Date

Expt. No. Nucleic Acid Metabolism Page No.

Nucleic acids are macromolecules present in all living cells. When they compines with protein they called nucleoproteins. The protein components are protamines & histones.

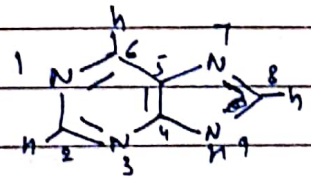
Nucleic acids are polymer of ~~nucleic acid~~ nucleotides linked by phosphodiester bond & called polynucleotides.

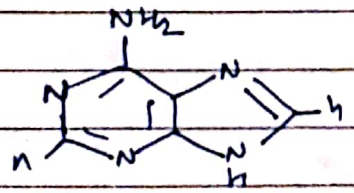
Two type
- DNA → ⊕ ~~small amount~~ in nuclei and small amount in mitrocondria
- RNA → 90% ⊕ in cell cytoplasm & 10% in nucleolus

Nucleotide component.
- Nitrogen base
- Pentose sugar
- A phosphate group

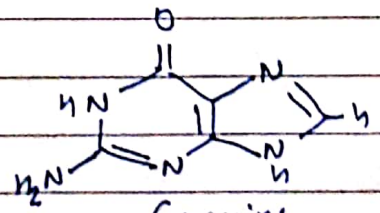
Nitrogen base :
- purine :- Adenine (A), Guanine (G)
- Pyrimidines :- Thymine (T), Cytosine (C), Uracil (U)

Purine Bases :





Adenine
(6-amino purine)



Guanine
(2-amino-6-oxo purine)

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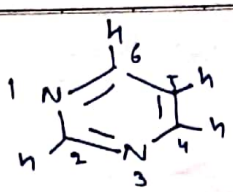
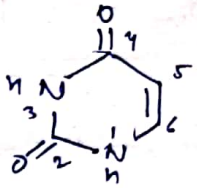
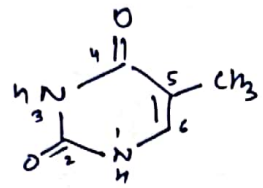
Pyrimidine Bases :-





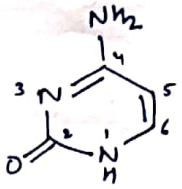
Uracil

(2,4-dioxo-pyrimidine)



Thymine

(2,4-dioxy-5-methyl pyrimidine)



Cytosine

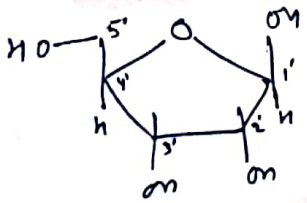
(2-oxo-4-amino pyrimidine)

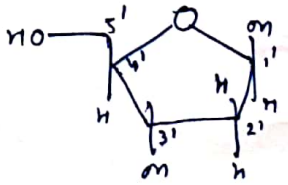
Cytosine & Uracil ⟶ found in RNA

Thymine & cytosine ⟶ found in DNA

(2) **Pentose sugar :-** Nucleic acid mainly differ due to presence of pentose sugar

(A) D-ribose sugar (B) 2-Deoxy ribose sugar





Nitrogen base & pentose sugar linked by N-glycosidic bond

Nucleoside :- Nitrogen base + pentose sugar

Nucleic Acid :- Nitrogen base + pentose sugar + phosphate group.

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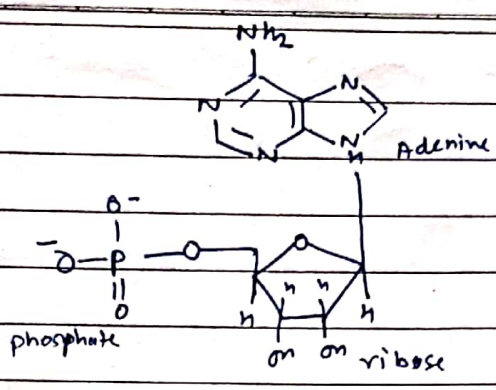
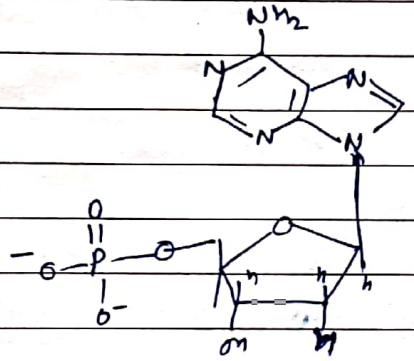


AMP
(Adenosine monophosphate)

Ribonucleotide



dAMP
(deoxyadenosine monophosphate

Different Ribonucleotides

AMP = Adenosine Monophosphate
GMP = Guanine monophosphate
UMP = Uridine monophosphate
CMP = Cytidine monophosphate

Different Deoxyribonucleotide :

dAMP = deoxy adenosine monophosphate
dGMP = deoxy Guanine monophosphate
dTMP = deoxy Thymidine monophosphate
dCMP = deoxy Cytidine monophosphate
dUMP = Deoxyuridine monophosphate

Teacher's Signature :

Biological Importance of Nucleotides:

Besides structural components of nucleic acids, several nucleotides participate in biochemical & physiological functions.

