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18/mhs06/058
Medical laboratory science
Clinical Biochemistry and Xenobiotics
BCH 202

Question
Study questions
1. Classify vitamins. Hence, write on the biochemical significance of vitamins.
2. Water soluble vitamins are precursors of coenzymes. With the aid of two named vitamins, describe the role of coenzymes in metabolism.
3. Describe the nomenclature of nucleosides, nucleotides, and nucleic acid.
4. With the aid of an adequate pathway, discuss the involvement of vitamin A in vision.
5. Account for the response of an individual's vision on exposure to bright light and dim light.
6. Describe the biosynthetic pathway involving the exposure of sunlight on skin, and its relation to a named vitamin.
7. Comment on the effects of acids and alkalis on nucleic acids.
8. Write on the contributions of Watson–Crick in the structure of DNA.
9. In a tabular form, differentiate between DNA and RNA.
10. Discuss the functions of nucleotides.

Answer

1. Classes of vitamins

A. Fat soluble vitamins
i) vitamin A
ii) vitamin D
iii) vitamin E
iv) vitamin K
B. Water soluble vitamins
i) thiamine
ii) riboflavin
iii) niacin
iv) pantothenic acid
v) pyridoxine
vi) biotin
vii) cobalamin
viii) vitamine C
The biochemical importance of vitamins include;

- Thiamine (B1) is a cofactor (TPP) for multiple enzymes including pyruvate dehydrogenase, alpha-ketoglutarate, transketolase, and branched-chain ketoacid dehydrogenase, all of which are involved in glucose breakdown. Deficiency can result in adenosine triphosphate (ATP) depletion, and often affects highly aerobic tissues such as the brain, nerves, and heart first. With heart involvement, it is called wet beriberi and is characterized by high-output heart failure, edema, and dyspnea on exertion. When the nervous system is involved, it is called dry beriberi, which is characterized by polyneuritis and symmetrical muscle wasting. Damage to the medial dorsal nucleus of the thalamus and the mammillary bodies in the brain can result in a condition called Wernicke encephalopathy, recognized by the classic triad of confusion, ophthalmoplegia, and ataxia, or Wernicke-Korsakoff syndrome when accompanying confabulation, personality change, and memory loss is present.[3] Thiamine deficiency often is part of the presentation in alcoholics secondary to malnutrition and malabsorption, in addition to patients suffering from malnutrition.
- Riboflavin (B2) is a cofactor in redox reactions (FAD and FMN). Deficiency leads to cheilosis (inflammation of lips and fissures of the mouth) as well as corneal vascularization. Of note, ultraviolet (UV) light can destroy riboflavin; hence it is always packaged in opaque containers.[4]
- Niacin (B3) is also utilized in redox reactions (as NAD+ and NADP+) and derives from tryptophan. Deficiency can present as pellagra, otherwise known as the 3-D's: diarrhea, dermatitis, and dementia. Deficiency is rare in the USA but can occur in alcoholics and those with

malnutrition. Niacin can be used to treat dyslipidemia, and a side effect is facial flushing, which can be avoided by treatment with aspirin.[5]

