



KARPAGAM ACADEMY OF HIGHER EDUCATION

(Deemed to be University Established Under Section 3 of UGC Act 1956)

Coimbatore – 641 021.

LECTURE PLAN

DEPARTMENT OF BIOCHEMISTRY

STAFF NAME: Dr.P.Anusooriya

SUBJECT NAME: METABOLISM OF AMINOACIDS AND NUCLEICACIDS

SUB.CODE:18BCU302

SEMESTER: III

CLASS: II B.Sc (BC)

Sl. No	Duration of Period	Topics to be Covered	Support material
Unit I: Overview of amino acid metabolism			
1	1	Overview of metabolism : Anabolism and catabolism	T1:241-243
2	1	Nitrogen cycle, incorporation of ammonia into biomolecules	R1: 248- 249
3	1	Metabolic fates of amino groups	R1: 254-256
4	1	Digestion and absorption of dietary proteins Protein calorie malnutrition - Kwashiorkar and Marasmus	T1:169-173
5	1	Nitrogen balance Transamination, Role of pyridoxal phosphate, Glucose-alanine cycle	T1:332-334 T1: 262-263
6	1	Kreb's bicycle Urea cycle Inherited defects of urea cycle	T1: 254-257
7	1	Catabolic pathways of individual amino acids. Glucogenic and ketogenic amino acids	T1: 341-360
8	1	Metabolism of one carbon units	T1: 368-372
9	1	Revision	
		Total no of hours planned for UNIT I = 9	
Unit II: Catabolism of amino acids			
1	1	Disorders of amino acids metabolism	T1:351-352
2	1	Phenylketonuria, Alkaptonuria	T1:352-353
3	1	Maple syrup urine disease	T1:365-366
4	1	Methylmalonic acidemia (MMA)	T1:366-367
5	1	Homocystinuria & Hartnup's disease.	T1:361-362
6	1	Overview of amino acid synthesis	R1: 262-263
7	1	Biosynthesis of non-essential amino acids and its regulation	T1:369-372
8	1	Revision	
		Total no of hours planned for UNIT II = 8	

Unit III: Precursor functions of amino acids			
1	1	Biosynthesis of creatine & creatinine	R1: 270-273
2	1	Polyamines (Putresine, spermine, spermidine)	T1: 375-377
3	1	Catecholamines (dopamine, epinephrine, norepinephrine)	T1:349: 350
4	1	Neurotransmitters (serotonin, GABA)	R2: 859-860
5	1	Porphyrin biosynthesis	T1: 374-376
6	1	Catabolism and disorders of porphyrin metabolism	R1: 279-288
7	1	Revision & Possible QP Discussion	
		Total no of hours planned for UNIT III = 7	
Unit- IV: Biosynthesis of purine and pyrimidine nucleotides			
1	1	<i>De novo</i> synthesis of purine nucleotides	R2: 862-866
2	1	<i>De novo</i> synthesis of pyrimidine nucleotides	R2: 864- 866
3	1	Regulation and salvage pathways	R2:866
4	1	Biosynthesis of deoxyribonucleotides	T1:300-302
5	1	Regulation of deoxyribonucleotides	T1:303
6	1	Conversion to triphosphates	T1: 303-309
7	2	Biosynthesis of coenzyme nucleotides	T1: 390-391
8	1	Revision	
		Total no of hours planned for UNIT IV = 9	
UNIT V Coenzymes			
1	1	Digestion of nucleic acids	R2: 865-870
2	1	Degradation of purine nucleotides.	R2:870-872
3	1	Degradation of pyrimidine nucleotides.	R2: 872-874
4	1	Inhibitors of nucleotide metabolism.	R1:308-309
5	1	Disorders of purine metabolism	R1: 309-310
6	1	Disorders of pyrimidine metabolism	R1: 310-311
7	1	Lesch-Nyhan syndrome, Gout	R2: 875-876
8	1	SCID, adenosine deaminase deficiency, Integration of metabolic pathways (carbohydrate, lipid and amino acid metabolic pathways), Tissue specific metabolism (Brain, muscle, and liver)	T1: 397-398
9	1	Revision	
		Total no of hours planned for UNIT V = 9	
Total planned Hours			48

Support Materials

T1: U.Sathyanarayana & U.Chakrapani (2013), Biochemistry 4th edition.

R1: Robert K.Murray,Daryl.k. Granner &Victor W.Rodwell (2006) Harper's Illustrated Biochemistry, 27th Edition.

R2: Nelson, D.L. and Cox, M.M., (2013). Lehninger: Principles of Biochemistry 6th ed., W.H. Freeman and Company (New York), ISBN:13:978-1-4641-0962-1 / ISBN:10:1-4641-0962.



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Semester III
4H-4C

17BCU302 METABOLISM OF AMINOACIDS AND NUCLEIC ACIDS

Course objectives

- To enable the students to understanding the molecules within cells and interactions between cells that allows construction of multi cellular organisms.
- To understand the molecular machinery of living cells.
- To understand the metabolic pathways of amino acids and nucleic acid metabolism.
- To learn the different ways of anabolism and catabolism of nucleic acids.

Course outcome

- Identify basic structures, names, and properties of nucleic acids
- Demonstrate overview of amino acid metabolism and catabolism of amino acids.
- Understand the chemical logic of metabolic pathways.
- Recognize and understand basic mechanisms of pathway regulation.

Unit 1

Overview of amino acid metabolism: Nitrogen cycle, incorporation of ammonia into biomolecules. Metabolic fates of amino groups. Digestion and absorption of dietary proteins. Protein calorie malnutrition - Kwashiorkar and Marasmus. Nitrogen balance, transamination, role of pyridoxal phosphate, glucose-alanine cycle, Krebs's bicycle, urea cycle and inherited defects of urea cycle.

Catabolism of amino acids: Catabolic pathways of individual amino acids. Glucogenic and ketogenic amino acids. Metabolism of one carbon units.

Unit 2

Catabolism of amino acids

Disorders of amino acids metabolism, phenylketonuria, alkaptonuria, maple syrup urine disease, methylmalonic acidemia (MMA), homocystinuria and Hartnup's disease.

Biosynthesis of amino acids

Overview of amino acid synthesis. Biosynthesis of non-essential amino acids and its regulation.

Unit 3

Precursor functions of amino acids

Biosynthesis of creatine and creatinine, polyamines (putresine, spermine, spermidine), catecholamines (dopamine, epinephrine, norepinephrine) and neurotransmitters (serotonin, GABA). Porphyrin biosynthesis, catabolism and disorders of porphyrin metabolism.

Unit 4

Biosynthesis of purine and pyrimidine nucleotides

De novo synthesis of purine and pyrimidine nucleotides, regulation and salvage pathways.

Deoxyribonucleotides and synthesis of nucleotide triphosphate

Biosynthesis of deoxyribonucleotides and its regulation, conversion to triphosphates, biosynthesis of coenzyme nucleotides.

Unit 5**Degradation of purine and pyrimidine nucleotides**

Digestion of nucleic acids, degradation of purine and pyrimidine nucleotides. Inhibitors of nucleotide metabolism. Disorders of purine and pyrimidine metabolism – Lesch-Nyhan syndrome, Gout, SCID, adenosine deaminase deficiency.

Integration of metabolism

Integration of metabolic pathways (carbohydrate, lipid and amino acid metabolic pathways), tissue specific metabolism (brain, muscle, and liver).

REFERENCES:

Nelson, D.L. and Cox, M.M., (2013). Lehninger: Principles of Biochemistry 6th ed., W.H. Freeman and Company (New York), ISBN:13:978-1-4641-0962-1 / ISBN:10:1-4641-0962.

Devlin, T.M., (2011). Textbook of Biochemistry with Clinical Correlations 7th ed., John Wiley & Sons, Inc. (New Jersey), ISBN:978-0-470-28173-4.

Berg, J.M., Tymoczko, J.L. and Stryer L., (2012). Biochemistry 7th ed., W.H. Freeman and Company (New York), ISBN:10:1-4292-2936-5, ISBN:13:978-1-4292-2936-4.

UNIT-I

SYLLABUS

Overview of amino acid metabolism: Nitrogen cycle, incorporation of ammonia into biomolecules. Metabolic fates of amino groups. Digestion and absorption of dietary proteins. Protein calorie malnutrition - Kwashiorkar and Marasmus. Nitrogen balance, transamination, role of pyridoxal phosphate, glucose-alanine cycle, Krebs's bicycle, urea cycle and inherited defects of urea cycle.

Catabolism of amino acids: Catabolic pathways of individual amino acids. Glucogenic and ketogenic amino acids. Metabolism of one carbon units.

Overview of amino acid metabolism

Metabolism of Amino Acids — General Aspects:

The amino acids undergo certain common reactions like transamination followed by deamination for the liberation of ammonia. The amino group of the amino acids is utilized for the formation of urea which is an excretory end product of protein metabolism.

The carbon skeleton of the amino acids is first converted to keto acids (by transamination) which meet one or more of the following fates:

1. Utilized to generate energy.
2. Used for the synthesis of glucose.
3. Diverted for the formation of fat or ketone bodies.
4. Involved in the production of non-essential amino acids.

A general picture of amino acid metabolism is depicted in Fig. 67.13.

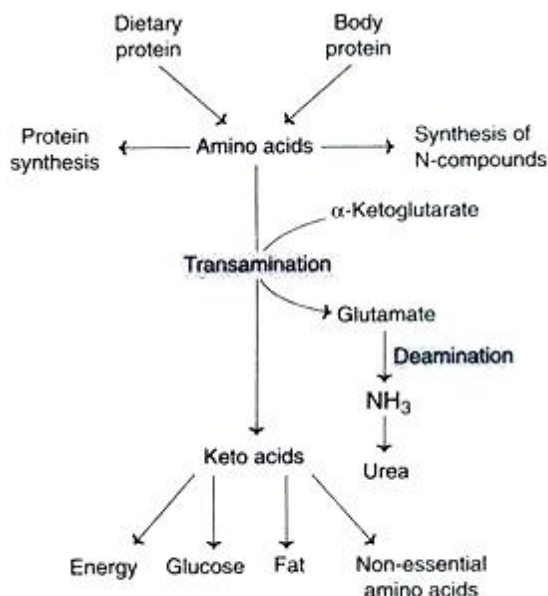
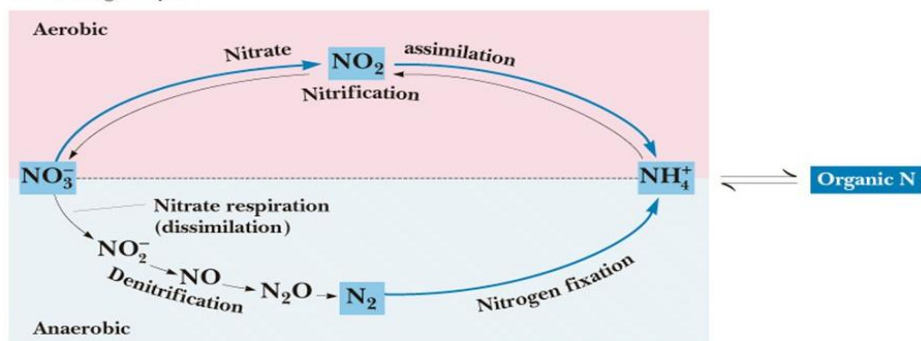


Fig. 67.13 : An overview of amino acid metabolism.

The nitrogen cycle

The Nitrogen Cycle:



All the living organisms are basically composed of carbon, hydrogen, oxygen, nitrogen and many other forms of chemical elements. These elements contribute to finally organize various biomolecules present in a cell. Nitrogen is next to carbon in importance in living organisms. In a living cell, nitrogen is an important constituent of amino acids, proteins, enzymes, vitamins,

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UNIT: **I Overview of amino acid metabolism**

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alkaloids and some growth hormones. Therefore, study of nitrogen metabolism is absolutely essential because the entire life process is dependent on these nitrogen-containing molecules. In this lesson, you will learn about various aspects of nitrogen metabolism including nitrogen fixation and nitrogen assimilation in plants.

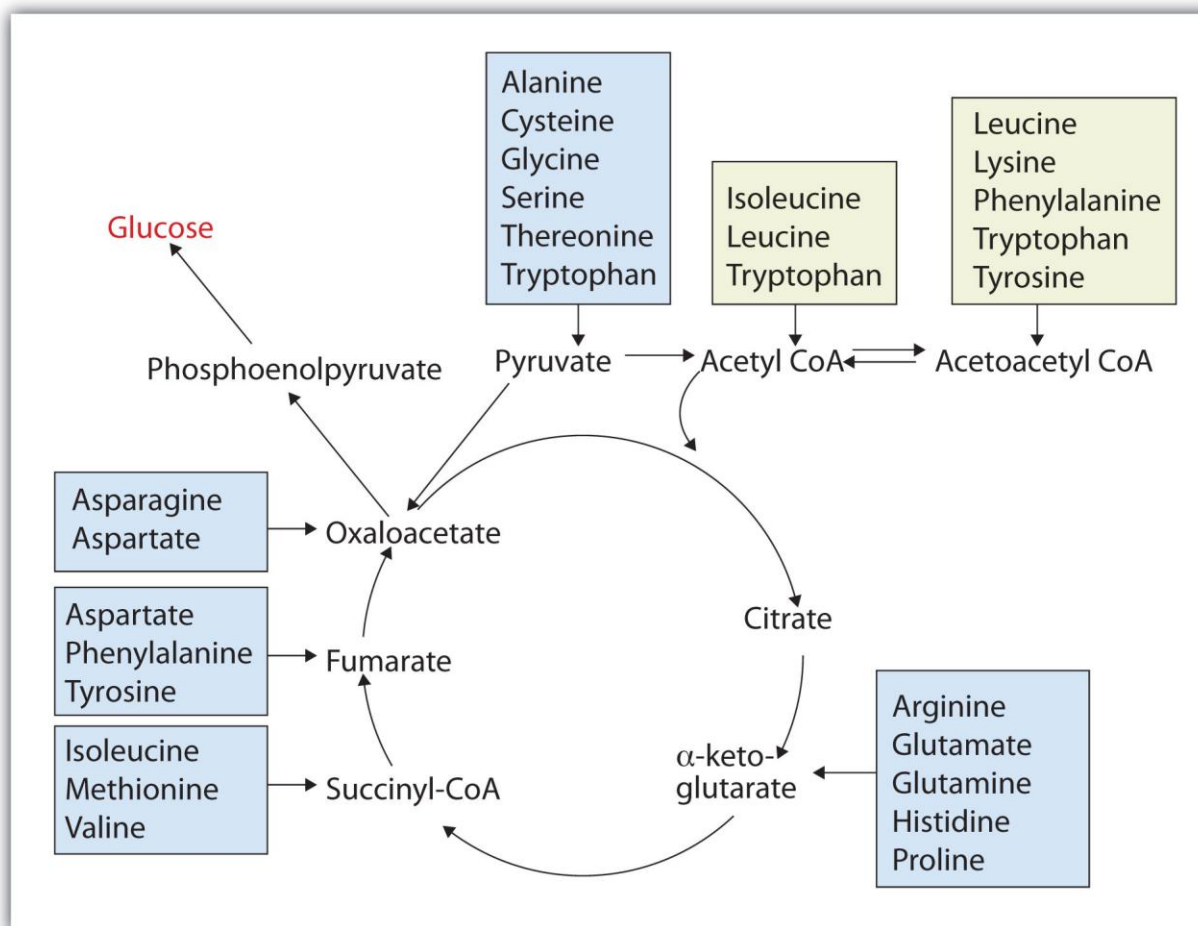
Nitrogen Cycle Plants and animals Nitrogen is an essential constituent of living beings. Nitrogenous bases are part of nucleic acids and proteins are made up of amino acids of which Nitrogen is an important constituent. You already know about the importance of these two biomolecules. Air has 78% N₂ but most of the living beings cannot utilize this atmospheric Nitrogen. Nitrogen cycle converts this nitrogen into a usable form. Lightning fixes Nitrogen to NH₃, and nitrogen fixing bacteria like Rhizobium (which live in roots of leguminous plants like pea, rajma, beans, pulses etc.) also convert N₂ into NH₃. Most plants absorb nitrates from soil and reduce it to NH₃ in the cells for further metabolic reactions. Dead organisms and their excreta like urea are decomposed by bacteria into NH₃ and by a different set of bacteria into nitrates. These are left in the soil for use by plants. In this way Nitrogen cycle is self regulated but human activities have caused steady loss of soil Nitrogen.