(A) **ATP:** serve as main source of energy ~~in cells~~ in metabolic pathways in cells. such as fatty acid synthesis, glycolysis, protein synthesis. physiological functions such as muscle contractions, nerve impulse transmissions also need ATP as energy source.

(B) **AMP:** It is component of many coenzymes such as NAD^+, $NADP^+$ FAD, coenzyme A. These are essential component of protein, lipid & carbohydrate metabolism.

cAMP: It is formed from ATP by Adenyl cyclase enzyme

$$ATP \xrightarrow{\text{Adenyl cyclase}} cAMP$$

↳ serve as secondary messenger for many hormones such as epinephrine, glucagon

cAMP :→ ~~act as~~ enhance degradation of stored food like

→ fat & glycogen by stimulating lipolysis & glycogenolysis

→ ↑ secretion of gastric acid by gastric mucosa

→ ↓ aggregation of blood platelets.

(c) GDP / GTP :- Participate in conversion of succinyl-CoA to succinate in Krebs cycle

→ GTP is required for activation of adenyl cyclase
→ GTP serve energy source in protein synthesis.

cGMP :- Cyclic guanosine monophosphate

GTP —(Guanylyl cyclase)→ cGMP

→ Act as second messenger & act as antagonistically to cAMP.
→ cGMP involved in relaxation of smooth muscle & vasodilation.

(d) UDP :- → Participate in glycogenesis
→ UDP-glucose takes part in galactose metabolism & required for synthesis of lactose

→ UDP-Glucuronic acid – required in detoxification

(e) CTP / CDP :- requires for biosynthesis of some phospholipids

→ CDP-Choline – involved in synthesis of sphingomyelin.

Metabolism of nucleic Acid

Purine & pyrimidine are dietary non essential components. Dietary nucleic acids & nucleotides do not provide essential constituents for biosynthesis of endogenous nucleic Acid.

In human the biosynthesis of purine & pyrimidines nucleotides performed by de novo routes. i.e. from amphibolic intermediates.

Biosynthesis of purine nucleotides

- AMP
- GMP

Both these nucleotides can be synthesized by

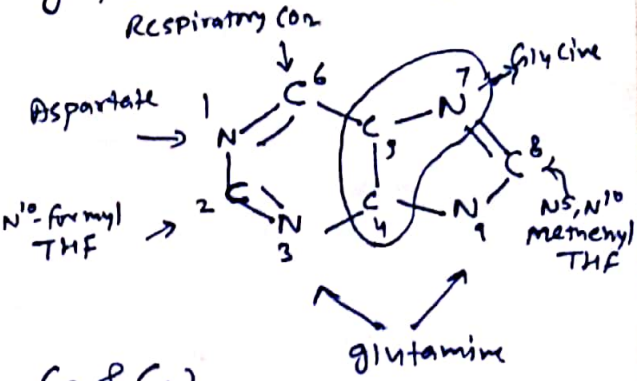
(A) → de novo pathway (new synthesis from amphibolic pathways)

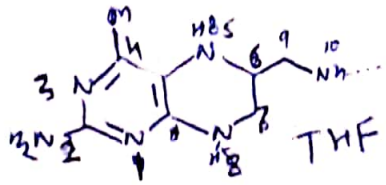
(B) → Salvage pathway

(A) De novo biosynthesis of purine nucleotides:

In this process the purine ring formed from different precursors such as

- → Glycine (provide C_4, C_5, N_7)
- → Aspartate (provide N_1)
- → Glutamine (provide N_3, N_9)
- → Tetrahydrofolate derivative provide C_2 & C_8)
- → CO_2 provides C_6





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Denovo Biosynthesis of purine

Ribose-5-phosphate (I)

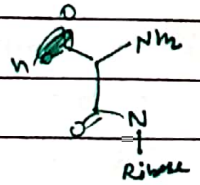
ATP, Mg^{+2}, AMP — (1) phosphoribosyl pyrophosphate synthetase (PRPP Synthetase)