- Pantothenic acid (B5) is a component of coenzyme A and fatty acid synthase, both of which are necessary for energy production and formation of hormones. Deficiency is characterized by dermatitis, enteritis, alopecia, and adrenal insufficiency.[6]
- Pyridoxine (B6) is converted to pyridoxal phosphate (PLP) and is part of reactions including transamination, decarboxylation, and glycogen phosphorylase. It is critical for the formation of red blood cells and deficiency can result in sideroblastic anemia, hyperirritability, convulsions, peripheral neuropathy, and mental confusion. Peripheral neuropathy is a potential side effect of isoniazid, a key drug utilized in the treatment of tuberculosis, and it is customary to supplement treatment with B6.[7]
- Biotin (B7) is necessary for the metabolism of protein, fats, and carbohydrates. Deficiency can lead to muscle pain, heart problems, anemia, and depression. Additionally, since biotin is a contributor to keratin, biotin has become popularized as a supplement to improve the quality of hair, skin, and nails. Large, unregulated doses of biotin can skew a variety of clinical tests, including thyroid tests T3 and T4, which can be either falsely elevated or falsely lowered depending on the particular assay; this is because nearly all immunoassays rely on the biotin-streptavidin attraction. This binding is also responsible for the biotin deficiency seen as a result of chronic consumption of large amounts of raw egg whites, as raw egg whites contain a high volume of intact avidin, which strongly binds biotin. When egg whites are cooked, the avidin denatures and does not bind biotin as avidly.[8] Of note, TSH levels are unaffected by biotin supplementation.
- Folate (B9) is converted to tetrahydrofolate and is vital DNA and RNA synthesis. Deficiency can result in neural tube defects, prompting folate supplementation during pregnancy, and macrocytic (MCV>100), megaloblastic anemia. Folate deficiency may also be a feature in alcohol use disorder.[9]
- Cobalamin (B12) is essential for erythropoiesis and growth of the nervous system. Deficiency may lead to pernicious anemia and subacute combined degeneration of the spinal cord. The macrocytic, megaloblastic anemia from B12 deficiency presents similarly to folate deficiency, and to differentiate them it’s imperative to obtain serum homocysteine and methylmalonic acid levels. In folate deficiency, homocysteine will elevate, but methylmalonic acid levels will be normal. In vitamin B12 deficiency, both homocysteine and methylmalonic acid levels will present as elevated. Additionally, B12 deficiency will present with neurologic symptoms whereas folate deficiency will not.[10]
- Vitamin C (Ascorbic Acid, Ascorbate) is needed for growth of collagen, wound healing, bone formation, enhancing the immune system, absorption of iron, strengthening blood vessels and acting as an antioxidant. When deficiency occurs, it can result in scurvy which can present with swollen and bleeding gums, loss of teeth, poor wound healing, and poor tissue growth.

2. Thiamine (B1)

Thiamine (vitamin B1) is a water soluble sulfur-containing vitamin that plays an essential role in energy metabolism, from the tricarboxylic acid cycle.
The critical role of thiamine in carbohydrate metabolism and its connection with GSH (reduced glutathione) generation. Thiamine, through TPP, is an indispensable cofactor for PDH without which the entry into the Krebs cycle is blocked that leads to lactate accumulation. TPP is also an essential cofactor of the enzymes: α-KDH for conversion of (α-ketoglutarate to succinyl CoA in the Krebs cycle, and Transketolase in the pentose phosphate pathway for regeneration of GSH from oxidized glutathione (GSSG) and energy production.
LDH, lactate dehydrogenase.
TPP, thiamine pyrophosphate;
PDH, pyruvate dehydrogenase;
α-KDH, α-ketoglutarate dehydrogenase.

RIBOFLAVIN (B2)

Riboflavin (vitamin B2) is an important part of the enzyme cofactors FAD (flavin-adenine dinucleotide) and FMN (flavin mononucleotide). The name "riboflavin" actually comes from "ribose" and "flavin". Like the other B vitamins, riboflavin is needed for the breaking down and processing of ketone bodies, lipids, carbohydrates, and proteins. Riboflavin is found in many different foods, such as meats and vegetables.As the digestion process occurs, many different flavoproteins that come from food are broken down and riboflavin is reabsorbed. The reverse reaction is mediated by acid phosphatase 6. FMN can be turned into to FAD via FAD synthetase, while the reverse reaction is mediated by nucleotide pyrophosphatase. FAD and FMN are essential hydrogen carriers and are involved in over 100 redox reactions that take part in energy metabolism.