The Fate of the Carbon Skeleton

Any amino acid can be converted into an intermediate of the citric acid cycle. Once the amino group is removed, usually by transamination, the α -keto acid that remains is catabolized by a pathway unique to that acid and consisting of one or more reactions. For example, phenylalanine undergoes a series of six reactions before it splits into fumarate and acetoacetate. Fumarate is an intermediate in the citric acid cycle, while acetoacetate must be converted to acetoacetyl-coenzyme A (CoA) and then to acetyl-CoA before it enters the citric acid cycle.

Those amino acids that can form any of the intermediates of carbohydrate metabolism can subsequently be converted to glucose via a metabolic pathway known as gluconeogenesis. These amino acids are called glucogenic amino acids. Amino acids that are converted to acetoacetyl-CoA or acetyl-CoA, which can be used for the synthesis of ketone bodies but not glucose, are

called ketogenic amino acids. Some amino acids fall into both categories. Leucine and lysine are the only amino acids that are exclusively ketogenic.



Digestion and absorption of dietary proteins

The process of digestion is defined as the 'process by which macromolecules in food are broken down into their component small-molecule subunits'. This breakdown would happen impossibly slowly without the involvement of digestive enzymes, which are themselves proteins. Enzymes are often named by adding the ending '-ase' to the name of the substance on which they work. So, the enzymes that break down peptide bonds are called peptidases (protein-digesting enzymes). Although all amino acids are joined by the same peptide bond, the type of R group on

the amino acids on either side of the bond affects the action of the peptidases so much that several different enzymes are usually needed to digest a protein molecule completely.

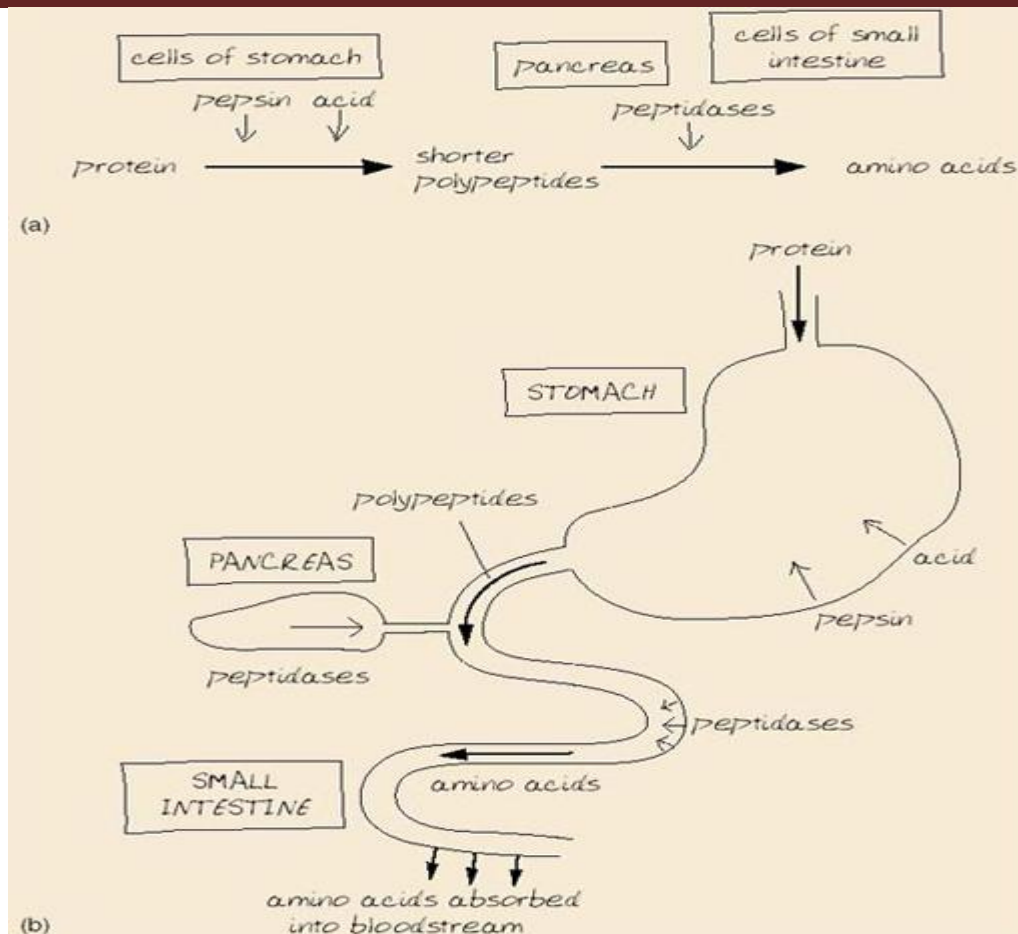
Protein digestion starts in the stomach, the walls of which secrete hydrochloric acid.

An enzyme, called pepsin, produced by cells lining the wall of the stomach, starts to attack some of the peptide bonds and splits the long protein chains into shorter polypeptides. Then more peptidases are released from the pancreas into the small intestine, where they split the polypeptide chains into even smaller lengths and begin to remove individual amino acids from the ends of the chains. Digestion of virtually all the protein in the food into individual amino acids is completed by more peptidases released directly from the cells lining the small intestine. The amino acids are then transported across the wall of the small intestine into the bloodstream. The blood carries them to all the cells of the body, where they can be absorbed and used by each type of cell to make its own particular types of protein by linking them together again, in the order determined by the DNA in the chromosomes.

Protein Digestion

Dietary proteins are very large complex molecules that cannot be absorbed from the intestine.

To be absorbed, dietary proteins must be digested to small simple molecules (amino acids), which are easily absorbed from the intestine.



I-Digestion in the stomach

Protein digestion begins in the stomach by gastric juice.

1- Role of gastric HCl

It causes denaturation of proteins.

It converts proteins to metaproteins, which are easily digested.

It activates pepsinogen to pepsin.

It makes pH in the stomach suitable for the action of pepsin.

2- Pepsin

It is an endopeptidase acting on central peptide bond in which amino group belongs to aromatic amino acids e.g. phenyl alanine, tyrosine and tryptophan.

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It is secreted in an inactive form called pepsinogen.

Its optimum pH: 1.5-2.2

It is activated by HCl then by autoactivation.

3- Rennin

It is a milk-clotting enzyme.

It is present in stomachs of infants and young animals.

Its optimum pH: 4

It acts on casein converting it to soluble paracasein, which in turn binds calcium ions forming insoluble calcium paracaseinate. Calcium paracaseinate is then digested by pepsin.

4- Gelatinase

It is an enzyme that liquefies gelatin.

The end products of protein digestion in the stomach are proteoses, peptones and large polypeptides.

II- Digestion in the small intestine

Digestion of proteins is completed in the small intestine by proteolytic enzymes present in pancreatic and intestinal juices.

A. Pancreatic Juice

1- Trypsin

It is an endopeptidase that hydrolyzes central peptide bond in which the carboxyl group belongs to basic amino acids e.g. arginine, lysine and histidine.

It is secreted in an inactive form called trypsinogen.

Its optimum pH: 8

It is activated by enterokinase enzyme then by autoactivation.

2- Chymotrypsin

It is an endopeptidase that hydrolyzes central peptide bond in which the carboxyl group belongs to aromatic amino acids.

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It is secreted in an inactive form called chymotrypsinogen.

It is activated by trypsin.

Its optimum pH: 8

3- Elastase

It is an endopeptidase acting on peptide bonds formed by glycine, alanine and serine.

It is secreted in an inactive form called proelastase.

It is activated by trypsin.

It digests elastin and collagen.

Its optimum pH: 8

4- Carboxypeptidase

It is an exopeptidase that hydrolyzes the terminal (peripheral) peptide bond at the carboxyl terminus (end) of the polypeptide chain.

It is secreted in an inactive form called procarboxypeptidase.

It is activated by trypsin.

Its optimum pH: 7.4

B. Intestinal Juice

1- Aminopeptidase

It is an exopeptidase that acts on the terminal peptide bond at the amino terminus of the polypeptide chain.

It releases a single amino acid

2- Tripeptidase

It acts on tripeptides

It releases a single amino acid and dipeptide

3- Dipeptidase

It acts on dipeptides

It releases 2 amino acids

The end products of protein digestion in the small intestine are amino acids

Protein Absorption

- It is an active process that needs energy.
- Energy needed is derived from hydrolysis of ATP.
- It occurs in small intestine.
- Absorption of amino acids is rapid in the duodenum and jejunum, but slow in the ileum.

Mechanisms of amino acids absorption

There are two mechanisms for amino acids absorption.

- 1- Carrier proteins transport system
- 2- Glutathione transport system (Glutamyl cycle)

1- Carrier proteins transport system

It is the main system for amino acid absorption.

It is an active process that needs energy.

The energy needed is derived from ATP.

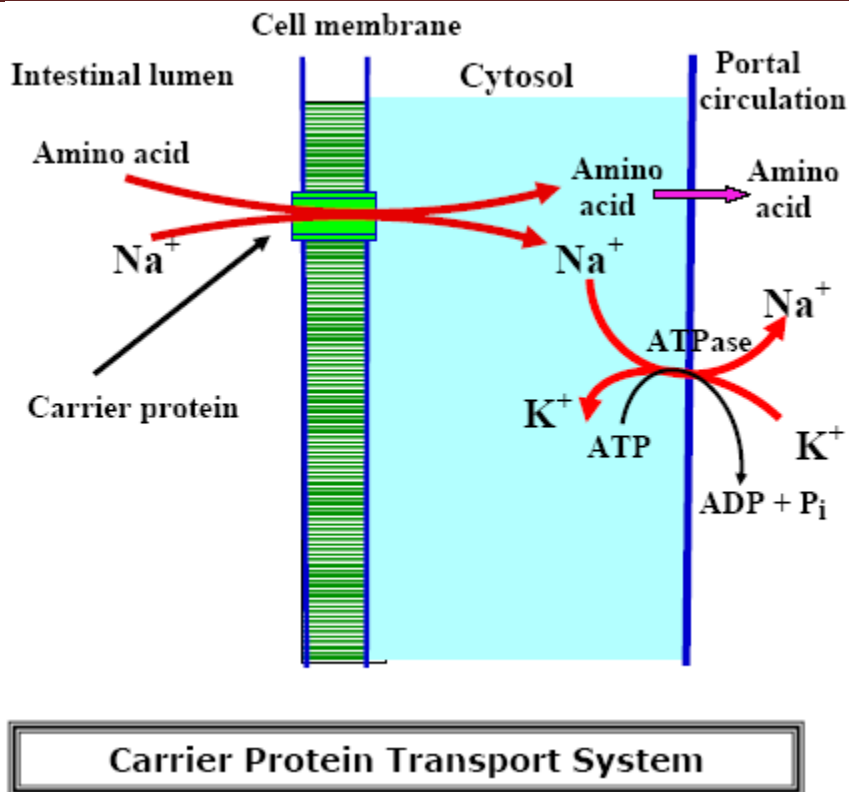
Absorption of one amino acid molecule needs one ATP molecule.

There are 7 carrier proteins, one for each group of amino acids.

Each carrier protein has two sites one for amino acid and one for Na^+ .

It co-transportes amino acid and Na^+ from intestinal lumen to cytosol of intestinal mucosa cells.

The absorbed amino acid passes to the portal circulation, while Na^+ is extruded out of the cell in exchange with K^+ by sodium pump.



2- Glutathione transport system (Glutamyl cycle)

Glutathione is used to transport amino acids from intestinal lumen to cytosol of intestinal mucosa cells.

It is an active process that needs energy.

The energy needed is derived from ATP.

Absorption of one amino acid molecule needs 3 ATP molecules.

Glutathione reacts with amino acid in the presence of glutamyl transpeptidase to form glutamyl amino acid.

glutamyl amino acid releases amino acid in the cytosol of intestinal mucosa cells with formation of 5-oxoproline that is used for regeneration of glutathione to begin another turn of the cycle.

Kwashiorkor

Kwashiorkor is a form of severe protein–energy malnutrition characterized by edema, irritability, ulcerating dermatoses, and an enlarged liver with fatty infiltrates. Sufficient calorie intake, but with insufficient protein consumption, distinguishes it from marasmus. Kwashiorkor cases occur in areas of famine or poor food supply.

Signs and symptoms

The defining sign of kwashiorkor in a malnourished child is pitting edema (swelling of the ankles and feet). Other signs include a distended abdomen, an enlarged liver with fatty infiltrates, thinning hair, loss of teeth, skin depigmentation and dermatitis. Children with kwashiorkor often develop irritability and anorexia. Generally, the disease can be treated by adding protein to the diet; however, it can have a long-term impact on a child's physical and mental development, and in severe cases may lead to death.

