BIOCHEMISTRY- BP203T

UNIT: 4 NUCLEIC ACID METABOLISM AND GENETIC INFORMATION TRANSFER

CLASS:2

TOPIC: BIOSYNTHESIS OF PURINES

BIOSYNTHESIS OF PURINES:

Many compounds contribute to the purine ring of the nucleotides

1. N1 of purine is derived from the amino group of aspartate.

2. C2 and C8 arise from formate of N10- formyl THF.

3. N3 and N9 are obtained from the amide group of glutamines.

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

The reactions are explained 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 amido transferase is controlled by feedback inhibition of nucleotides (IMP, AMP, and GMP).

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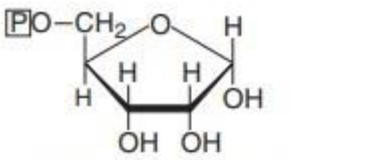
This reaction is the 'committed step' in purine nucleotide biosynthesis.

3. Phosphoribosyl amine 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 formyl glycinamide ribosyl 5-phosphate.

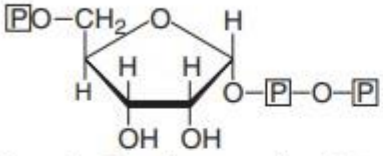
5. Glutamine transfers the second amido group to produce formyl glycinamidine ribosyl 5-phosphate.

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



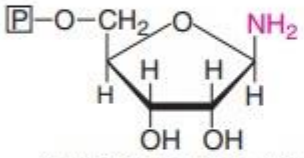
α-D-Ribose-5-phosphate

ATP → AMP (PRPP synthetase)



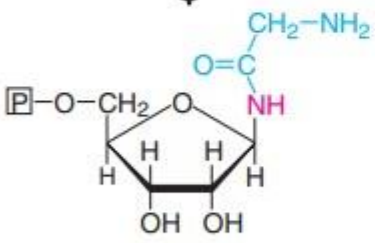
5-Phosphoribosyl α-pyrophosphate

Glutamine + H_2O → Glutamate + PPi (PRPP glutamyl amidotransferase)



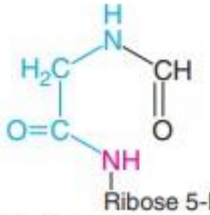
β-5-Phosphoribosylamine

Glycine + ATP → ADP + Pi (Synthetase)



Glycinamide ribosyl 5-phosphate

N^{10}-Formyl THF → THF (Formyltransferase)

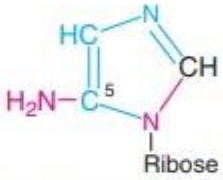


Formylglycinamide ribosyl 5-phosphate

Glutamine + ATP → Glutamate + ADP + Pi (Synthetase)

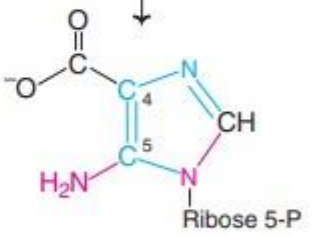
Formylglycinamidine ribosyl-5-phosphate

ATP → ADP + Pi + H_2O (Synthetase)



5-Aminoimidazole ribosyl-5-phosphate

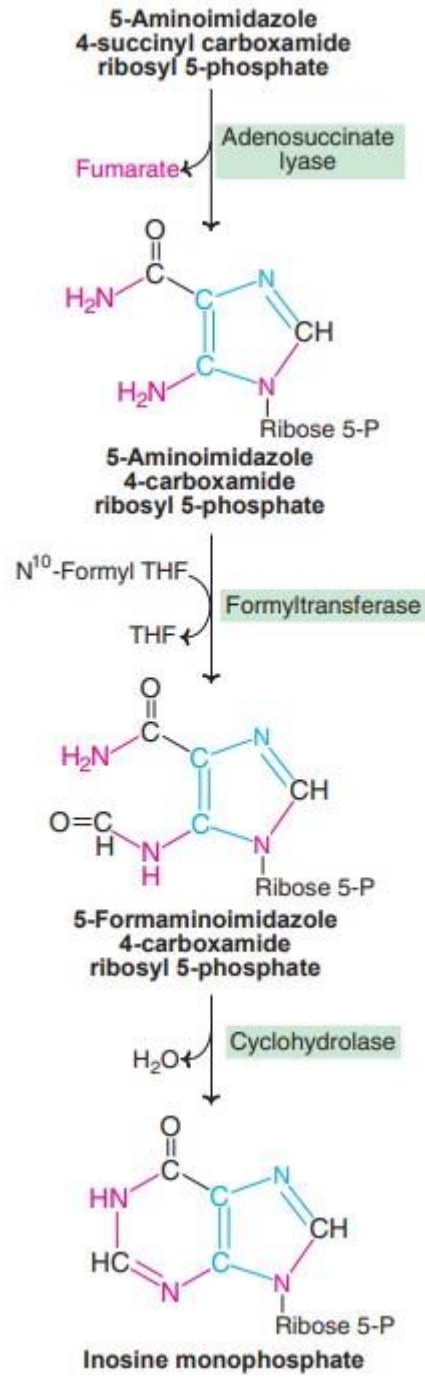
CO_2 → (Carboxylase)