PRPP (II)

Glutamine, H_2O — (2) PRPP Glutamyl amidotransferase — Glutamate, PP_i

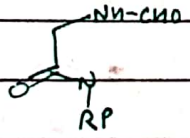
5-phosphoribosylamine (III)

Glycine, ATP, Mg^{+2} — (3) phosphoribosyl glycinamide synthetase — ADP + P_i



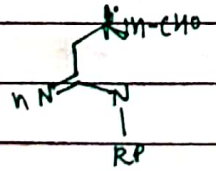
Glycinamide ribosyl-5-phosphate (IV)

N^5, N^{10}-methenyl THF — (4) formyl transferase — THF



formylglycinamide ribosyl-5-phosphate (V)

Glutamine, ATP, Mg^{+2} — (V)Synthetase (5) — Glutamate

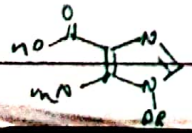


formylglycinamidine ribosyl-5-phosphate (VI)

ATP, Mg^{+2}, Ring closure, H_2O — (VII) Synthetase (6)

Aminoimidazole-ribosyl-5-phosphate (VII)

CO_2 — (VII) Carboxylase (7)



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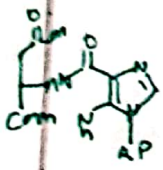
Aminoimidazole Carboxylate-ribosyl-5-phosphate (VIII)

PTO

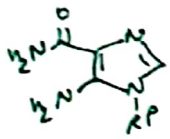
Aminoimidazole Carboxylate-β-ribosyl-5-phosphate

Aspartate
H_2O
(1X) Synthetase
(8)



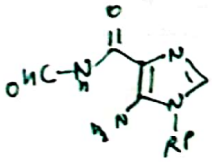
Amino imidazole succinyl Carboxamide-ribosyl-5-phosphate (1X)

Adenylosuccinase
(9)
Fumerase



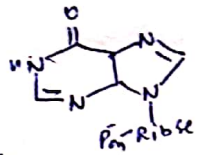
Amino imidazole Carboxamide-ribosyl-5-phosphate (X)

N^{10}-formyl THF
Formyl transferase
(10)
THF



Formimino Carboxamide ribosyl ribosyl-5-phosphate (X1)

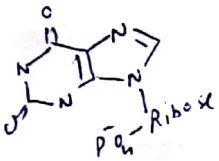
Ring closure
H_2O
Inosine monophosphate (IMP) Cyclohydrolase
(11)



IMP

Adenylosuccinate synthetase
Aspartate
GTP, Mg^{+2}
H_2O

IMP dehydrogenase
(14)
NAD^+
$NADH+H^+$



Xanthosine monophosphate (XMP)

Glutamine
ATP
Glutamate
Guanosine phosphate synthetase
(15)

Guanosine monophosphate (GMP)