Marasmus is a form of severe malnutrition characterized by energy deficiency. A child with marasmus looks emaciated. Body weight is reduced to less than 62.36% of the normal (expected) body weight for the age. Marasmus occurrence increases prior to age 1, whereas kwashiorkor occurrence increases after 18 months. It can be distinguished from kwashiorkor in that kwashiorkor is protein deficiency with adequate energy intake whereas marasmus is inadequate energy intake in all forms, including protein. This clear-cut separation of marasmus and kwashiorkor is however not always clinically evident as kwashiorkor is often seen in a context of insufficient caloric intake, and mixed clinical pictures, called marasmic kwashiorkor, are possible. Protein wasting in kwashiorkor generally leads to edema and ascites, while muscular wasting and loss of subcutaneous fat are the main clinical signs of marasmus.

Signs and symptoms

Marasmus is commonly represented by a shrunken, wasted appearance, loss of muscle mass and subcutaneous fat mass. Edema is not a sign of marasmus and is only present in kwashiorkor, and marasmic kwashiorkor. Other symptoms of marasmus include unusual body temperature (hypothermia, pyrexia), anemia, dehydration (as characterized with consistent thirst and

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shrunk eyes), hypovolemic shock (weak radial pulse, cold extremities, decreased consciousness), tachypnea (pneumonia, heart failure), abdominal manifestations (distension, decreased or metallic bowel sounds, large or small liver, blood or mucus in the stools), ocular manifestations (corneal lesions associated with vitamin A deficiency), dermal manifestations (evidence of infection, purpura, and ear, nose, and throat symptoms (otitis, rhinitis).

Protein degradation/Nitrogen balance

A. Cells constantly turn over proteins

It's a normal process, balanced by protein intake.

Proteins can be degraded if they are:

damaged by free radicals

oxidative damage

misfolded

no longer needed.

B. "Nitrogen Balance" expresses the balance between anabolism and catabolism

1. Measured by assessing dietary N intake vs urinary N output (as urea)

2. "Positive" nitrogen balance (net storage of nitrogenous compounds):

childhood growth

pregnancy

muscle building

healing

3. "Negative" nitrogen balance (net breakdown of stored nitrogenous compounds):

illness

uterine resorption

starvation

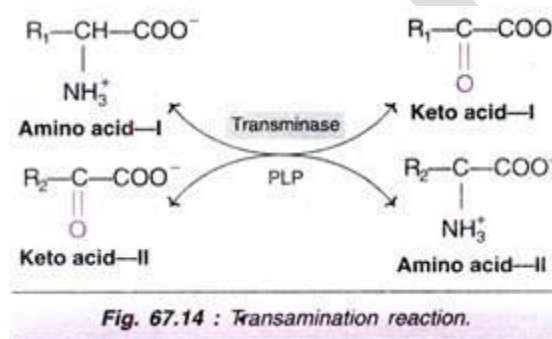
amino acid deficiency

wounding

4. In negative nitrogen balance, the liver may be taxed in handling excess nitrogenous waste. We will revisit this when we discuss pathologies of the nitrogen disposal pathways.

Transamination:

The transfer of an amino ($\sim\text{NH}_2$) group from an amino acid to a keto acid is known as transamination (Fig. 67.14). This process involves the inter-conversion of a pair of amino acids and a pair of keto acids, catalysed by a group of enzymes called transaminases (recently, aminotransferases).



The salient features of transamination are:

1. All transaminases require pyridoxal phosphate (PLP), a coenzyme derived from vitamin B₆.
2. There is no free NH_3 liberated; only the transfer of amino group occurs.
3. Transamination is reversible.
4. It involves both catabolism (degradation) and anabolism (synthesis) of amino acids.

Transamination is ultimately responsible for the synthesis of non-essential amino acids.

5. Transamination diverts the excess amino acids towards energy generation.
6. The amino acids undergo transamination to finally concentrate nitrogen in glutamate.

Glutamate is the only amino acid that undergoes oxidative deamination to a significant extent to liberate free N_3 for urea synthesis.

7. All amino acids except lysine, threonine, proline and hydroxyproline participate in transamination.

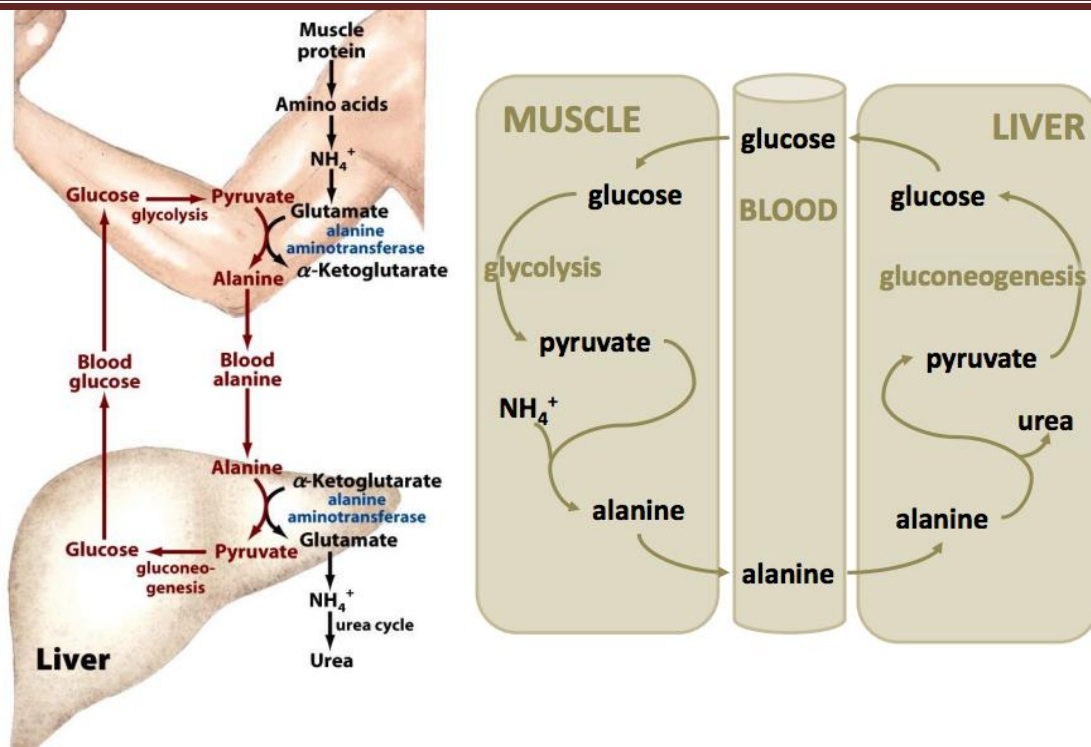
Glucose-alanine cycle

The Cahill cycle, also known as the alanine cycle or glucose-alanine cycle, is the series of reactions in which amino groups and carbons from muscle are transported to the liver. It is quite similar to the Cori cycle in the cycling of nutrients between skeletal muscle and the liver. When muscles degrade amino acids for energy needs, the resulting nitrogen is transaminated to pyruvate to form alanine. This is performed by the enzyme alanine transaminase, which converts L-glutamate and pyruvate into α -ketoglutarate and L-alanine. The resulting L-alanine is shuttled to the liver where the nitrogen enters the urea cycle and the pyruvate is used to make glucose.

The Cahill cycle is less productive than the Cori cycle, which uses lactate, since a byproduct of energy production from alanine is production of urea. Removal of the urea is energy-dependent, requiring four "high-energy" phosphate bonds (3 ATP hydrolyzed to 2 ADP and one AMP), thus the net ATP produced is less than that found in the Cori cycle. However, unlike in the Cori cycle, NADH is conserved because lactate is not formed. This allows for it to be oxidized via the electron transport chain. This pathway requires the presence of alanine aminotransferase, which is restricted to tissues such as muscle, liver, and the intestine. Therefore, this pathway is used instead of the Cori cycle only when an aminotransferase is present, when there is a need to transfer ammonia to the liver and when the body is in a state of catabolism (muscle breakdown).

The alanine cycle also serves other purposes:

- Recycles carbon skeletons between muscle and liver
- Transports ammonia to the liver and is converted into urea.



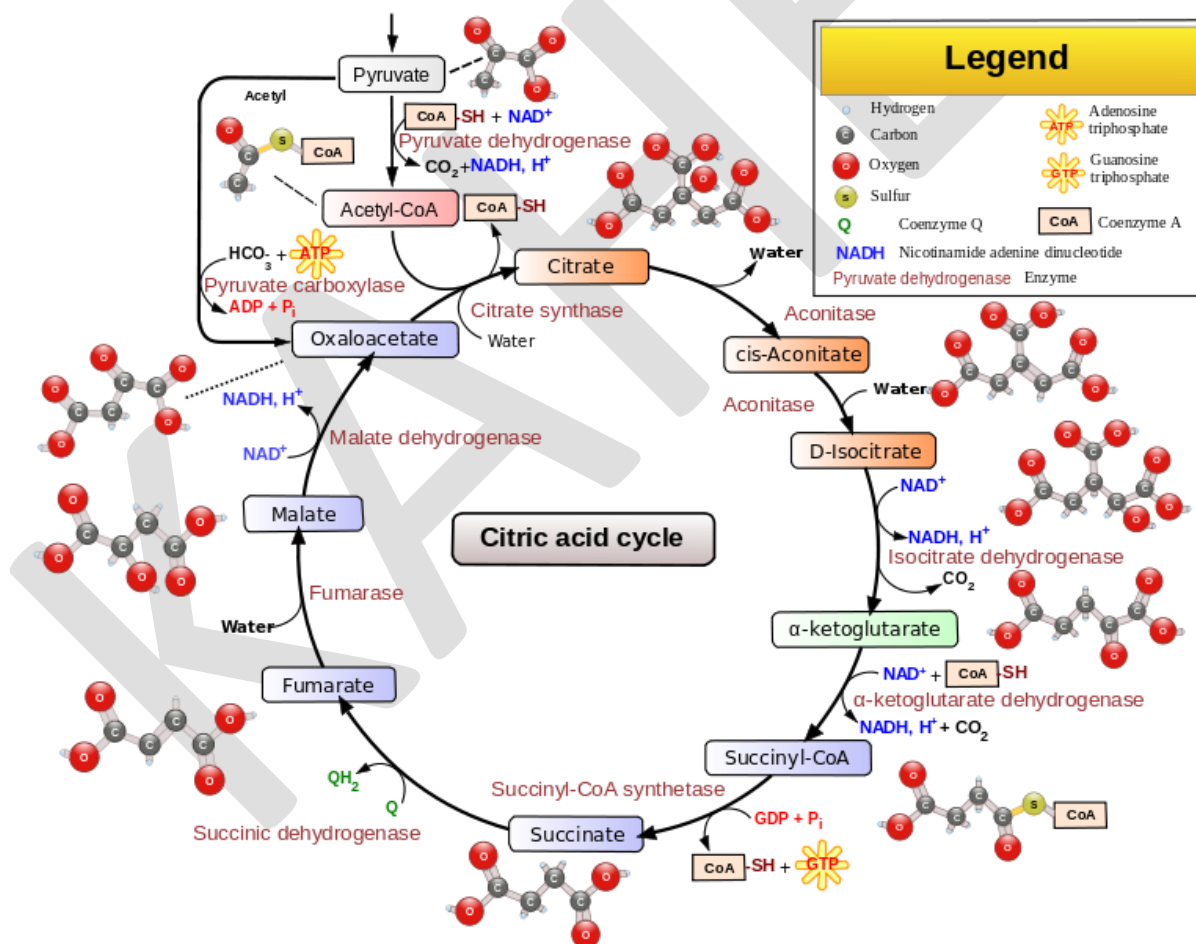
Citric acid cycle

The citric acid cycle (CAC) – also known as the tricarboxylic acid (TCA) cycle or the Krebs cycle – is a series of chemical reactions used by all aerobic organisms to release stored energy through the oxidation of acetyl-CoA derived from carbohydrates, fats, and proteins into carbon dioxide and chemical energy in the form of adenosine triphosphate (ATP). In addition, the cycle provides precursors of certain amino acids, as well as the reducing agent NADH, that are used in numerous other biochemical reactions. Its central importance to many biochemical pathways suggests that it was one of the earliest established components of cellular metabolism and may have originated abiogenically.

The name of this metabolic pathway is derived from the citric acid (a type of tricarboxylic acid, often called citrate, as the ionized form predominates at biological pH) that is consumed and then regenerated by this sequence of reactions to complete the cycle. The cycle consumes acetate (in the form of acetyl-CoA) and water, reduces NAD⁺ to NADH, and produces

carbon dioxide as a waste byproduct. The NADH generated by the citric acid cycle is fed into the oxidative phosphorylation (electron transport) pathway. The net result of these two closely linked pathways is the oxidation of nutrients to produce usable chemical energy in the form of ATP.

In eukaryotic cells, the citric acid cycle occurs in the matrix of the mitochondrion. In prokaryotic cells, such as bacteria which lack mitochondria, the citric acid cycle reaction sequence is performed in the cytosol with the proton gradient for ATP production being across the cell's surface (plasma membrane) rather than the inner membrane of the mitochondrion.



Urea Cycle:

Urea is the end product of protein metabolism (amino acid metabolism). The nitrogen of amino acids converted to ammonia is toxic to the body. It is converted to urea and detoxified. As such, urea accounts for 80-90% of the nitrogen containing substances excreted in urine.

Urea is synthesized in liver and transported to kidneys for excretion in urine. Urea cycle is the first metabolic cycle that was elucidated by Hans Krebs and Kurt Henseleit (1932), hence it is known as Krebs-Henseleit cycle. The individual reactions, however, were described in more detail later on by Ratner and Cohen.

Urea has two amino (—NH_2) groups, one derived from NH_3 and the other from aspartate. Carbon atom is supplied by CO_2 . Urea synthesis is a five-step cyclic process, with five distinct enzymes. The first two enzymes are present in mitochondria while the rest are localized in cytosol. The reactions of urea cycle are depicted in Fig. 67.15.