3. NUCLEOSIDES

When ribose or 2-deoxyribose is combined with a pentose sugar, purine or pyrimidine base, then the combination
is called nucleoside. A nucleoside is a nucleotide that is missing the phosphate portion. Adenine, guanine, and cytosine are found
Thus Nucleoside = Sugar + Nitrogen Base

Naming System for Nucleosides:

| For DNA | Nomenclature |
|---|---|
| Adenine, guanine, cytosine, thymine. | Deoxyadenosine, Deoxyguanosine, Deoxycitidine, and Deoxythimidine respectively. |
| For RNA | Nomenclature |
| Adenine, guanine, cytosine, and Uracil | Adenosine, guanosine, Cytidine and uridine respectively. |

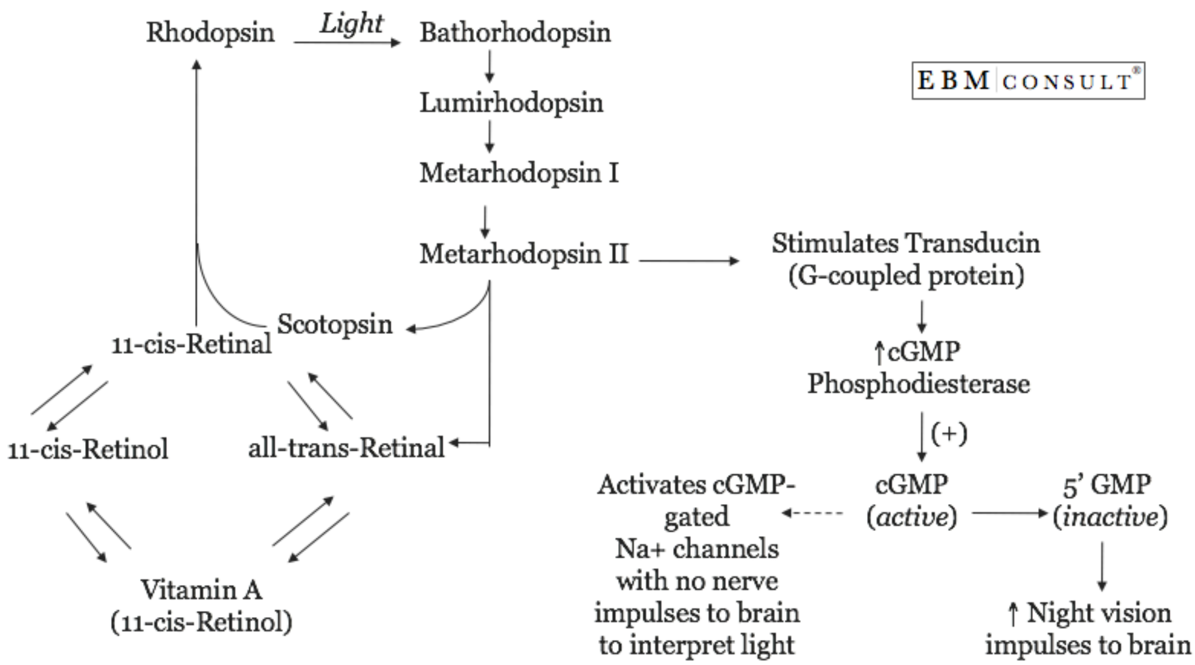
Nucleotides:
The nucleotides are named according to their
Adenine Deoxyadenosine nitrogenous base. For e.g. a nucleotide containing Deoxyribose thymine is called thymine nucleotide.
Guanine Deoxyguanosine
Thus Nucleotide = Pentose Sugar + Nitrogen base
+ Phosphate Group
Cytosine Deoxycitidine
or Nucleotide = Nucleoside + Phosphate Group

Naming System for Nucleotides

| For DNA | Nomenclature |
|---|---|
| Adenine, guanine, cytosine, thymine. | Deoxyadenosine 5’- monophosphate (dAMP), deoxyguanosine 5’- monophosphate.... |
| For RNA | Nomenclature |

