Lecture title: Nucleotides Metabolism

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Biochemical Importance

1. Deoxyribonucleotides are required for DNA synthesis.
2. Ribonucleotides are required for RNA synthesis.
3. Biosynthesis of purine and pyrimidine nucleotides is essential for DNA replication, (cell division), and growth of all types of mammalian cells, bacteria and virus. If the supply of nucleotides is blocked, cell division (viral replication) and growth is arrest. So, compounds, which can block nucleotide biosynthesis effectively stop growth of cells, bacteria and virus. Indeed, many anti-tumor, anti-bacterial and anti-viral agents currently used are inhibitors of nucleotide (nucleic acid) biosynthesis.
4. Nucleotide metabolism is defective in diseases like gout, and immunodeficiency syndrome.

Biosynthesis of Nucleotides

There are two types of pathways for nucleotide biosynthesis.

1. *De novo* pathways

2. Salvage pathways

Biochemical importance

Bacterial growth, viral growth and tumor growth requires nucleic acid synthesis. This in turn depends on nucleotide biosynthesis. Hence, inhibitors of nucleotide biosynthesis are potential antibacterial, antiviral and anti-tumor (cancer) agents. Since normal cell growth also requires nucleic acid biosynthesis these agents cause side or toxic

affects.

However, the severity of toxic effects varies from one drug to another drug. Rapidly dividing epithelial cells of gastrointestinal tract, bone marrow stem cells and hair follicles are affected most by these agents. Hence, symptoms like decreased blood count, gastrointestinal disturbances and hair loss may occur in individuals undergoing treatment with these agents.

Salvage pathways for nucleotide biosynthesis

1. These pathways produce nucleotides from preformed purine and pyrimidine bases and nucleosides.

2. Endogenous nucleic acid breakdown, foreign DNA and RNA, which enters body through infectious agents breakdown and digestion of dietary nucleic acids are the sources for preformed bases and nucleosides.

3. Synthesis of nucleotides from preformed bases and nucleosides saves considerable cellular energy.

4. Moreover certain cells like RBCs, WBCs, and brain tissue lack enzymes of *de novo* pathways and hence they entirely depend on salvage pathways for nucleotide biosynthesis.

5. Liver supplies free bases and nucleosides to salvage pathways of brain, erythrocytes and leukocytes.

6. These salvage pathways helps in recycling of 90% of preformed bases and nucleosides in the body.

Degradation of Purine nucleotides

1. Liver is the major organ involved in degradation of purine nucleotides.

Lysosomal enzymes converts nucleic acids to nucleotides. Majority of purine nucleotides so produced are AMP and GMP.

Medical Importance

Catabolism of purine nucleotides is abnormal in some diseases. Hence normal fate of uric acid which is end product of purine catabolism.

Gout

It is common disease associated with excessive purine catabolism. It is characterized by hyperuricemia and excessive excretion of uric acid in urine.

Hyperuricemia or gout is due to

(a) Over production of uric acid.

(b) Impaired excretion of uric acid.

Hypoxanthine analog

Allopurinol is the drug used in the treatment of gout. It is a hypoxanthine analog which is substrate for xanthine oxidase.

Degradation of pyrimidine nucleotides

Liver is the major organ involved in breakdown of pyrimidine nucleotides.

Pyrimidine nucleotide are degraded to amino acids : alanine and Beta-amino isobutyric acid (BAIB) by cleaving pyrimidine ring.