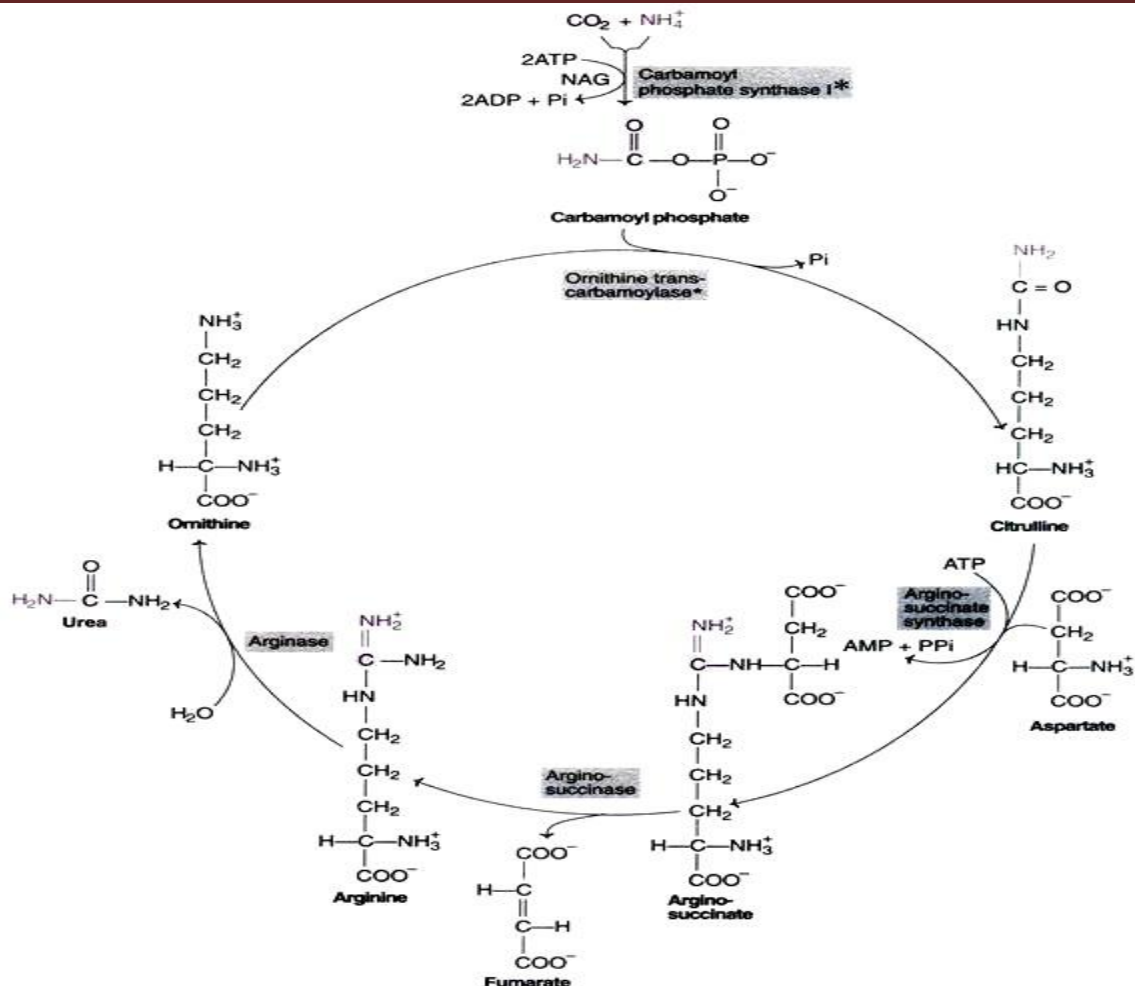
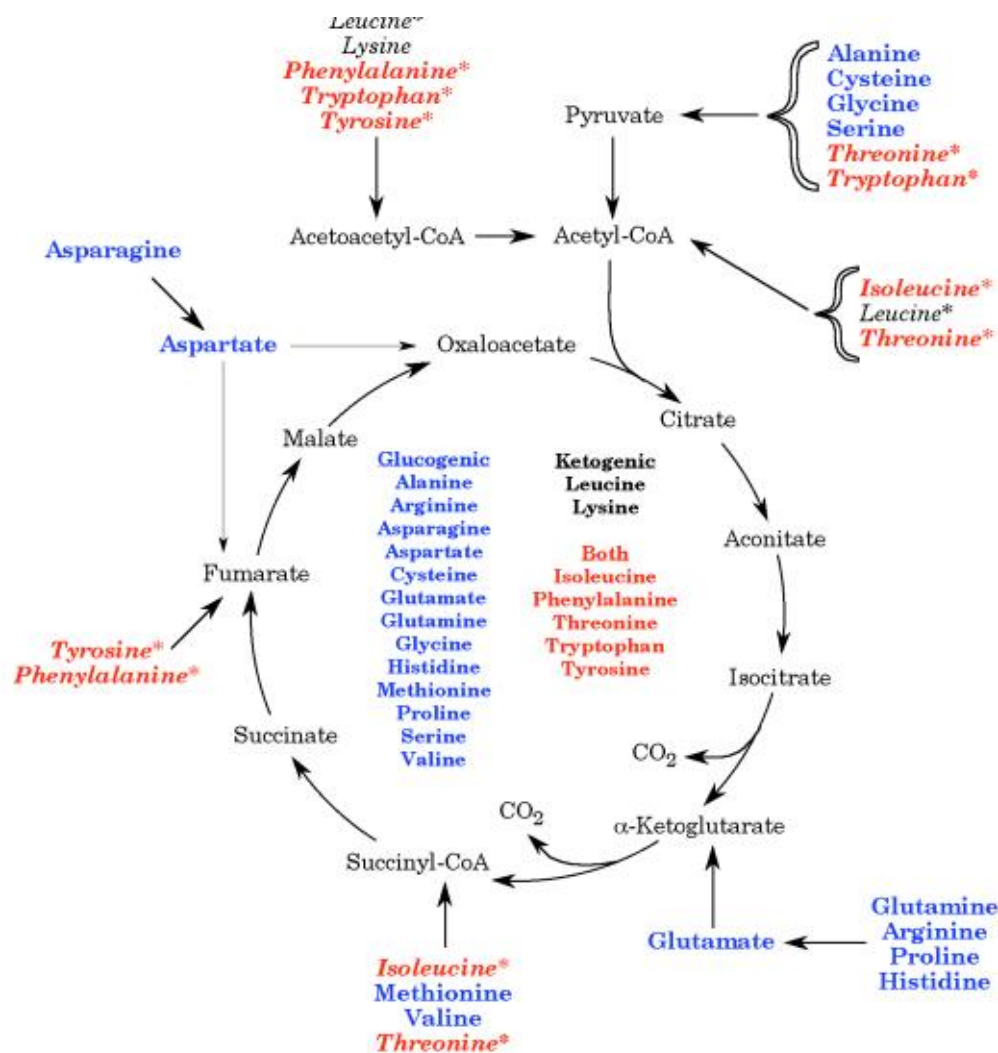


Fig. 67.15 : Reactions of urea cycle (NAG–N-acetylglutamate; (in the formation of urea, one amino group is derived from free ammonium ion while the other is from aspartate; carbon is obtained from CO_2 ;
 *mitochondrial enzymes, the rest of the enzymes are cytosomal).

Metabolism of Individual Amino Acids:



The metabolisms of certain individual amino acids are very briefly given in the form of overviews.

Glycine:

Glycine (Gly, G) is a non-essential, optically inactive and glucogenic (precursor for glucose) amino acid. It is indispensable for chicks. The outline of glycine metabolism is depicted in Fig. 67.16. Glycine is actively involved in the synthesis of many specialized products (heme, purines,

creatine etc.) in the body, besides its incorporation into proteins, synthesis of serine and glucose and participation in one-carbon metabolism.

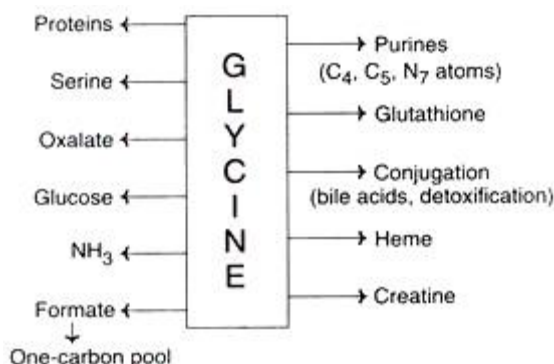


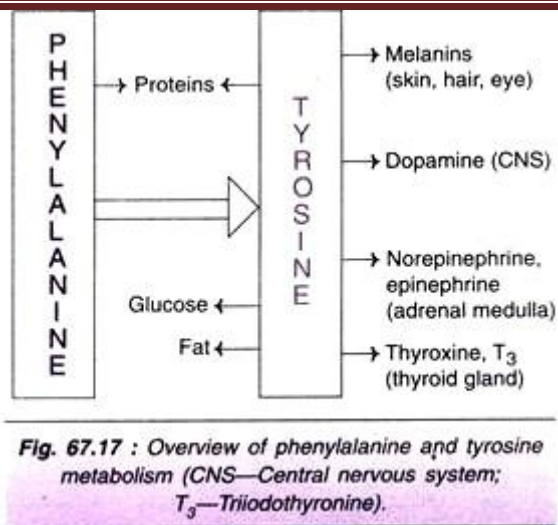
Fig. 67.16 : Overview of glycine metabolism.

Phenylalanine and Tyrosine:

Phenylalanine (Phe, F) and tyrosine (Tyr, Y) are structurally related aromatic amino acids.

Phenylalanine is an essential amino acid while tyrosine is non-essential. Besides its incorporation into proteins, the only function of phenylalanine is its conversion to tyrosine. For this reason, ingestion of tyrosine can reduce the dietary requirement of phenylalanine. This phenomenon is referred to as 'sparing action' of tyrosine on phenylalanine.

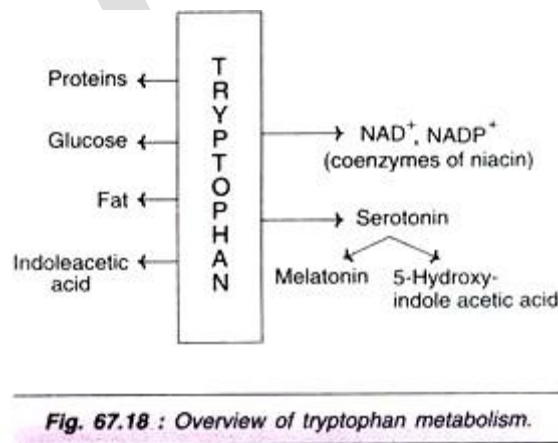
The predominant metabolism of phenylalanine occurs through tyrosine. Tyrosine is incorporated into proteins and is involved in the synthesis of a variety of biologically important compounds—epinephrine, norepinephrine, dopamine (catecholamine's), thyroid hormones—and the pigment melanin (Fig. 67.17).



During the course of degradation, phenylalanine and tyrosine are converted to metabolites which can serve as precursors for the synthesis of glucose and fat. Hence, these amino acids are both glucogenic and keto-genic.

Tryptophan:

Tryptophan (Trp, W) was the first to be identified as an essential amino acid. It contains an indole ring and chemically it is α -amino β -indole propionic acid. Tryptophan is both glucogenic and keto-genic in nature. It is a precursor for the synthesis of important compounds, namely NAD⁺ and NADP⁺ (coenzymes of niacin), serotonin and melatonin (Fig. 67.18).



Sulfur Amino Acids:

The sulfur-containing amino acids are methionine, cysteine and cystine. Among these, only methionine is essential. It serves as a precursor for the synthesis of cysteine and cystine which are, therefore, non-essential. An overview of the metabolism of the sulfur amino acids is depicted in Fig. 67.19.

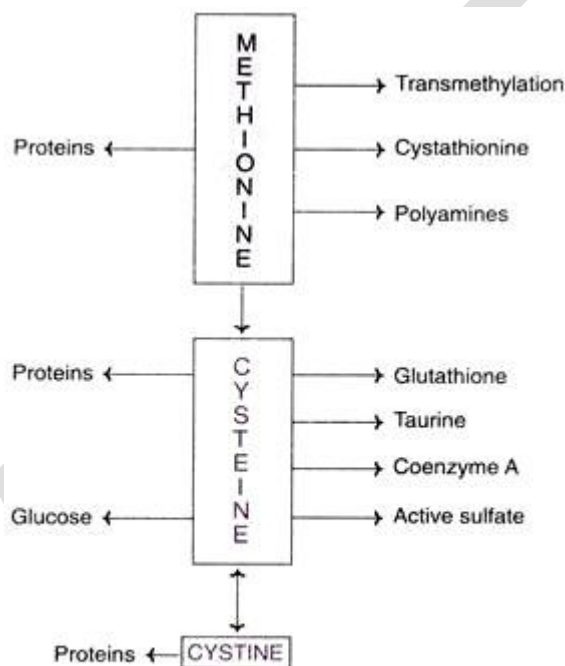


Fig. 67.19 : Overview of the metabolism of sulfur amino acids.

Glutamate and Glutamine:

Glutamate and glutamine are non-essential glycolytic amino acids. Both of them play a predominant role in the amino acid metabolism and are directly involved in the final transfer of amino group for urea synthesis. In Fig. 67.20, an outline of glutamate and glutamine metabolism is given.

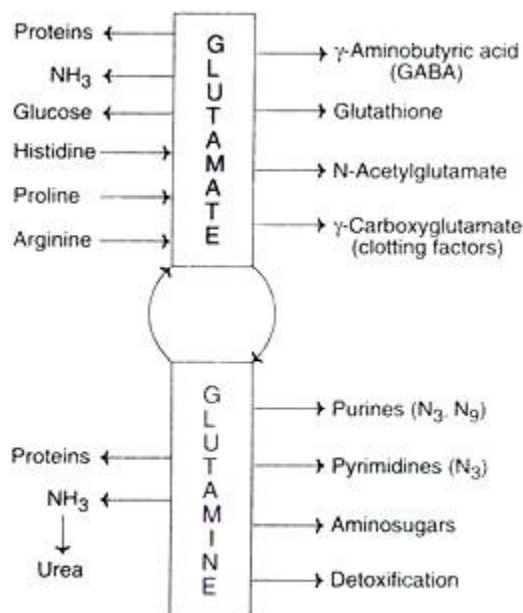


Fig. 67.20 : Overview of glutamate and glutamine metabolism.

Fate of Carbon Skeleton of Amino Acids:

After the removal of amino groups, the carbon skeleton of amino acids is converted to intermediates of TCA cycle or their precursors.

The carbon skeleton finally has one or more of the following fates:

1. Oxidation via TCA cycle to produce energy (about 10-15% of body needs).
2. Synthesis of glucose.
3. Formation of lipids—fatty acids and ketone bodies.
4. Synthesis of non-essential amino acids.

The carbon skeletons of the 20 standard amino acids (or the amino acids of proteins) are degraded to one of the following seven products—pyruvate, α -ketoglutarate, succinyl CoA, fumarate, oxaloacetate, acetyl CoA and acetoacetate.

Some authors use the term amphibolic (Greek: amphiboles— uncertain) intermediates to these compounds due to their multiple metabolic functions. The amino acids are classified into three groups, based on the nature of the metabolic end products of carbon skeleton (Table 67.1).