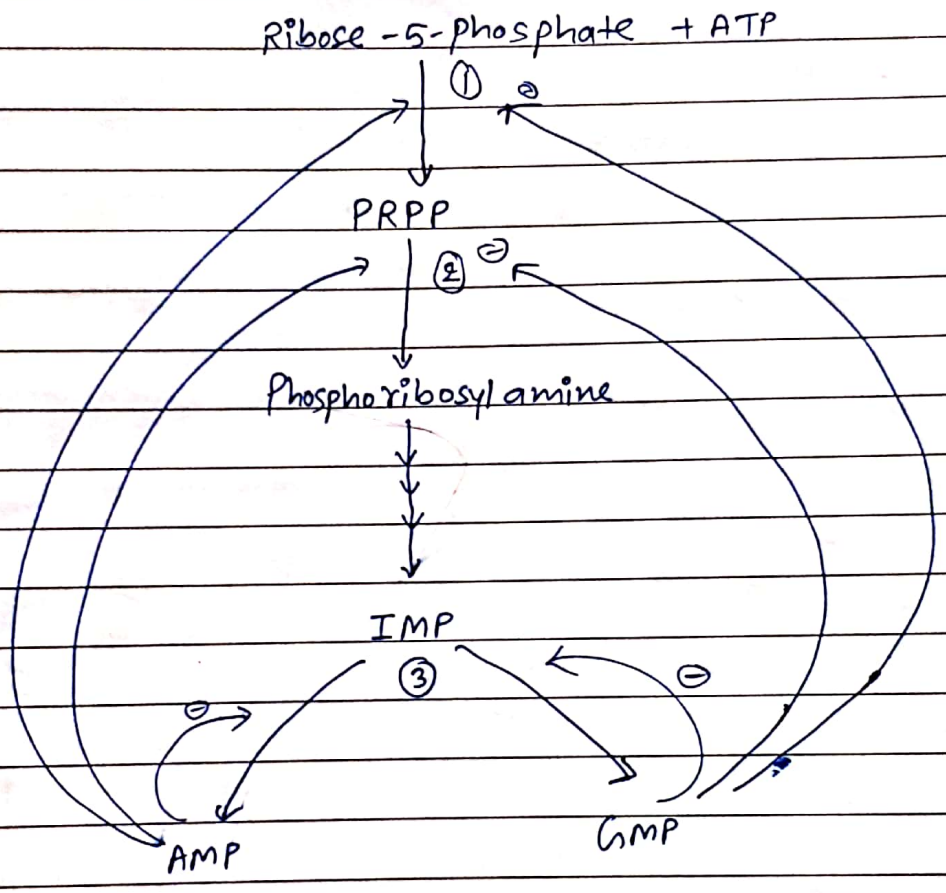
Adenylo succinate

Adenylosuccinase
Fumerate

Adenosine monophosphate (AMP)

De novo biosynthesis of purine nucleotides

Regulation of de-novo purine nucleotide biosynthesis



Synthesis of purine nucleotide controlled by
- Conc. of PRPP ← availability of Ribose-5-phosphate / Activity of PRPP synthase
- Feed back regulation at different sites

(i) PRPP synthase ⟶ Allosterically feedback inhibition by AMP & GMP

(ii) PRPP-glutamyl amido-transferase ⟶ feed back inhibition by AMP & GMP

(iii) Adenylosuccinate synthase ⟶ AMP

(iv) IMP dehydrogenase ⟶ GMP

(B) Biosynthesis of purine nucleotide by Salvage Pathway:

Salvage pathway: Conversion of free purine to nucleotide is called salvage pathway.

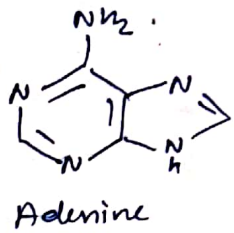
Salvage means property saved from loss.

→ Metabolic degradation of nucleotides or nucleic acid produce purine bases i.e. Adenine, guanine, Hypoxanthine

→ This pathway is simpler (single reaction) and require very less energy.

→ This pathway is found in such tissue which are incapable to synthesize purine nucleotides by denovo pathway.

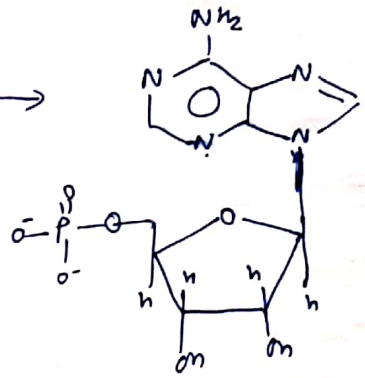
Tissue such as human brain, erythrocytes



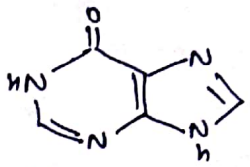
Adenine

Adenine phosphoribosyl transferase

(APRTase)



AMP



Hypoxanthine

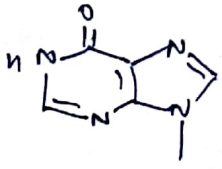
Hypoxanthine-guanine phosphoribosyl transferase

(HGPRTase)

↑⊖

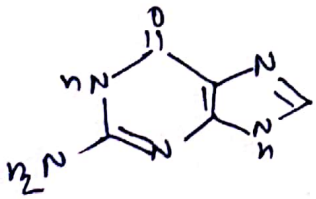
AMP & GMP

↓⊖



IMP

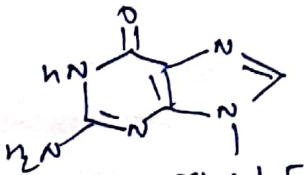
Ribosyl-5-phosphate



Guanine

Hypoxanthine-guanine phosphoribosyl-transferase

(HGPRTase)