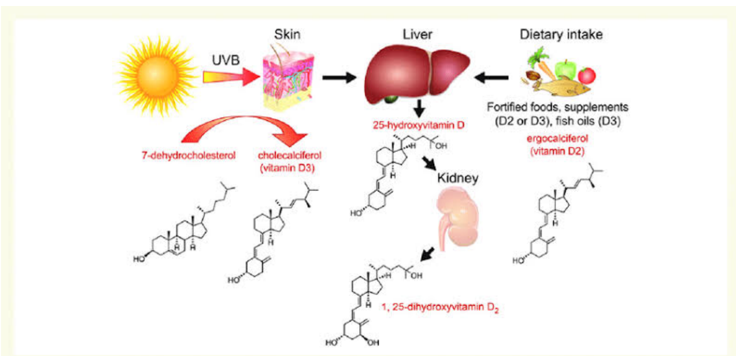
| | |
|---|---|
| Adenine, guanine, cytosine, and Uracil | Adenosine-5-monophosphate, guanosine-5-monophosphate... |

4. Vitamin A has been shown to be useful in helping with nighttime vision, but not daytime vision. Our ability to see is dependent on two main photoreceptors that sit in the posterior aspect of the eye, the rods and cones (with the rods outnumbering the cones by a ratio of 20:1). To be able to see, light must first enter into and pass through the lens of the eye and then travel through the posterior segment (vitreous chamber). Next, light must travel through ten layers of the neural retina to get to the rods and cones. The rods and cones are made up of an inner segment that contains the nucleus and an outer segment that is made up of discs that contain light-absorbing photopigments. When comparing the two photoreceptors, the rods are useful for night vision and the cones are useful for day vision. Vitamin A is one of the required precursors for the formation of rhodopsin, the photopigment found in rods. Rhodopsin helps us to see at night and without vitamin A, rhodopsin cannot form and "night blindness" occurs.




5. In dim light, the pupil expands to allow more light to enter the eye. In bright light, it contracts. The hole in the centre of the iris is the pupil. The amount of light entering the eye is controlled by the muscles of the iris which contract or dilate the pupils. The pupil becomes larger in less light to allow more light to go in and in bright light it constricts or becomes smaller to restrict the amount of light going in.

6. The biosynthetic pathway involving the exposure of sunlight on skin:



Our skin naturally contains a precursor to vitamin D. When the sun's ultraviolet rays touch the skin, they convert the precursor to a molecule called vitamin D3, which then follows a metabolic pathway through the liver and finally to the kidneys, where it's converted into a molecule called calcitriol. Vitamin D obtained from food or supplements must also follow that metabolic pathway to become active.

7. The damage that an acid or an alkali can cause to DNA depends on the concentration in which the nucleic acid is been exposed to and also another major factor to be considered here is which type of DNA is considered, i.e. Genomic DNA or Plasmid DNA, if Genomic then whether prokaryotic, viral or eukaryotic, etc.

Considering the effect of alkali to the genomic DNA:

1. If DNA is exposed to low concentration of alkali:

Low concentration of alkali will not be too harmful to the nucleic acid though some damage is obviously incurred like for instance denaturation of some binding proteins or breakage of a few hydrogen bonds of the base pairing,etc.

2. If DNA is exposed to moderate concentration of alkali:

Moderate concentrate of alkali causes deprotonation and the hydrogen bonding between the base pairs is disrupted causing the DNA to denature.

3. If DNA is exposed to high concentration of alkali:

High concentration of base will induce a hydrolysis of the phosphodiester bonds of the DNA and the DNA will be cleaved into smaller fragments.

Alkali treatment is often used for isolation of plasmid DNA or any other extra chromosomal material so as to ensure the degradation of genomic DNA to avoid contamination of it into the desired product.

·Considering the effect of Acid on Genomic DNA:

1.If DNA is exposed to low pH conditions:

At low pH i.e. acidic conditions, the DNA is deprived of the purines. This causes DNA melting. Also since A+G content is lost 50% of the sequence of the DNA is lost.