TABLE 67.1 Classification of amino acids based on the fate of carbon skeleton		
<i>Glycogenic (glucogenic)</i>	<i>Glycogenic and Ketogenic</i>	<i>Ketogenic</i>
Alanine	Phenylalanine*	Leucine*
Arginine*	Isoleucine*	Lysine*
Aspartate	Tyrosine	
Cysteine	Tryptophan*	
Glutamine		
Glutamate		
Glycine		
Histidine*		
Hydroxyproline		
Methionine*		
Proline		
Serine		
Threonine*		
Valine*		

*Essential amino acids; (Helpful tips to recall—ketogenic amino acids start with letter 'L'; PITT for glyco-and ketogenic amino acids; rest of the 20 amino acids are only glycogenic).

Inborn Errors of Amino Acid Metabolism—A Summary:

Several inherited disorders are associated with amino acid metabolism. In Table 67.2, a summary of major diseases and the enzyme defects is given.

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COURSE NAME: METABOLISM OF AMINO ACIDS AND NUCLEIC ACIDS

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UNIT: I Overview of amino acid metabolism

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TABLE 67.2 Inborn errors of amino acid metabolism

<i>Disorder</i>	<i>Metabolic defect (enzyme/other)</i>
I. Phenylalanine and tyrosine	
1. Phenylketonuria	Phenylalanine hydroxylase
2. Tyrosinemia type II	Tyrosine transaminase
3. Neonatal tyrosinemia	p-Hydroxy phenylpyruvate dioxygenase
4. Alkaptonuria	Homogentisate oxidase
5. Tyrosinosis (tyrosinemia type I)	Maleyl acetoacetate isomerase or fumaryl acetoacetate hydrolase
6. Albinism	Tyrosinase
II. Sulfur amino acids (methionine, cysteine and cystine)	
7. Cystinuria	Defect in renal reabsorption
8. Cystinosis	Impairment in cystine utilization (defect in lysosomal function)
9. Homocystinuria type I	Cystathionine synthetase
10. Homocystinuria type II	N ⁵ , N ¹⁰ -Methylene THF reductase
11. Homocystinuria type III	N ⁵ -Methyl THF-homocysteine methyltransferase
12. Cystathionuria	Cystathioninase
III. Glycine	
13. Glycinuria	Defect in renal reabsorption
14. Primary hyperoxaluria	Glycine transaminase
IV. Tryptophan	
15. Hartnup's disease	Defective intestinal absorption
V. Branched chain amino acids (valine, leucine and isoleucine)	
16. Maple syrup urine disease	Branched chain α -keto acid dehydrogenase
17. Intermittent branched chain ketonuria	Variant of the above enzyme (less severe)
18. Hypervalinemia	Valine transaminase
19. Isovaleric acidemia	Isovaleryl CoA dehydrogenase
VI. Histidine	
20. Histidinemia	Histidase
VII. Proline	
21. Hyperprolinemia type I	Proline oxidase

Inborn Errors of Amino Acid Metabolism—A Summary:

Several inherited disorders are associated with amino acid metabolism. In Table 67.2, a summary of major diseases and the enzyme defects is given.

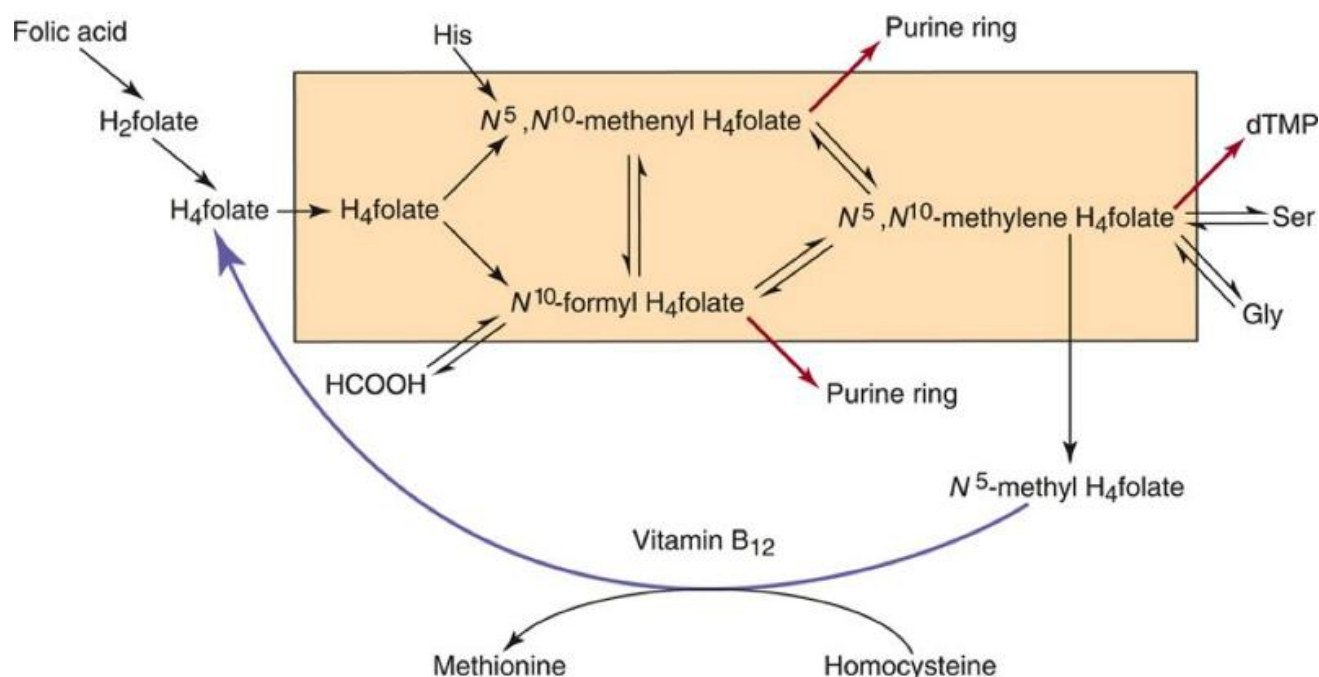
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20. Histidinemia	Histidase
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21. Hyperprolinemia type I	Proline oxidase

One-carbon Metabolism: Basic Concepts

There is a group of biochemical reactions that have a special set of enzymes and coenzymes. They are involved in amino acid metabolism and also play roles in nucleotide metabolism. This group of reactions is referred to as **one-carbon metabolism** because what they have in common is the transfer of one-carbon groups.

One-carbon metabolism exists because one-carbon groups are too volatile and need to be attached to something while being processed.

A brief summary of the reactions involved in one-carbon metabolism is given in Devlin, Figure 26.17



Essentially, there are three ways of moving groups of atoms containing a single carbon atom using the following molecules:

1. **Tetrahydrofolate (THF)** as a cofactor in enzymatic reactions.
2. **S-adenosylmethionine (SAM)** as a methyl (-CH₃) donor.
3. **Vitamin B₁₂ (Cobalamin)** as a co-enzyme in methylation and rearrangement reactions.

TETRAHYDROFOLATE (THF)

THF is the most versatile one-carbon donor in biosynthetic reactions. THF is composed of three types of groups. THF is derived from the vitamin folic acid (folate). Folate is made by plants and microorganisms and we obtain it from our diets e.g., green leafy vegetables, beans, among others. We eat folate and use the enzyme **dihydrofolate reductase** to convert it into tetrahydrofolate, which is the active form that carries 1-carbon groups in a variety of reactions.

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The structure of folate is given in Devlin, Figure 26.17.

A key feature of THF is that it can carry a variety of 1-carbon groups.

These are listed in the table below:

<u>Oxidation State</u>	<u>Structure</u>	<u>Name</u>
Most reduced	-CH ₃	Methyl
Intermediate	-CH ₂ -	Methylene
Most oxidized	-CHO	Formyl
	-CHNH	Formimino
	-CH=	Methenyl

There are enzymes whose job it is to attach a 1-carbon group to THF, others to change the nature of that 1-carbon group, and others to transfer the 1-carbon group from THF onto a substrate.

One-carbon groups are being added to or removed from THF and are changing their nature while bound to THF.



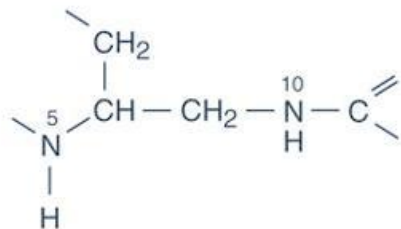
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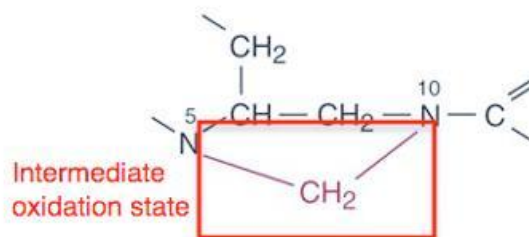
COURSE CODE: 17BCU302

UNIT: I Overview of amino acid metabolism

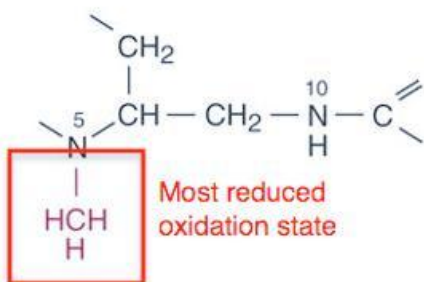
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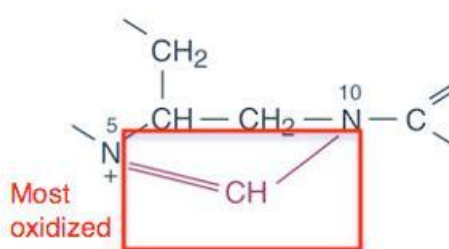
Tetrahydrofolate (H₄folate)



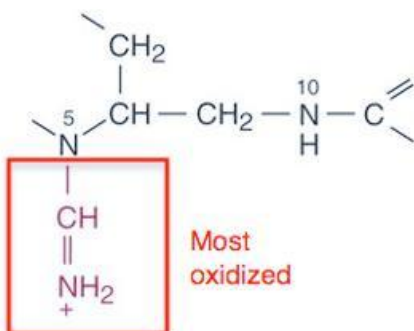
N⁵,N¹⁰-Methylene H₄folate



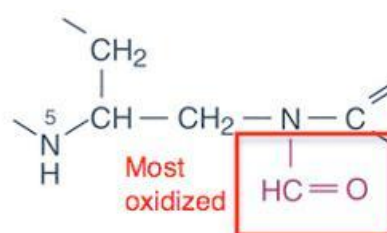
N⁵-Methyl H₄folate



N⁵,N¹⁰-Methenyl H₄folate



N⁵-Formimino H₄folate



N¹⁰-Formyl H₄folate

POSSIBLE QUESTIONS

UNIT-I

2 marks:

1. Define nitrification
2. Define denitrification
3. Importance of trypsin
4. Give an account on pancreatic enzymes
5. Differentiate kwashiorkor and marasmus
6. Define transamination
7. Define nitrogen balance
8. List any five glucogenic amino acids
9. List the ketogenic amino acids
10. Give the importance of THFA

8 marks

1. Enumerate the importance of nitrogen cycle in amino acid metabolism
2. Write about the metabolic fates of amino groups
3. Brief note on digestion and absorption of dietary proteins
4. Explain about Kwashiorkor and marasmus
5. Detailed note on Cahill cycle
6. Discuss about TCA cycle
7. Ornithine cycle and its importance
8. Mention in detail about inherited disorders of urea cycle
9. Give an account on metabolism of one carbon units
10. Discuss about catabolic pathways of individual amino acids in relation with glucogenic and ketogenic

KARPAGAM ACADEMY OF HIGHER EDUCATION
DEPARTMENT OF BIOCHEMISTRY
II-B.Sc., BIOCHEMISTRY
METABOLISM OF AMINOACIDS AND NUCLEIC ACIDS (18BCU302)
MULTIPLE CHOICE QUESTIONS

S.N	Questions	Option A	Option B	Option C	Option D	Answer
1	Which of the following is correct regarding Nitrogen cycle?	N ₂ cycle is a sedimentary cycle	N is the most abundant nutrient for plants	The major reservoir of Nitrogen is atmosphere	All of these	The major reservoir of Nitrogen is atmosphere
2	Biological nitrogen fixation is the conversion of	Conversion of N ₂ to NO ₃ ⁻ and NH ₃	Conversion of N ₂ to N	Conversion of N ₂ to urea	Conversion of N ₂ to NH ₃	Conversion of N ₂ to NH ₃
3	The conversion of Ammonia (NH ₃) to nitrite (NO ₂ ⁻) and then to nitrates (NO ₃ ⁻) is called	Nitrification	Ammonification	Assimilation	Denitrification	Nitrification
4	The process that convert nitrates (NO ₃ ⁻) back to nitrogen gas (N ₂) there by replenishing N ₂ in the atmosphere is called	Nitrification	Denitrification	Deamination	Nitrogen fixation	Denitrification
5	Nitrosomonas converts	Nitrate to nitrite	Nitrite to nitrate	Ammonia to nitrites	Nitrites to ammonia	Ammonia to nitrites
6	Nitrosomonas and Nitrobacter are	Ammonifying bacteria	Denitrifying bacteria	Nitrogen fixing bacteria	Nitrifying bacteria	Nitrifying bacteria
7	Arrange the following process of nitrogen cycle in proper sequence i) Denitrification ii) Nitrogen fixation iii) Ammonification iv) Nitrification	ii-iii-iv-i	i-ii-iii-iv	i-iii-ii-iv	iv-iii-ii-i	ii-iii-iv-i
8	Name of enzyme present in pancreatic juice is called	Pepsin	Amylase	Trypsin	Lipase	Trypsin
9	The building blocks of Proteins are ____ .	Pentoses	Amino acids	Peptides	Enzymes	Amino acids
10	An example for protein malnutrition -- .	Mid-gut	Encephalitis	Marasmus	Scurvy	Marasmus
11	Kwashiorkar is the disease of malnutrition mainly due to reduction of -	Lipids	Carbohydrates	Proteins	Water	Proteins
12	_____ is distinguishing factor between Kwashiorkar and Marasmus	Albinism	Edema	Weakness	Fatigue	Edema