5-Aminoimidazole carboxylate ribosyl 5-phosphate

Aspartate + ATP → ADP + Pi (Synthetase)

5-Aminoimidazole 4-succinyl carboxamide 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 formamino-imidazole 4-carboxamide ribosyl 5-phosphate.

With this reaction, all the carbon and nitrogen atoms of purine ring are contributed by the respective sources.

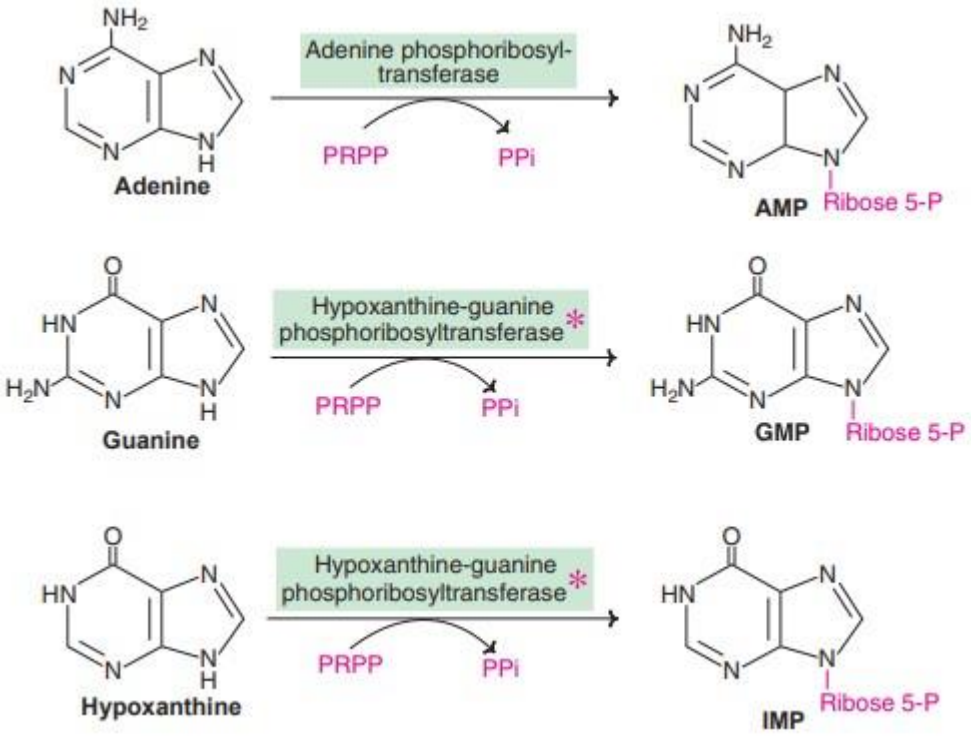
11. The final reaction catalysed by cyclohydrolase leads to ring closure with an elimination of water molecule.

The product obtained is inosine monophosphate (IMP), the parent purine nucleotide from which other purine nucleotides can be synthesized.

Salvage pathway for purines

The free purines (adenine, guanine and hypoxanthine) are formed in the normal turnover of nucleic acids (particularly RNA), and also obtained from the dietary sources.

The purines can be directly converted to the corresponding nucleotides, and this process is known as 'salvage pathway' .



Adenine phosphoribosyl transferase catalyses the formation of AMP from adenine.

Hypoxanthine-guanine phosphoribosyl transferase (HGPRT) converts guanine and hypoxanthine, respectively, to GMP and IMP.

Phosphoribosyl pyrophosphate (PRPP) is the donor of ribose 5-phosphate in the salvage pathway.

The salvage pathway is particularly important in certain tissues such as erythrocytes and brain where de novo (a new) synthesis of purine nucleotides is not operative.

DEGRADATION OF PURINE NUCLEOTIDES:

The end product of purine metabolism in humans is uric acid. The sequence of reactions in purine nucleotide degradation is

1. The nucleotide monophosphates (AMP, IMP and GMP) are converted to their respective nucleoside forms (adenosine, inosine and guanosine) by the action of nucleotidase.

2. The amino group, either from AMP or adenosine, can be removed to produce IMP or inosine, respectively.

3. Inosine and guanosine are, respectively, converted to hypoxanthine and guanine (purine bases) by purine nucleoside phosphorylase. Adenosine is not degraded by this enzyme, hence it has to be converted to inosine.

