

## NUCLEOTIDES

### Occurrence

Nucleotides are present in all types of cells.

### MEDICAL AND BIOLOGICAL IMPORTANCE

1. Nucleotides are high energy compounds.
2. Nucleotides are required for formation of co-enzymes of some members of vitamins B complex group.
3. Some nucleotides are called as 'second messenger' because many hormones exert their action through nucleotides.
4. Some nucleotides act as carrier or donor of activated sugars, sulphates and nitrogenous compounds.
5. Some nucleotides are involved in signal transduction.
6. Some nucleotides are involved in regulation of metabolic pathways.
7. Nucleotides act as alarmones. They regulate cell metabolism and alarm cell when all is not well in cell.
8. Synthetic analogs of nucleosides and nitrogenous bases are anticancer and antiviral agents.
9. Some nitrogenous bases are CNS stimulants.
10. Some bases act as anti-oxidants.
11. Some nucleotide analogs are mutagens.
12. Nucleosides also act as carriers of groups or compounds.
13. Nucleotides are building blocks of nucleic acids.
14. Purines play major role in cardiovascular biology in normal and pathological conditions. They are involved in cardiac aging, angiogenesis, hypertension etc. Purino receptors are identified in cardiovascular system.
15. Cyclic nucleotide cAMP is involved in regeneration of nervous tissues that are injured.
16. Some nucleotides are involved in regulation of ion channel activity. For example, ATP sensitive K<sup>+</sup> channel couple cell metabolism to either cell excitability or potassium secretion.
17. Purine nucleotides support rotation of  $\gamma$ -subunit of ATP synthase of electron transport chain. Extra ring in purines is indispensable for the operation of molecular motor.

### Chemical nature of nucleotides

Hydrolysis of nucleotides produce nitrogen bases, sugars and phosphate.

*Nitrogenous bases.* Nucleotides contain two types of nitrogenous bases. They are purine bases and pyrimidine bases.

### Purine bases

They are derived from parent compound purine. Purine contains heterocyclic ring system. Fusion of pyrimidine ring with imidazole yields purine ring. The carbon (c) and

nitrogen (N) atoms of purine ring are numbered in anti-clockwise direction .

The purines present in nucleotides are adenine and guanine.

Other purine bases are hypoxanthine and xanthine. They are intermediates in the formation of adenine and guanine nucleotides. Uric acid is another purine base. It is the end product of purine nucleotide catabolism.

### **Physicochemical properties of purine bases**

1. Purine bases are sparingly soluble in water. Uric acid and xanthine tend to crystalize at physiological pH at high concentration.
2. Purine bases absorb light in UV region at 260 nm. This property is used for detection and quantitation of purine nucleotides.
3. Purine bases are capable of forming hydrogen bonds.
4. Purine bases like guanine exhibit keto-enol tautomerism at body pH. The ketoform predominates. However, small amount of enol form is present
5. Purine bases exhibit amino-imino tautomerism at body pH. However, amino form predominates

### **Pyrimidine bases**

Pyrimidine bases are derived from parent compound pyrimidine. Pyrimidine is a heterocyclic compound.

The pyrimidine bases present in nucleotides are cytosine, uracil and thymine.

Other pyrimidine bases are orotic acid and dihydroorotic acid. They are intermediates in the formation of pyrimidine nucleotides.

### **Physicochemical properties of pyrimidine bases**

1. Pyrimidine bases are soluble in water at body pH.
2. Pyrimidine bases also absorb UV light at 260 nm. This property is used to detect and estimate pyrimidine nucleotides.
3. They are capable of forming hydrogen bonds.
4. They too exhibit keto-enol tautomerism as well as amino-imino tautomerism like purine bases.

### **Unusual or minor purine and pyrimidine bases**

These bases are present in trace amounts in nucleotides compared to above mentioned bases. Hence, they are referred as minor bases or rare bases. They are dihydrouracil, thiouracil, isopentenyladenine, methyl adenine, dimethyl adenine, methylguanine, dimethylguanine, methyl cytosine and hydroxy methyl cytosine.

In plants some pharmacologically active purine bases are identified. They are caffeine of coffee, theophylline of tea, and theobromine of cocoa. Caffeine and theophylline act as CNS stimulants. Recently antioxidant function of caffeine has been discovered. Some inhalers contain theophylline which are used by asthmatics. Mostly it relieves nasal and bronchial congestion.

## **Sugars**

Two types of pentose sugars are found in nucleotides. They are ribose and deoxy ribose. Nucleotides are named according to the type of sugar present. If the sugar is deoxyribose then nucleotide is named as deoxyribonucleotide. Similarly, if the sugar is ribose then nucleotide is named as ribonucleotide.