13	Which of the following is a common compound shared by the TCA cycle and the Urea cycle?	α - Keto glutarate	Succinyl co A	Oxalo acetate	Fumarate	Fumarate
14	Which of the followings is a common nitrogen acceptor for all reactions involving transaminases?	α - Keto glutarate	Pyruvate	Oxaloacetate	Acetoacetate	α - Keto glutarate
15	Urea is synthesized in –	Cytoplasm	Mitochondria	Both cytoplasm and mitochondria	In lysosomes	Both cytoplasm and mitochondria
16	Blood urea decreases in all of the following conditions, except	Liver cirrhosis	Pregnancy	Renal failure	Urea cycle disorders	Renal failure
17	All of the following amino acids are donors of one carbon compounds except	Histidine	Tyrosine	Tryptophan	Serine	Tyrosine
18	Citric acid cycle is involved in breakdown of	Vitamins	Carbohydrates	Proteins	Carbohydrates and proteins	Carbohydrates and proteins
19	Other names for citric acid cycle are	Krebs cycle	Tricarboxylic acid cycle	Both A and B	Kerbs cycle	Both A and B
20	How many molecules of ATPs are synthesized per NADH oxidation?	2	1	3	4	3
21	Why is the TCA cycle the central pathway of metabolism of the cell?	It occurs in the center of the cell	Its intermediates are commonly used by other metabolic reactions	All other metabolic pathways depend upon it	None of the above	Its intermediates are commonly used by other metabolic reactions
22	Oxidation of a molecule involves	Gain of electron	Loss of electron	Gain of proton	Loss of proton	Loss of electron
23	Citric acid cycle occurs in	Cytoplasm	Mitochondria	Endoplasmic reticulum	Golgi bodies	Mitochondria
24	Histidine is degraded to α -ketoglutarate and is described as a	Gluco amino acid	Glucogenic amino acid	Ketogenic amino acid	Keto-gluco amino acid	Glucogenic amino acid
25	Which of the following amino acids is considered as both ketogenic and glucogenic?	Valine	Tryptophan	Lysine	Leucine	Tryptophan
26	A glucogenic amino acid is one which is degraded to	Keto-sugars	Either acetyl CoA or acetoacetyl CoA	Pyruvate or citric acid cycle intermediates	None of the above	Pyruvate or citric acid cycle intermediates
27	Which of the following is the best described glucogenic amino acid?	Lysine	Tryptophan	Valine	None of these	Valine

28	An example of a transamination process is	Glutamate = hexanoic acid + NH ₃	Aspartate + hexanoic acid = glutamate + oxaloacetate	Aspartate + α ketoglutarate = glutamate + oxaloacetate	Glutamate = α -ketoglutarate + NH ₃	Aspartate + α ketoglutarate = glutamate + oxaloacetate
29	Transamination is the process where	Carboxyl group is transferred from amino acid	The transfer of an amino group from one molecule to another	Polymerisation of amino acid takes place	None of the above	The transfer of an amino group from one molecule to another
30	Transaminase enzymes are present in	Liver	Pancreas	Intestine	Muscle	Liver
31	Symptoms of kwashiorkor include	Cracked and scaly skin	Loss of appetite	Excess sweating	Itching	Cracked and scaly skin
32	Protein deficiency in children is called as	Beriberi	Scurvy	Diabetes	Kwashiorkor	Kwashiorkor
33	All are vitamin deficiency diseases except	Marasmus	Rickets	Scurvy	Cheilosis	Marasmus
34	Lining of duodenum releases enzyme called	Trypsin	Trypsinogen	Erepsin	Sterol esterase	Trypsinogen
35	Thick secretions which cover inside of stomach are called	Mucosa	Zymogen	Gastric	Mucus	Mucus
36	Site of urea cycle is?	Liver	Kidney	Gut	Lungs	Liver
37	Which of the following statements about the metabolism of amino acids is correct?	Essential amino acids can be formed from other amino acids supplied in the diet.	Excess dietary amino acids cannot be converted to other metabolites.	Excess dietary amino acids that cannot be oxidised are stored as muscle proteins.	Essential amino acids cannot be formed from other amino acids but must be supplied in the diet.	Essential amino acids cannot be formed from other amino acids but must be supplied in the diet.
38	Which of the following statements about transamination reactions is correct?	Transamination reactions involve ATP hydrolysis.	Transamination reactions are irreversible.	Transamination reactions require NAD ⁺ or NADP ⁺ .	Transamination reactions require pyridoxal-5'-phosphate	Transamination reactions require pyridoxal-5'-phosphate
39	Which of the following statements about the urea cycle is correct?	Argininosuccinate is lysed to urea and ornithine in the urea cycle.	Carbamoyl phosphate supplies both of the nitrogen atoms of urea in the urea cycle.	The formation of urea from the urea cycle yields energy.	Arginine is hydrolysed to urea and ornithine in the urea cycle.	Arginine is hydrolysed to urea and ornithine in the urea cycle.

40	Tyrosine is degraded to acetoacetyl CoA and fumarate and is described as a	Glucogenic amino acid	Ketogenic amino acid	Ketogenic and glucogenic amino acid	Keto-gluco amino acid	Ketogenic and glucogenic amino acid
41	The net ATPs produced per cycle of TCA	12	20	25	36	12
42	The FADH ₂ will give rise to _____	3	4	2	5	2
43	The GTP will give rise to _____ molecules of ATP	3	4	1	5	1
44	Chose the incorrect statement about amino acid Glycine	One carbon donor	Required for the synthesis of haem	Forms oxalates upon catabolism	Both glucogenic as well as ketogenic	Both glucogenic as well as ketogenic
45	Which out of the followings is required as a coenzyme for the transamination reactions?	Coenzyme A	Pyridoxal-P	Folic acid	Cobalamine	Pyridoxal-P
46	What is normal nitrogen balance?	N ingested = N excreted	N ingested < Nitrogen excreted	N ingested > N excreted	N ingested ≠ N excreted	N ingested = N excreted
47	What is negative nitrogen balance?	N ingested = N excreted	N ingested <	N ingested > N	N ingested ≠ N	N ingested <
48	What is positive nitrogen balance?	N ingested = N excreted	N ingested <	N ingested > N	N ingested ≠ N	N ingested > N
49	Release of pancreatic juice is stimulated by	Enterokinase	Cholecystokinin	Trypsinogen	Secretin	Cholecystokinin
50	Protein digestion starts in _____	Mouth	Stomach	Liver	Bile	Stomach
51	Which of the following amino acids is not converted to acetoacetyl co A upon metabolism ?	Tyrosine	Leucine	Lysine	Valine	Valine
52	Which of the following enzymes requires adenosine triphosphate (ATP) to mediate its reactions	Argino Succinate synthetase	Argino Succinate lyase	Arginase	Glutaminase	Argino Succinate synthetase
53	Hyperammonemia is a condition denotes	Very high NH ₃ levels in blood	Very low NH ₃ levels in blood	Urea formation	Glutamate synthesis	Very high NH ₃ levels in blood
54	If a person's urine contains unusually high concentrations of urea, which one of the following diets has he or she probably been eating recently?	High carbohydrate, very low protein	Very high carbohydrate, no protein, no fat	Very very high fat, high carbohydrate, no protein	Very low carbohydrate, very high protein	Very low carbohydrate, very high protein
55	Serine or cysteine may enter the citric acid cycle as acetyl-CoA after conversion to:	Oxaloacetate	Propionate	Pyruvate	Succinate	Pyruvate
56	Which of these is <i>not</i> a protease that acts in the small intestine?	Chymotrypsin	Enteropeptidase	Secretin	Trypsin	Secretin

57	In amino acid catabolism, the first reaction for many amino acids is a	Decarboxylation requiring thiamine pyrophosphate (TPP)	Hydroxylation requiring NADPH and O ₂	Reduction requiring pyridoxal phosphate (PLP)	Transamination requiring pyridoxal phosphate (PLP)	Transamination requiring pyridoxal phosphate (PLP)
58	Glucose alanine cycle was otherwise called as _____	Cori cycle	Ornithine cycle	Cahill cycle	Kreb cycle	Cahill cycle
59	A toxic waste product of protein metabolism that must be excreted from the body is	Ammonia	Carbon dioxide	Urea	Uric acid	Ammonia
60	Which of the following is the best described glucogenic amino acid?	Lysine	Tryptophan	Valine	None of these	Valine

Catabolism of amino acids

Disorders of amino acids metabolism, phenylketonuria, alkaptonuria, maple syrup urine disease, methylmalonic acidemia (MMA), homocystinuria and Hartnup's disease.

Biosynthesis of amino acids

Overview of amino acid synthesis. Biosynthesis of non-essential amino acids and its regulation.

Amino acids are the building blocks of proteins and have many functions in the body. Hereditary disorders of amino acid processing can result from defects either in the breakdown of amino acids or in the body's ability to get amino acids into cells. Because these disorders cause symptoms early in life, newborns are routinely screened for several common ones. In the United States, newborns are commonly screened for phenylketonuria, maple syrup urine disease, homocystinuria, tyrosinemia, and a number of other inherited disorders, although screening varies from state to state.

PHENYLKETONURIA (PKU)

Phenylketonuria occurs in infants born without the ability to normally break down an amino acid called phenylalanine. Phenylalanine, which is toxic to the brain, builds up in the blood.

- Phenylketonuria is caused by lack of the enzyme needed to convert phenylalanine to tyrosine.
- Symptoms include intellectual disability, seizures, nausea, vomiting, an eczema-like rash, and a mousy body odor.
- The diagnosis is based on a blood test.
- A strict phenylalanine-restricted diet allows for normal growth and development.

Phenylketonuria (PKU) is a disorder that causes a buildup of the amino acid phenylalanine, which is an essential amino acid that cannot be synthesized in the body but is present in food. Excess phenylalanine is normally converted to tyrosine, another amino acid, and eliminated from the body. Without the enzyme that converts it to tyrosine, phenylalanine builds up in the blood and is toxic to the brain, causing intellectual disability.

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Symptoms

Newborns with PKU rarely have symptoms right away, although sometimes they are sleepy or eat poorly. If not treated, affected infants progressively develop intellectual disability over the first few years of life, eventually becoming severe. Other symptoms include seizures, nausea and vomiting, an eczema-like rash, lighter skin and hair than their family members, aggressive or self-injurious behavior, hyperactivity, and sometimes psychiatric symptoms. Untreated children often give off a mousy body and urine odor as a result of a by-product of phenylalanine (phenylacetic acid) in their urine and sweat.

Diagnosis

PKU is usually diagnosed with a routine screening test.

PKU occurs in most ethnic groups. If PKU runs in the family and DNA is available from an affected family member, amniocentesis or chorionic villus sampling with DNA analysis can be done to determine whether a fetus has the disorder.

Parents and siblings of children with PKU can be tested to find out whether they carry the gene that causes the disease. If two carriers conceive a child, that child has a 1 in 4 chance of being born with the disease.

Prognosis

A phenylalanine-restricted diet, if started early and maintained well, allows for normal development. However, if very strict control of the diet is not maintained, affected children may begin to have difficulties in school. Dietary restrictions started after 2 to 3 years of age may control extreme hyperactivity and seizures and raise the child's eventual intelligence quotient (IQ) but do not reverse intellectual disability. Recent evidence suggests that some intellectually disabled adults with PKU (born before newborn screening tests were available) may function better when they follow the PKU diet.

A phenylalanine-restricted diet should continue for life, or intelligence may decrease and neurologic and mental problems may ensue.

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Prevention and Treatment

To prevent intellectual disability, people must restrict phenylalanine intake (but not eliminate it altogether because people need some phenylalanine to live) beginning in the first few weeks of life. Because all natural sources of protein contain too much phenylalanine for children with PKU, affected children cannot have meat, milk, or other common foods that contain protein. Instead, they must eat a variety of processed foods, which are specially manufactured to be phenylalanine-free. Low-protein natural foods, such as fruits, vegetables, and restricted amounts of certain grain cereals, can be eaten. Special nutritional products, including infant formula without phenylalanine, are also available. Future treatments may include cell transplantation and gene therapy.

Alkaptonuria is a rare inherited disorder. It occurs when your body can't produce enough of an enzyme called homogentisic dioxygenase (HGD). This enzyme is used to break down a toxic substance called homogentisic acid. When you don't produce enough HGD, homogentisic acid builds up in your body.

The buildup of homogentisic acid causes your bones and cartilage to become discolored and brittle. This typically leads to osteoarthritis, especially in your spine and large joints. People with alkaptonuria also have urine that turns dark brown or black when it's exposed to air.

Symptoms:

Dark stains on a baby's diaper are one of the earliest signs of alkaptonuria. There are few other symptoms during childhood.

Symptoms become more obvious as you age. Your urine may turn dark brown or black when it's exposed to air. By the time you reach your 20s or 30s, you may notice signs of early-onset osteoarthritis. For example, you may notice chronic stiffness or pain in your lower back or large joints.

Other symptoms of alkaptonuria include:

- dark spots in the sclera (white) of your eyes
- thickened and darkened cartilage in your ears
- blue speckled discoloration of your skin, particularly around sweat glands

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- dark-colored sweat or sweat stains
- black earwax
- kidney stones and prostate stones
- arthritis (especially hip and knee joints)

Alkaptonuria can also lead to heart problems. The buildup of homogentisic acid causes your heart valves to harden. This can keep them from closing properly, resulting in aortic and mitral valve disorders. In severe cases, heart valve replacement may be necessary. The buildup also causes your blood vessels to harden. This raises your risk of high blood pressure.

Causes:

Alkaptonuria is caused by a mutation on your homogentisate 1,2-dioxygenase (HGD) gene. It's an autosomally recessive condition.

Treatment:

No treatment modality has been unequivocally demonstrated to reduce the complications of alkaptonuria. Main treatment attempts have focused on preventing ochronosis through the reduction of accumulating homogentisic acid. Such commonly recommended treatments include large doses of ascorbic acid (vitamin C) or dietary restriction of amino acids phenylalanine and tyrosine. However, vitamin C treatment has not shown to be effective, and protein restriction (which can be difficult to adhere to) has not shown to be effective in clinical studies.

Several recent studies have suggested that the herbicide nitisinone may be effective in the treatment of alkaptonuria. Nitisinone inhibits the enzyme, 4-hydroxyphenylpyruvate dioxygenase, responsible for converting tyrosine to homogentisic acid, thereby blocking the production and accumulation of HGA. Nitisinone has been used for some time at much higher doses in the treatment of type I tyrosinemia. Nitisinone treatment has been shown to cause a larger than 95% reduction in plasma and urinary HGA. The main drawback is accumulation of tyrosine, the long-term risks of which are unknown; there is a particular concern about damage to the cornea of the eye. Long-term use would require frequent monitoring for complications.

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MAPLE SYRUP URINE DISEASE

Maple syrup urine disease is caused by lack of the enzyme needed to metabolize amino acids. By-products of these amino acids cause the urine to smell like maple syrup.

Children with maple syrup urine disease are unable to metabolize certain amino acids. By-products of these amino acids build up, causing neurologic changes, including seizures and intellectual disability. These by-products also cause body fluids, such as urine and sweat, to smell like maple syrup. This disease is most common among Mennonite families.

There are many forms of maple syrup urine disease. In the most severe form, infants develop neurologic abnormalities, including seizures and coma, during the first week of life and can die within days to weeks. In the milder forms, children initially appear normal but during infection, surgery, or other physical stress, they can develop vomiting, staggering, confusion, and coma.

Since 2007, nearly every state in the United States has required that all newborns be screened for maple syrup urine disease with a blood test.

