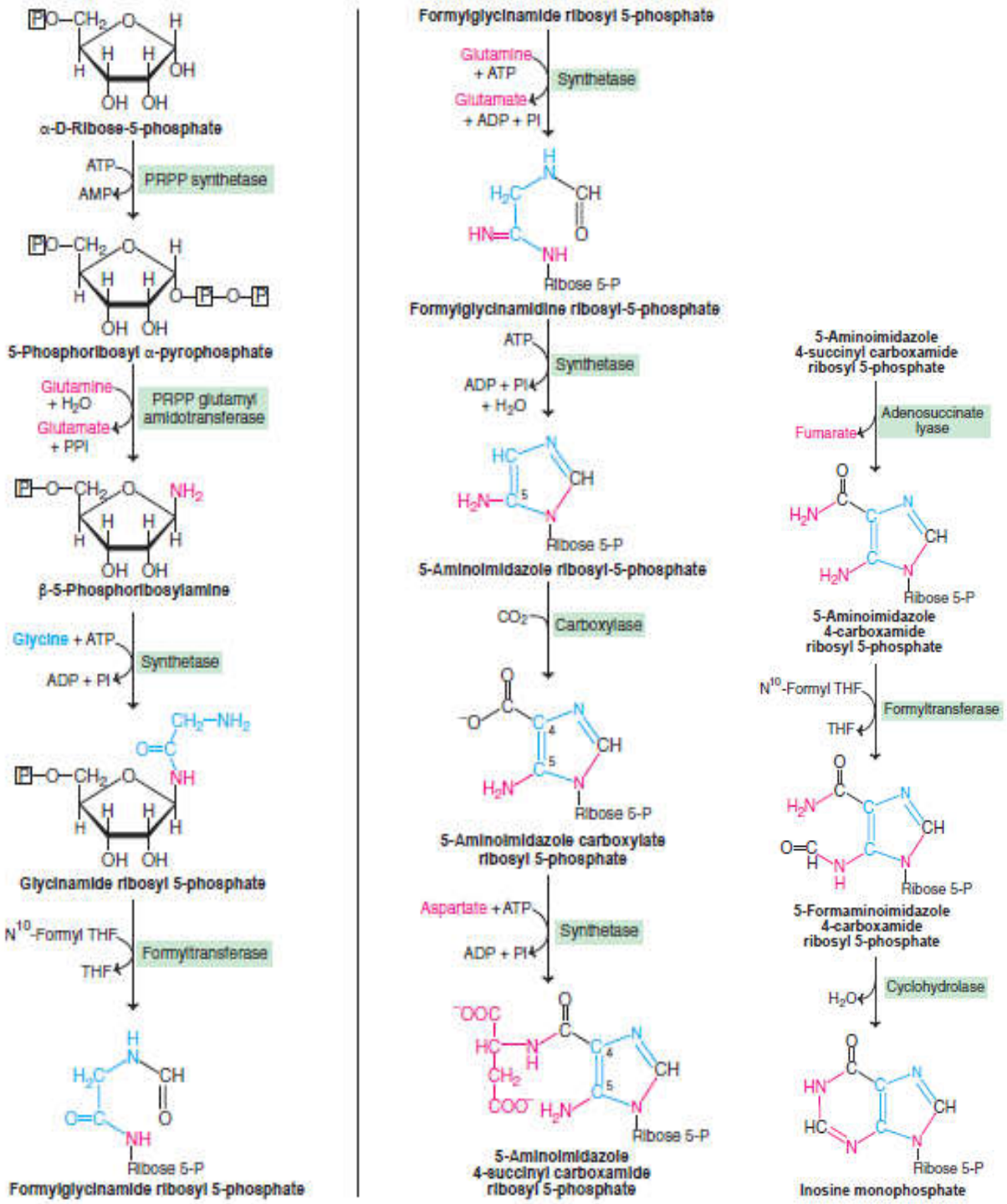

Figure 2: The metabolic pathway for the synthesis of inosine monophosphate, the parent purine nucleotide (PRPP–Phosphoribosyl pyrophosphate; PPi–Pyrophosphate).