### **Some characteristic features of sugar present in nucleotides**

1. Normally it is a 5-numbered furanose ring.
2. Only D-isomer is present.
3. Configuration around first carbon atom is ' $\beta$ '-form.
4. As mentioned earlier in deoxyribose, only hydrogen is present instead of OH group of 2 carbon atom of furanose ring.

## **Nucleosides**

A nucleoside is composed of purine and pyrimidine base and sugar. In the case of purine nucleosides, the sugar is attached to N-9 of purine ring where as in pyrimidine nucleosides the sugar is attached to N-1 of pyrimidine ring . So, the type of linkage is Nglycosidic and sugar can be ribose or deoxyribose.

corresponding nucleotides

### **NOMENCLATURE OF NUCLEOSIDES**

Nucleosides are named as derivatives of bases. For example, adenine linked to ribose is called as adenosine. Capital letter A is used to indicate adenine containing nucleoside. If adenine is linked to deoxyribose then it is named as deoxy adenosine and it is abbreviated as dA.

### **Base Nucleosides Abbreviation**

Adenine Adenosine A

Deoxyadenosine dA

Guanine Guanosine G

Deoxyguanosine dG

Hypoxanthine Inosine I

Xanthine Xanthosine

Cytosine Cytidine C

Deoxycytidine dC

Thymine Ribothymidine T

Deoxythymidine dT

Uracil Uridine U

Dehydrouracil Pseudouridine  $\Psi$

Orotic acid Orotidine O

## **Nucleotides**

They are phosphorylated nucleosides. Usually one or two of hydroxyl groups of ribose

(deoxyribose) are phosphorylated. Thus, a nucleotide has three structural components. They are nitrogenous base, sugar and phosphate. Phosphate is attached to ribose through an ester linkage.

### **Nomenclature of nucleotides**

Since nucleotides are phosphorylated nucleosides, the name of a nucleotide is composed of name of nucleoside and phosphate. The attachment position of phosphate to ribose is indicated with Arabic numeral. Further, a prime mark after numeral is used to differentiate numbered position of ribose from the numbered position of base. Usually nucleotides containing single phosphate are called as monophosphates. Thus a nucleotide of adenosine containing one phosphate on C-3 of ribose is named as adenosine monophosphate (AMP) and adenosine-3'-phosphate (A-3'-P) more precisely. If the sugar is deoxyribose then it is called as deoxy adenosine-3'-phosphate (dA-3'-P). If the phosphate is attached to C-5 of ribose then it is named as adenosine-5'-phosphate. Generally nucleotide mono phosphates in which phosphate is attached to C-5 of ribose are named without primed numeral. Hence, adenosine-5'-phosphate is called as *adenosine monophosphate* .

Because of phosphate nucleotides are acidic in nature. Hence they are named by adding word 'lic acid' to the name of the base or nucleoside. For example nucleotide of adenine is called as adenylic acid. Nucleotide of uracil is named as uridylic acid

### **Nucleoside di and triphosphates**

They are nucleosides in which two or three phosphate groups are attached to C-5 or C-3 of ribose. Since they are phosphorylated nucleosides they are nucleotides also. For example, adenosine with two phosphates attached to ribose is called as adenosine diphosphate (ADP). Likewise adenosine triphosphate (ATP).

Phosphates are in acid anhydride forms.

#### **Name of diphosphate Abbreviation**

Adenosine diphosphate ADP  
Deoxy Adenosine dADP diphosphate

Guanosine diphosphate GDP  
Deoxy Guanosine dGDP Diphosphate

Cytidine diphosphate CDP  
Deoxy Cytidine dCDP diphosphate  
Thymidine diphosphate TDP  
Deoxy Thymidine dTDP diphosphate  
Uridine diphosphate UDP

#### **Name of triphosphate Abbreviation**

Adenosine triphosphate ATP  
Deoxy Adenosine dATP triphosphate

Guanosine triphosphate GTP  
Deoxy Guanosine dGTP triphosphate

Cytidine triphosphate CTP  
Deoxy Cytidine dCTP triphosphate  
Thymidine triphosphate TTP  
Deoxy Thymidine dTTP triphosphate  
Uridine triphosphate UTP

### **Dinucleotides**

They consist of two nucleotides. They are joined together by phosphodiester linkage. 3'-OH of first nucleotide is linked to 5'-OH of second nucleotide through the phosphodiester

linkage .

Two co-enzymes, which are dinucleotides are NAD<sup>+</sup> (NADP<sup>+</sup>) and FAD. But in these dinucleotides, nucleotides are held together through anhydride linkage formed between phosphate of first nucleotide and phosphate of second nucleotide . Further in FAD the glycosidic linkage between sugar and base is absent.

### **Oligonucleotides**

They consist of less than ten nucleotides but more than two nucleotides. Nucleotides are joined by phosphodiester linkage.

Example: oligo adenylate.