Infants with severe disease are treated with dialysis. Some children with mild disease benefit from injections of vitamin B₁ (thiamin). After the disease has been brought under control, children must always consume a special artificial diet that is low in three amino acids (leucine, isoleucine, and valine). During times of physical stress or flare-ups, it may be necessary to monitor blood tests and give fluids by vein.

HOMOCYSTINURIA

Homocystinuria is caused by lack of the enzyme needed to metabolize homocysteine. This disorder can cause a number of symptoms, including decreased vision and skeletal abnormalities. Children with homocystinuria are unable to metabolize the amino acid homocysteine, which, along with certain toxic by-products, builds up to cause a variety of symptoms. Symptoms may be mild or severe, depending on the particular enzyme defect.

Infants with this disorder are normal at birth. The first symptoms, including dislocation of the lens of the eye, causing severely decreased vision, usually begin after 3 years of age. Most children have skeletal abnormalities, including osteoporosis. Children are usually tall and thin with a curved spine, chest deformities, elongated limbs, and long, spiderlike fingers. Without

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early diagnosis and treatment, mental (psychiatric) and behavioral disorders and intellectual disability are common. Homocystinuria makes the blood more likely to clot spontaneously, resulting in strokes, high blood pressure, and many other serious problems.

Since 2008, nearly every state in the United States has required that all newborns be screened for homocystinuria with a blood test. A test measuring enzyme function in liver or skin cells confirms the diagnosis.

Some children with homocystinuria improve when given vitamin B₆ (pyridoxine) or vitamin B₁₂ (cobalamin).

Hartnup's disease:

Hartnup disease is an autosomal recessive disorder caused by impaired neutral (ie, monoaminomonocarboxylic) amino acid transport in the apical brush border membrane of the small intestine and the proximal tubule of the kidney. Patients present with pellagralike skin eruptions, cerebellar ataxia, and gross aminoaciduria.

Prognosis:

Hartnup disease is manifested by a wide clinical spectrum. Most patients remain asymptomatic, but, in a minority of patients, skin photosensitivity and neurologic and psychiatric symptoms may have a considerable influence on quality of life. Rarely, severe CNS involvement may lead to death. Mental retardation and short stature have been described in a few patients. Malnutrition and a low-protein diet are the primary factors that contribute to morbidity.

Signs and symptoms

Hartnup disease manifests during infancy with variable clinical presentation: failure to thrive, photosensitivity, intermittent ataxia, nystagmus, and tremor. Nicotinamide is necessary for neutral amino acid transporter production in the proximal renal tubules found in the kidney, and intestinal mucosal cells found in the small intestine. Therefore, a symptom stemming from this disorder results in increased amounts of amino acids in the urine. Pellagra, a similar condition, is also caused by low nicotinamide; this disorder results in dermatitis, diarrhea, and dementia. Hartnup disease is a disorder of amino acid transport in the intestine and kidneys; otherwise, the intestine and kidneys function normally, and the effects of the disease occur

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mainly in the brain and skin. Symptoms may begin in infancy or early childhood, but sometimes they begin as late as early adulthood. Symptoms may be triggered by sunlight, fever, drugs, or emotional or physical stress. A period of poor nutrition nearly always precedes an attack. The attacks usually become progressively less frequent with age. Most symptoms occur sporadically and are caused by a deficiency of niacinamide. A rash develops on parts of the body exposed to the sun. Mental retardation, short stature, headaches, unsteady gait, and collapsing or fainting are common. Psychiatric problems (such as anxiety, rapid mood changes, delusions, and hallucinations) may also result.

Treatment

A high-protein diet can overcome the deficient transport of neutral amino acids in most patients. Poor nutrition leads to more frequent and more severe attacks of the disease, which is otherwise asymptomatic. All patients who are symptomatic are advised to use physical and chemical protection from sunlight: avoid excessive exposure to sunlight, wear protective clothing, and use chemical sunscreens with a SPF of 15 or greater. Patients also should avoid other aggravating factors, such as photosensitizing drugs, as much as possible. In patients with niacin deficiency and symptomatic disease, daily supplementation with nicotinic acid or nicotinamide reduces both the number and severity of attacks. Neurologic and psychiatric treatment is needed in patients with severe central nervous system involvement.

Biosynthesis of non essential amino acids:

In order to synthesize amino acids, a source of nitrogen is needed. In animals glutamate and glutamine play the pivotal roles. The α -amino group of most of the amino acids comes from the transamination reaction transferring the amino group from glutamate to an α -ketoacid acceptor. Glutamate is synthesized from ammonia and α -ketoglutarate by the action of glutamate dehydrogenase.

Essential and Nonessential Amino Acids

Nonessential amino acids are those that are synthesized by mammals, while the essential amino acids must be obtained from dietary sources. Why would an organism evolve in such a way that it could not exist in the absence of certain amino acids? Most likely, the ready availability of

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these amino acids in lower organisms (plants and microorganisms) obviated the need for the higher organism to continue to produce them. The pathways for their synthesis were selected out. Not having to synthesize an additional ten amino acids (and regulate their synthesis) represents a major economy, then. Nevertheless, it remains for us to become familiar with the synthetic pathways for these essential amino acids in plants and microorganisms, and it turns out that they are generally more complicated than the pathways for nonessential amino acid synthesis and they are also species-specific.

The twenty amino acids can be divided into two groups of 10 amino acids. Ten are essential and 10 are nonessential. However, this is really not an accurate dichotomy, as there is overlap between the two groups, as is indicated in the text accompanying the following two charts:

The Ten "Nonessential" Amino Acids
Alanine
Asparagine
Aspartate
Cysteine (requires sulfhydryl group from methionine)
Glutamate
Glutamine
Glycine
Proline
Serine
Tyrosine (synthesized from phenylalanine)

Note that tyrosine is really an essential amino acid, as it is synthesized by the hydroxylation of phenylalanine, an essential amino acid. Also, in animals, the sulfhydryl group of cysteine is

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derived from methionine, which is an essential amino acid, so cysteine can also be considered essential.

The ten "essential" amino acids are:

The Ten "Essential" Amino Acids
Arginine
Histidine
Isoleucine
Leucine
Lysine
Methionine
Phenylalanine
Threonine
Tryptophan
Valine

Synthesis of Nonessential Amino Acids

Ignoring tyrosine (as its immediate precursor is phenylalanine, an essential amino acid), all of the nonessential amino acids (and we will include arginine here) are synthesized from intermediates of major metabolic pathways. Furthermore, the carbon skeletons of these amino acids are traceable to their corresponding α -ketoacids. Therefore, it could be possible to synthesize any one of the nonessential amino acids directly by transaminating its corresponding α -ketoacid, if that ketoacid exists as a common intermediate. A "transamination reaction", in which an amino group is transferred from an amino acid to the α -carbon of a ketoacid, is catalyzed by an aminotransferase.

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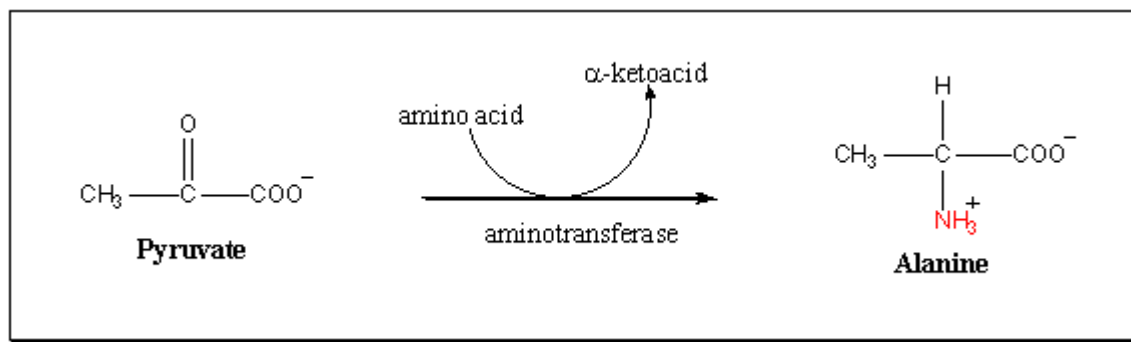
Three very common α -ketoacids can be transaminated in one step to their corresponding amino acid:

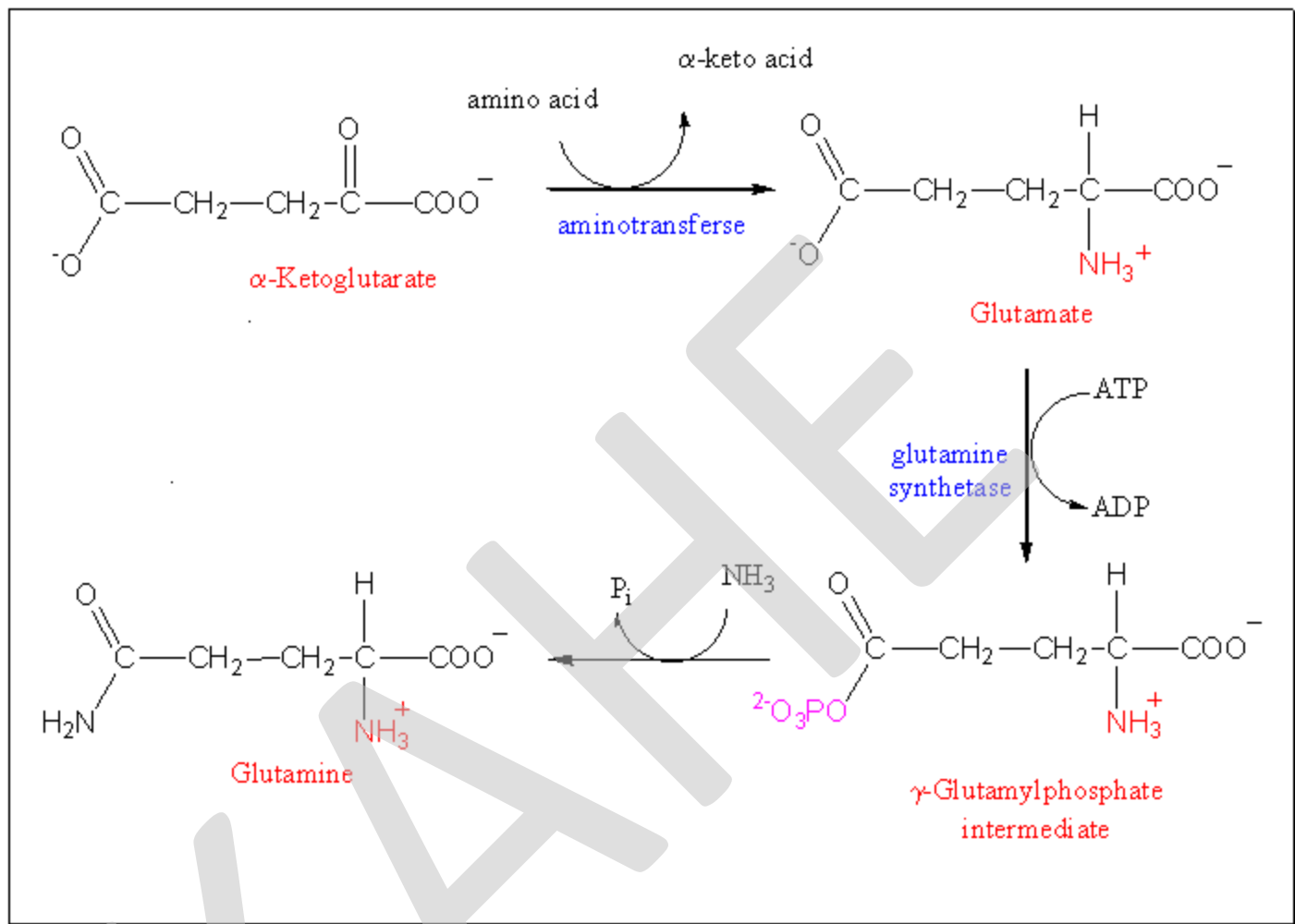
Pyruvate (glycolytic end product) --> alanine

Oxaloacetate (citric acid cycle intermediate) --> aspartate

α -ketoglutarate (citric acid cycle intermediate) --> glutamate

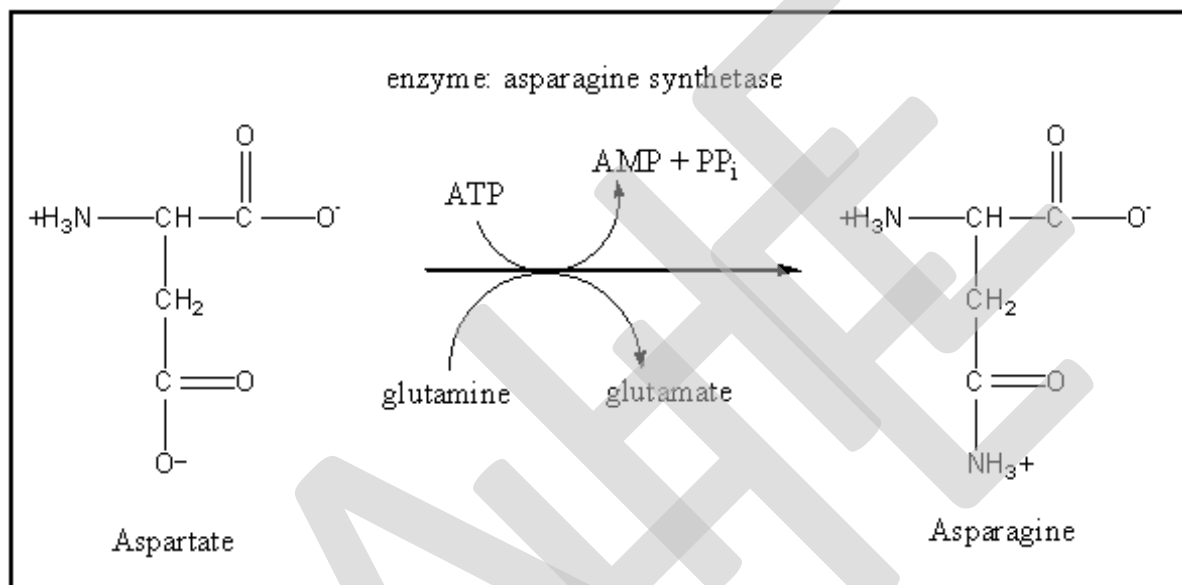
The individual reactions are:





Asparagine and glutamine are the products of amidations of aspartate and glutamate, respectively. Thus, asparagine and glutamine, and the remaining nonessential amino acids are not directly the result of transamination of α -ketoacids because these are not common intermediates of the other pathways. Still, we will be able to trace the carbon skeletons of all of these back to an α -ketoacid. I make this point not because of any profound implications inherent in it, but rather as a way to simplify the learning of synthetic pathways of the nonessential amino acids.