4. Guanine undergoes deamination by guanase to form xanthine.

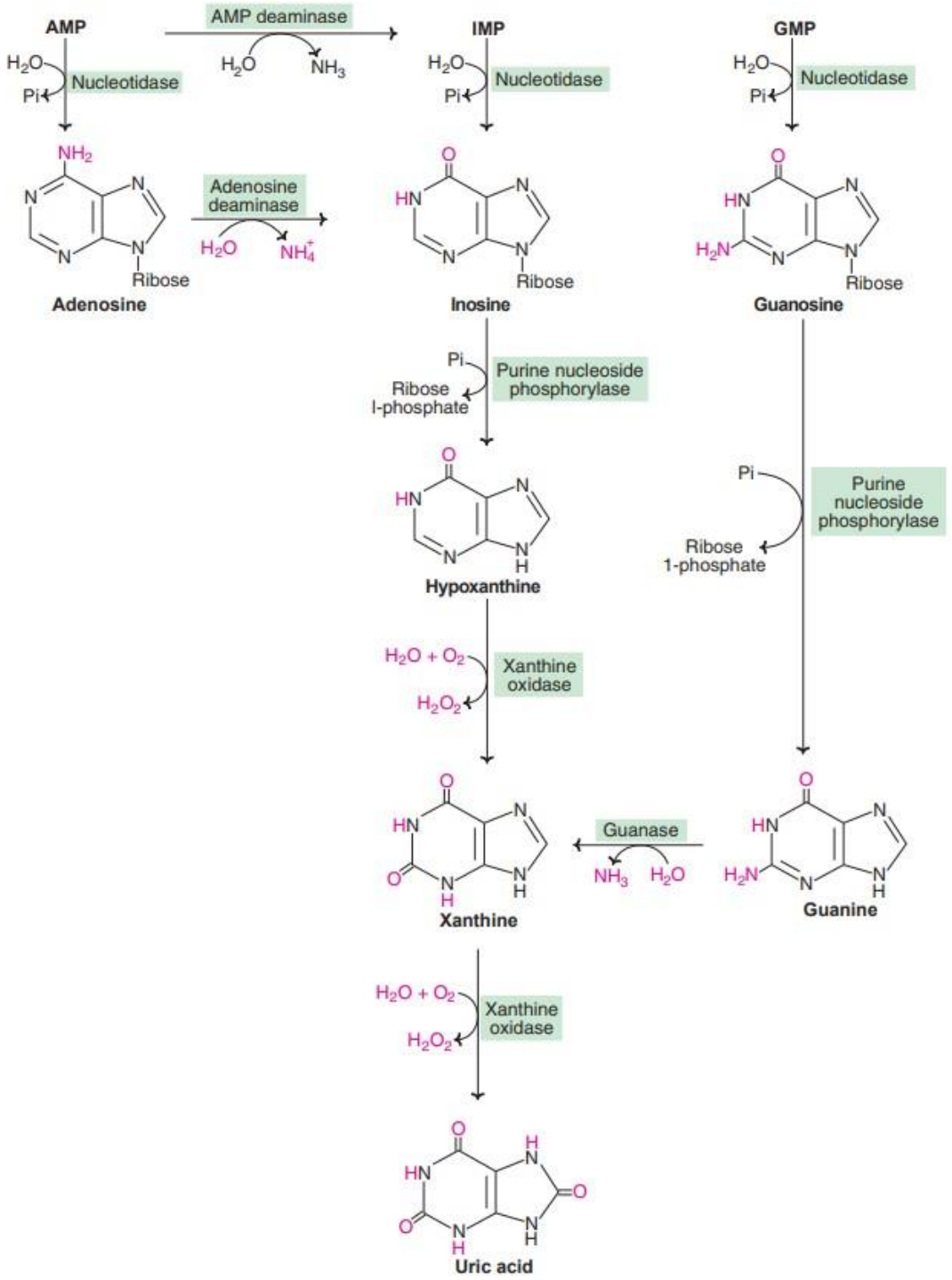
5. Xanthine oxidase is an important enzyme that converts hypoxanthine to xanthine, and xanthine to uric acid.

This enzyme contains FAD, molybdenum and iron, and is exclusively found in liver and small intestine. Xanthine oxidase liberates H2O2 which is harmful to the tissues.

Catalase cleaves H2O2 to H2O and O2. Uric acid (2,6,8-trioxypurine) is the final excretory product of purine metabolism in humans.

Uric acid can serve as an important antioxidant by getting itself converted (non-enzymatically) to allantoin.

It is believed that the antioxidant role of ascorbic acid in primates is replaced by uric acid, since these animals have lost the ability to synthesize ascorbic acid.



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