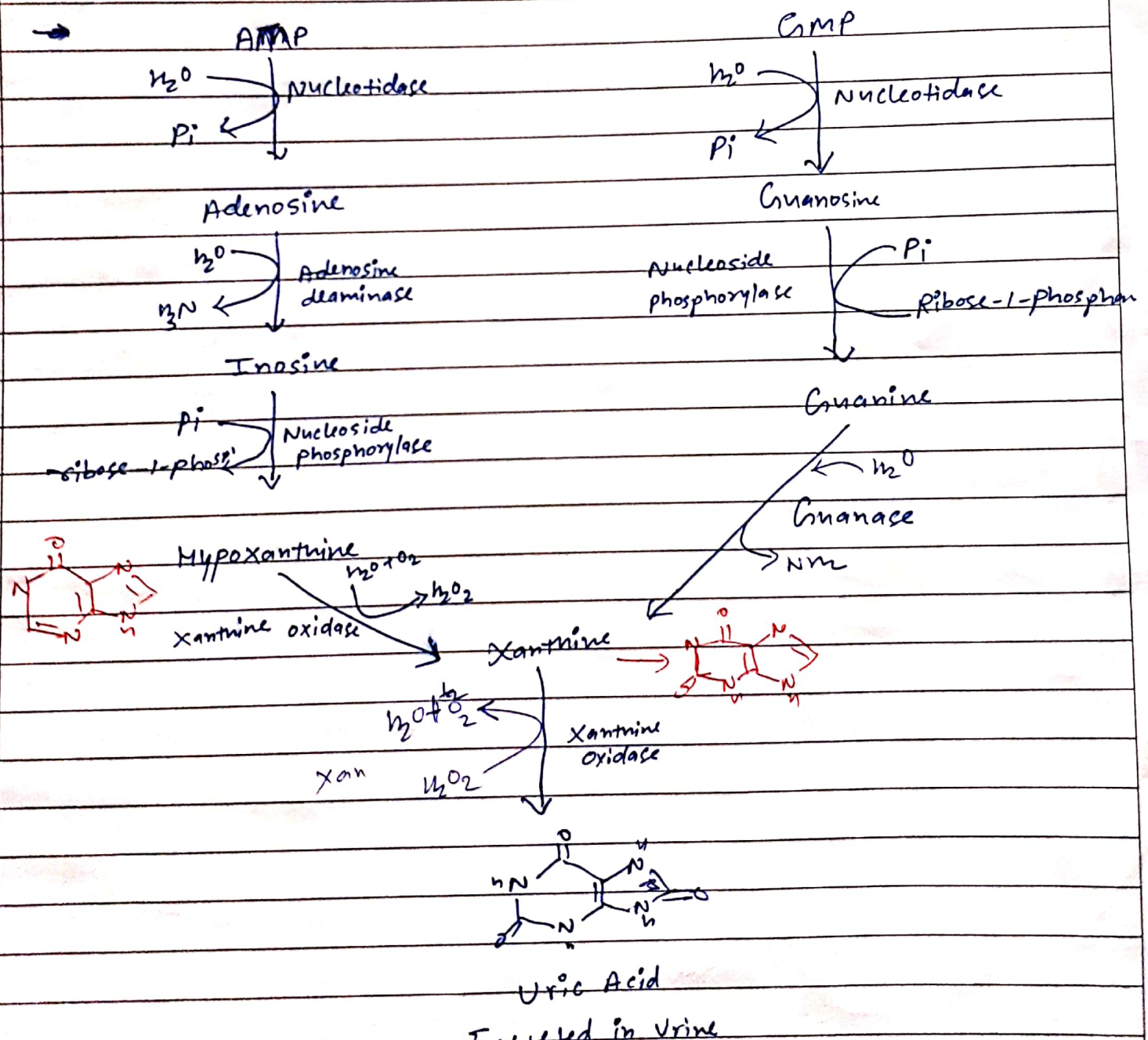
Ribosyl-5-phosphate

GMP

Catabolism of Purine Nucleotides

→ The Catabolic end product of purine nucleotides is Uric acid

→



Disorder of purine metabolism:

(1) Gout :. Catagorised by ↑ level of uric acid in serum due to less excretion & more production.

The disease associated with hyperuricemia

→ disease Characterised by deposition of urate crystal in soft tissue that affect joints & then lead to painfull arthritis

→ deposition of excess urate in kidney (kidney stones) tubules & lead to kidney failure.

primary gouts

(due to deficeny in feed back inhibition of enzyme of denovo pathway) & deficiency salvage pathway

Secondary gouts

→ excess degradation of purine nucleotide to uric acid in disease condition such as Cancers, psoriasis, trauma

→ Decreased elimination of uric acid due to reduced glomerular filtration rate

Treatment :. nutritional & drug therapy

(1) Avoid food containing rich in purine such as coffee, Tea, liver

(2) drug → Allopurinal → analog of Hypoxanthin → which inhibit compitatively Xanthine oxidase → decrease formation of uric acid & ↑ excretion of soluble Xanthine & Hypoxanthine.