### **Naturally occurring nucleotides**

Cells contain several free nucleotides. Several biological processes depends on free nucleotides.

#### **Adenine nucleotides and their functions**

1. ATP is energy currency of cell. In mammalian cells, its concentration is about 1 mM/L.
2. Oxidative phosphorylation of respiratory chain requires ADP. ADP is a high energy compound.
3. ATP, ADP and AMP are allosteric effectors of several enzymes.
4. Several hormones exerts their action through cyclic AMP or cAMP .
5. Phosphoadenosine phosphosulfate (PAPS) is the donor of sulfate groups in many biosynthetic reactions .
6. Adenine nucleotides are constituents of FAD and NAD<sup>+</sup>, NADP<sup>+</sup> (Fig. 14.6), coenzyme A and vitamin B12 co-enzyme.
7. Diadenosine triphosphate and diadenosine poly phosphate are neurotransmitters and affect platelet aggregation and blood pressure.
8. Oligoadenylate is mediator for interferon action.
9. ATP is required for protein biosynthesi

#### **Guanine nucleotides and their functions**

1. GTP and GDP are high energy compounds. They participate in energy-dependent reactions.
2. GTP is required for protein biosynthesis.
3. Many hormones mediate their action though cyclic GMP or cGMP. cGMP is involved in vasodilation and smooth muscle relaxation.
4. G-proteins, which requires GTP and GDP are involved in signal transduction of several biological processes like vision, taste, metabolic regulation, olfaction, and cancer.
5. RNA is catalytically active in presence of GMP or Ribozyme action depends on GMP.
6. GDP is carrier of activated sugars in biosynthesis of mucopolysaccharides.

#### **Hypoxanthine nucleotides**

1. IDP and IMP are high energy compounds.

2. IMP is intermediate in purine ribonucleotide synthesis.

### **Uracil nucleotides**

1. UTP and UDP are high energy compounds.
2. UDP is carrier of activated sugars and amino sugars needed for the synthesis of glycogen, glycoprotein, gangliosides etc.
3. UDP-glucuronate serve as donor of glucuronide in conjugation reactions. For example, formation of bilirubin diglucuronide and detoxication reactions.

### **Cytosine nucleotides**

1. CTP and CDP are high energy compounds.
2. CDP-choline serve as donor of choline in biosynthesis of phospholipid.
3. CMP-NANA is donor of NANA in biosynthesis of gangliosides.
4. Cyclic CMP also exist in cells.

### **Adenine nucleoside**

S-adenosyl methionine is a adenine nucleoside. It is the donor of methyl groups in biosynthesis reactions.

### **Purine and pyrimidine analogs**

Several synthetic analogs of purines and pyrimidines are used as anti-cancer agents. Their actions are detailed in next chapter.

#### **Purine analogs**

1. Mercaptopurine
2. Thioguanine
3. 2-Aminopurine
4. Allopurinol
5. Azathiopurine. A modified mercaptopurine. It is an immune suppressive agent.

#### **Pyrimidine analogs**

1. 5-Fluorouracil

#### **Nucleoside analogs**

Nucleoside analogs containing modified bases or sugars are used as anti-cancer agents, anti-viral agents and mutagens.

1. **Deazauridine** It is nucleoside with unnatural base. It is anti-cancer drug.
2. **6-Azauridine** Another nucleoside with unnatural base. An anti-cancer agent.
3. **Adenine arabinoside (Ara-A)** It is a nucleoside with abnormal pentose. It acts as anti-cancer agent as well as anti-viral agent.
4. **Arabinosyl cytosine (Ara-C)** It is a cytosine arabinoside used in cancer treatment.
5. **AZT (3'-azido-3'-deoxy thymidine) or Azido thymidine** It is used in treatment of AIDS. It can prevent progression of the disease if given at an early stage.
6. **Dideoxy cytidine** It is used in viral infections.
7. **Bromodeoxy uridine** It is a mutagen.
8. **Iododeoxy uridine** It is an anti-viral agent.
9. **Fluorodeoxy uridine** It is anti-cancer agent.

## **EXERCISES**

### **ESSAY QUESTIONS**

1. Give an account of naturally occurring nucleotides.
2. Define nucleoside, nucleotide. Give purine and pyrimidine based example for each. Write functions of nucleotides and nucleosides.

### **SHORT QUESTIONS**

1. Name purine and pyrimidine bases found in nucleic acids.
2. Write structures of purine and pyrimidine bases indicating numbers of carbon and nitrogen atoms.
3. Write composition of nucleoside, nucleotide, dinucleotide and oligonucleotide.
4. Write functions of adenine nucleotides.
5. Write briefly about unusual nucleosides.
6. Name pyrimidine nucleoside analogs. Write their clinical importance.
7. Write cAMP and PAPS structures label components.
8. Write on nucleoside and nucleotide triphosphates.