Synthesis of AMP and GMP from IMP

Inosine monophosphate is the immediate precursor for the formation of AMP and GMP (**Figure 3**). Aspartate condenses with IMP in the presence of GTP to produce adenylsuccinate which, on cleavage, forms AMP. For the synthesis of GMP, IMP undergoes NAD^+ dependent dehydrogenation to form xanthosine monophosphate (XMP). Glutamine then transfers amide nitrogen to XMP to produce GMP. 6-Mercaptopurine is an inhibitor of the synthesis of AMP and GMP. It acts on the enzyme adenylsuccinase (of AMP pathway) and IMP dehydrogenase (of GMP pathway).

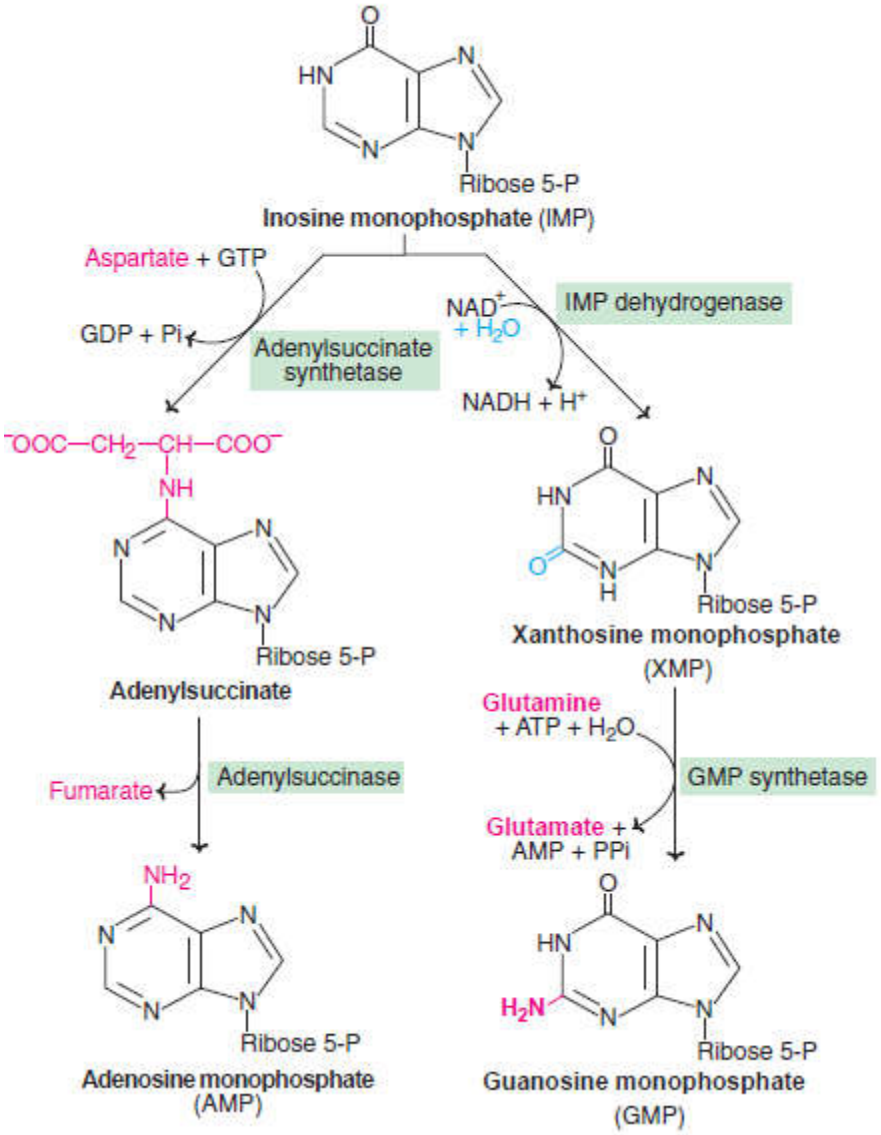

Figure3: Synthesis of AMP and GMP from inosine monophosphate.