2.If DNA is exposed to extremely low pH conditions ($pH<3$)

At extremely low pH i.e. high acidic conditions the phosphodiester bonding of the DNA is disrupted which cleaves the DNA into nucleosides and nucleotides.

The effect of acid on DNA is the reason as to why the pH in the stomach is low. Since the pH is nearing 2.0 most of the bacterial load is reduced prior to digestion and decontaminated food is passed further.

Acid effect on RNA is variable. RNA is more resistant to acid hydrolysis compared to DNA.

8. Watson and Crick Propose the Double Helix:

Chargaff's realization that A = T and C = G, combined with some crucially important X-ray crystallography work by English researchers Rosalind Franklin and Maurice Wilkins, contributed to Watson and Crick's derivation of the three-dimensional, double-helical model for the structure of DNA. Watson and Crick's discovery was also made possible by recent advances in model building, or the assembly of possible three-dimensional structures based upon known molecular distances and bond angles, a technique advanced by American biochemist Linus Pauling. In fact, Watson and Crick were worried that they would be "scooped" by Pauling, who proposed a different model for the three-dimensional structure of DNA just months before they did. In the end, however, Pauling's prediction was incorrect. Using cardboard cutouts representing the individual chemical components of the four bases and other nucleotide subunits, Watson and Crick shifted molecules around on their desktops, as though putting together a puzzle. They were misled for a while by an erroneous understanding of how the different elements in thymine and guanine (specifically, the carbon, nitrogen, hydrogen, and oxygen rings) were configured. Only upon the suggestion of American scientist Jerry Donohue did Watson decide to make new cardboard cutouts of the two bases, to see if perhaps a different atomic configuration would make a difference. It did. Not only did the complementary bases now fit together perfectly (i.e., A with T and C with G), with each pair held together by hydrogen bonds, but the structure also reflected Chargaff's rule

9. Both DNA and RNA are used to store genetic information, but there are clear differences between them.

| Main Differences Between DNA and RNA | | |
|---|---|---|
| **Comparison** | **DNA** | **RNA** |
| Name | DeoxyriboNucleic Acid | RiboNucleic Acid |
| Function | Long-term storage of genetic information; transmission of genetic information to make other cells and new organisms. | Used to transfer the genetic code from the nucleus to the ribosomes to make proteins. RNA is used to transmit genetic information in some organisms and may have been the molecule used to store genetic blueprints in primitive organisms. |
| Structural Features | B-form double helix. DNA is a double-stranded molecule consisting of a long chain of nucleotides. | A-form helix. RNA usually is a single-strand helix consisting of shorter chains of nucleotides. |
| Composition of Bases and Sugars | deoxyribose sugar<br>phosphate backbone<br>adenine, guanine, cytosine, thymine bases | ribose sugar<br>phosphate backbone<br>adenine, guanine, cytosine, uracil bases |

| | | |
|---|---|---|
| Propagation | DNA is self-replicating. | RNA is synthesized from DNA on an as-needed basis. |
| Base Pairing | AT (adenine-thymine)<br>GC (guanine-cytosine) | AU (adenine-uracil)<br>GC (guanine-cytosine) |
| Reactivity | The C-H bonds in DNA make it fairly stable, plus the body destroys enzymes that would attack DNA. The small grooves in the helix also serve as protection, providing minimal space for enzymes to attach. | The O-H bond in the ribose of RNA makes the molecule more reactive, compared with DNA. RNA is not stable under alkaline conditions, plus the large grooves in the molecule make it susceptible to enzyme attack. RNA is constantly produced, used, degraded, and recycled. |
| Ultraviolet Damage | DNA is susceptible to UV damage. | Compared with DNA, RNA is relatively resistant to UV damage. |

10. A nucleotide is an organic molecule that is the building block of DNA and RNA. In addition to their roles as the subunits of nucleic acids, nucleotides have a variety of other functions in every cell: as energy carriers, components of enzyme cofactors, and chemical messengers.

Nucleotides Carry Chemical Energy in Cells:
Nucleotides may have one, two, or three phosphate groups covalently linked at the 5' hydroxyl of ribose. These are referred to as nucleoside mono-, di-, and triphosphates, respectively. Starting from the ribose, the three phosphates are generally labeled α, β, and γ. Nucleoside triphosphates are used as a source of chemical energy to drive a wide variety of biochemical reactions. ATP is by far the most widely used, but UTP, GTP, and CTP are used in specific reactions. Nucleoside triphosphates also serve as the activated precursors of DNA and RNA synthesis.
The hydrolysis of ATP and the other nucleoside triphosphates is an energy-yielding reaction because of the chemistry of the triphosphate structure. The bond between the ribose and the αphosphate is an ester linkage. The α-β and β-γ linkages are phosphoric acid anhydrides. Hydrolysis of the ester linkage yields about 14 kJ/mol, whereas hydrolysis of each of the anhydride bonds yields about 30 kJ/mol. In biosynthesis, ATP hydrolysis often drives less favorable metabolic reactions (i.e., those with $\Delta G0' > 0$). When coupled to a reaction with a positive free-energy change, ATP hydrolysis shifts the equilibrium of the overall process to favor product formation.

Nucleotides Are Components of Many Enzyme Cofactors
A variety of enzyme cofactors serving a wide range of chemical functions include adenosine as part of their structure. They are unrelated structurally except for the presence of adenosine. In none of these cofactors does the adenosine portion participate directly in the primary function, but removal of adenosine from these structures generally results in a drastic reduction of their activities. For example, removal of the adenosine nucleotide (3'-P-ADP)from acetoacetyl-CoA reduces its reactivity as a substrate for β-ketoacylCoA transferase (an enzyme of lipid metabolism) by a factor of 106. Although the reason for this requirement for adenosine has not been examined in detail, it must involve the binding energy between enzyme and substrate (or cofactor) that is used both in catalysis and to stabilize the initial ES complex. In the case of CoA transferase, the nucleotide appears to be a binding "handle" that helps to pull the substrate into the active site. Similar roles may be found for the nucleoside portion of other nucleotide cofactors.

Some Nucleotides Are Intermediates in Cellular Communication
Cells respond to their environment by taking cues from hormones or other chemical signals in the surrounding medium. The interaction of these extracellular chemical signals (first messengers) with receptors on the cell surface often leads to the production of second messengers inside the cell, which in turn lead to adaptive changes in the cell interior. Often, the second messenger is a nucleotide.
One of the most common second messengers is the nucleotide adenosine 3',5'-cyclic monophosphate (cyclic AMP, or cAMP), formed from ATP in a reaction catalyzed by adenylate cyclase, associated with the inner face of the plasma membrane. Cyclic AMP serves regulatory functions in virtually every cell outside the plant kingdom. Guanosine 3',5'-cyclic monophosphate (cGMP) occurs in many cells and also has regulatory functions.
Another regulatory nucleotide, ppGpp, is produced in bacteria in response to the slowdown in protein synthesis that occurs during amino acid starvation. This nucleotide inhibits the synthesis of the rRNA and tRNA molecules needed for protein synthesis, preventing the unnecessary production of nucleic acids.

In summary;

Nucleotides are the basic units of nucleic acids (DNA and RNA). Though, nucleoside monophosphates found in nucleic acids, actually nucleoside triphosphates are the raw materials for their synthesis.
2. Cyclic Nucleotides Act as Regulatory Chemicals. Cyclic AMP (cAMP) functions as second messengers in many hormone actions, while cyclic GMP (cGMP) functions in Ca++ or calmodulin mediated responses.

3. Nucleotides of B-Complex Vitamins Function as Coenzymes. For example, $NAD^+$, $NADP^+$, FMN, FAD are coenzymes useful in oxidation-reduction reactions.
4. Higher nucleotides function as energy carriers, e.g. ATP, GTP, UTP and TTP. Out of these ATP is the universal energy carrier of the cell.