Aspartate is transaminated to asparagine in an ATP-dependent reaction catalyzed by asparagine synthetase, and glutamine is the amino group donor:



The synthesis of glutamine is a two-step one in which glutamate is first "activated" to a glutamylphosphate intermediate, followed by a reaction in which NH_3 displaces the phosphate group:

So, the synthesis of asparagine is intrinsically tied to that of glutamine, and it turns out that glutamine is the amino group donor in the formation of numerous biosynthetic products, as well as being a storage form of NH_3 . Therefore, one would expect that glutamine synthetase, the enzyme responsible for the amidation of glutamate, plays a central role in the regulation of nitrogen metabolism. We will now look into this control in more detail, before proceeding to the biosynthesis of the remaining nonessential amino acids.

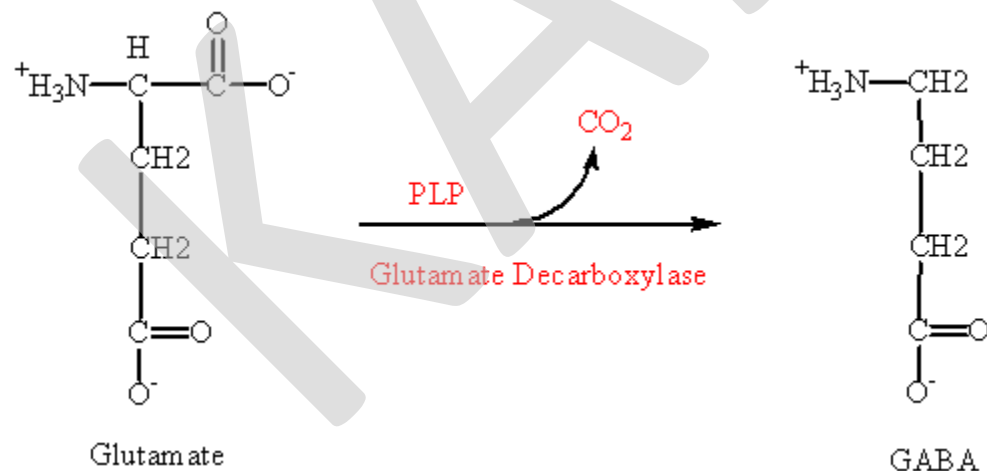
The α -ketoglutarate produced is then available for accepting amino groups in other transamination reactions, but the accumulation of ammonia as the other product of this reaction is a problem because, in high concentrations, it is toxic. To keep the level of NH_3 in a controlled range, a rising level of α -ketoglutarate activates glutamine synthetase, increasing the production of glutamine, which donates its amino group in various other reactions.

Proline, Ornithine and Arginine are derived from Glutamate

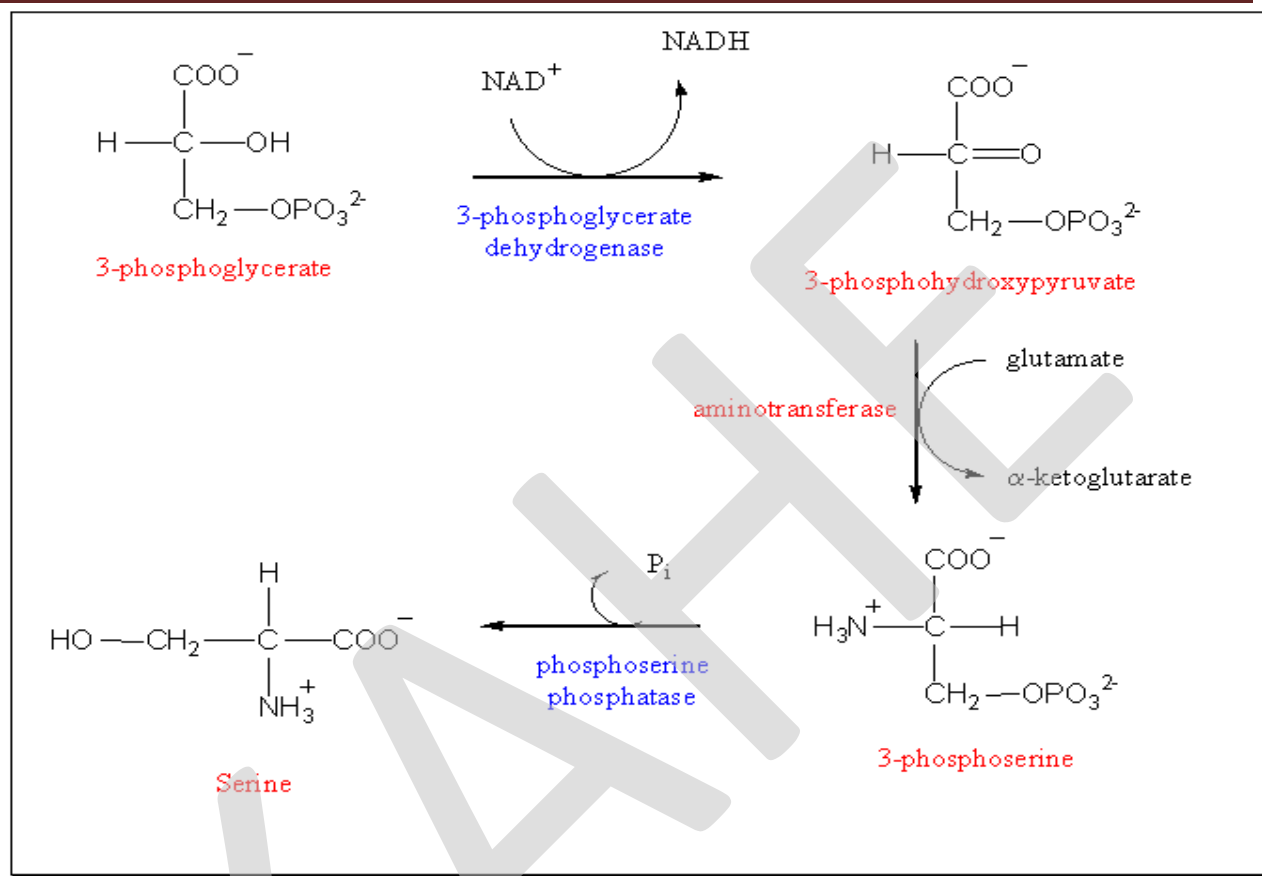
The first step involves phosphorylation of glutamate by ATP with the enzyme g-glutamyl kinase, followed by reduction to glutamate-5-semialdehyde which spontaneously cyclizes (no enzyme required) to an internal Schiff base. The formation of the semialdehyde also requires the presence of either NADP or NADPH.

The semialdehyde is a branch point, however. One branch leads to proline while the other branch leads to ornithine and arginine. Glutamate-5-semialdehyde is transaminated to ornithine and glutamate is the amino group donor. Ornithine, a urea cycle intermediate, is converted to arginine through the urea cycle.

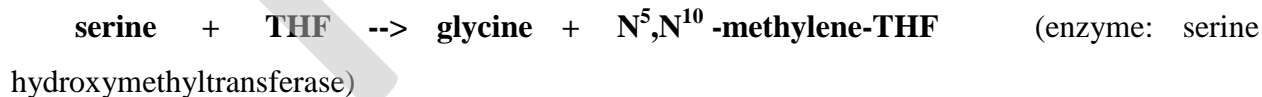
To further highlight the importance of glutamate, it is converted to the physiologically active amine, g-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the brain:



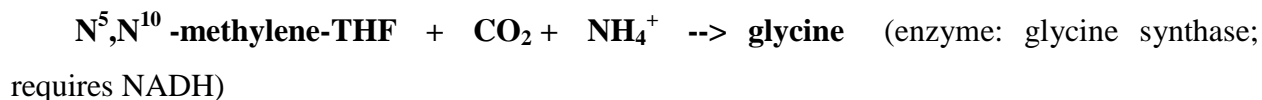
The glycolytic intermediate, 3-phosphoglycerate, is converted to serine, cysteine and glycine.



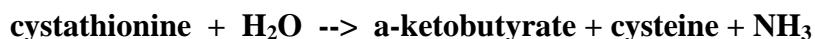
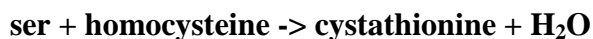
Note the participation of glutamate as the amino group donor. Serine is converted to glycine in the following reaction:



Glycine is also formed in a condensation reaction as follows:



Cysteine is synthesized from serine and homocysteine (methionine breakdown product):





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DEPARTMENT OF BIOCHEMISTRY
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METABOLISM OF AMINOACIDS AND NUCLEIC ACIDS (18BCU302)
MULTIPLE CHOICE QUESTIONS

UNIT II

S.N	Questions	Option A	Option B	Option C	Option D	Answer
1	A person with phenylketonuria cannot convert	Phenylalanine to tyrosine	Phenylalanine to isoleucine	Phenol into ketones	Phenylalanine to lysine	Phenylalanine to tyrosine
2	Which one is a hereditary disease?	Cataract	Leprosy	Blindness	Phenylketonuria	Phenylketonuria
3	Which of the following is a disorder with an autosomal dominant mode of inheritance (i.e. if you inherit the gene you get the disorder)?	Phenylketonuria	Parkinson's disease	Huntington's disease	Late onset Alzheimer's disease	Phenylketonuria
4	Which of the following amino acid is sweet in taste?	Glycine	Alanine	Glutamic acid	Aspartate	Glycine
5	The amino acid commonly used as an ingredient in the buffers of SDS PAGE.	Aspartic acid	Glutamic acid	Glycine	Aspartic acid and Lysine together	Glycine
6	Which of the following amino acid will be absent in α (alpha) helix structure of protein?	Glycine	Galine	Glutamic acid	Proline	Proline
7	Aminolevulinic acid, the first product in porphyrin biosynthesis in eukaryotes, is synthesized from ____ and succinyl-CoA.	Valine	Tryptophan	Methionine	Glycine	Glycine

8	Which of the following enzyme contain Selenocysteine?	Nitrate reductase	Catalase	Glutathione peroxidase	Peroxidase	Glutathione peroxidase
9	Amino acid used in the ‘stripping’ of Western blotting experiment is:	Glutamic acid	Phenyl alanine	Alanine	Glycine	Glycine
10	Total number of proteinogenic (protein building) amino acids in the living world is ____.	20	21	22	23	22
11	Amino acid selenocysteine is coded by_____.	UAA	UAG	UGA	AUG	UGA
12	Which of the following is not an essential amino acid?	Proline	Histidine	Leucine	Methionine	Proline
13	What is the molecular weight of Glycine?	75 g·mol ⁻¹	80 g·mol ⁻¹	90 g·mol ⁻¹	95 g·mol ⁻¹	75 g·mol ⁻¹
14	Among the 20 standard proteins coding amino acids, which one is least occurs in proteins?	Glycine	Alanine	Tryptophan	Methionine	Tryptophan
15	The most toxic compounds is	Tyrosine	Phenylpyruvate	Lysine	Phenylalanine	Phenylpyruvate
16	A person with phenylketonuria is advised not to consume which of the following products?	Glycine containing foods	Fat containing food	Glucose	Phenyl alanine rich food	Phenyl alanine rich food
17	In the normal breakdown of phenylalanine, it is initially degraded to	Fumarate	Tyrosine	Lysine	Phenylpuruvate	Tyrosine
18	A person suffering from phenylketonuria on consumption food containing high phenylalanine may lead to the accumulation of	Phenylalanine	Phenylpyruvate	Tyrosine	Isoleucine	Phenylpyruvate

19	In alkaptonuria	Patient's urine contains homogenetic acid	Urine becomes black	Black colored urine contains homogentisic acid	Urine contains phenylalanine.	Black colored urine contains homogentisic acid
20	Deficiency of enzyme branched chain ketoacid dehydrogenase leading to a block in the metabolism of branched chain amino acids observed in ?	Maple syrup urine disease	Hartnup's disease	Alkaptonuria	Phenylketonuria	Maple syrup urine disease
21	N ₂ makes up about 80% of the atmosphere. This is the source of nitrogen for all living things. The nitrogen cycle describes the movement of N ₂ from the atmosphere to living things. Which of the following statements are true?	Bacteria reduce N ₂ to NH ₃ .	Bacteria oxidize N ₂ to 2 NO ₃ ⁻ .	All bacteria carry out nitrogen fixation.	N ^o N is highly reactive.	Bacteria reduce N ₂ to NH ₃ .
22	The nitrogenase complex converts N ₂ into NH ₄ ⁺ by the addition of electrons. Which of the following is NOT true of this complex?	It requires Fe-S protein.	Pyruvate is always the source of electrons.	It requires ATP.	It requires Mo-Fe protein.	Pyruvate is always the source of electrons.
23	Biosynthesis of Amino Acids Animal cells incorporate NH ₄ ⁺ into organic molecules. The addition of an NH ₄ ⁺ molecule to a ketoglutarate to produce glutamate requires:	NADH	NADP ⁺	NADPH	NAD ⁺	NADPH
24	The addition of an NH ₄ ⁺ molecule to glutamate produces glutamine. This process requires:	NADPH	NADP ⁺	NAD ⁺	ATP	ATP

25	Which of the following statements about amino acid synthesis is NOT correct?	The carbon skeletons of amino acids come from glycolysis, citric acid, or phosphogluconate intermediates	All amino acids are derived from a common precursor.	The amino group is usually derived from glutamate.	Humans can only synthesize ten of the amino acids.	All amino acids are derived from a common precursor.
26	What is the role of tetrahydrofolate and S-adenosyl methione?	The transfer of electrons.	The transfer one-carbon units.	Both act as reductants.	Both act as oxidizers.	The transfer one-carbon units.
27	The site of amino acid catabolism is the:	Stomach	Small intestine	Large intestine	Liver	Liver
28	The first step in the catabolism of most amino acids is	Removal of carboxylate groups	Enzymatic hydrolysis of peptide bonds	Removal of the amino group	Zymogen cleavage	Removal of the amino group
29	Which of the following are true of amino acid catabolism?	Pyridoxal phosphate acts as an amino group carrier.	All amino acids are degraded into citric acid cycle intermediates.	Amino groups are transferred to arginine.	Pyridoxal phosphate transfers one-carbon units.	Pyridoxal phosphate acts as an amino group carrier.
30	NH ₄ ⁺ is toxic to cells and must be eliminated. Vertebrates utilize the urea cycle to achieve this. Which of the following is NOT true of the urea cycle?	NH ₄ ⁺ elimination is a spontaneous process.	It requires ATP.	Both of the nitrogens on urea are derived from glutamate.	The synthesis of arginine is part of the urea cycle.	NH ₄ ⁺ elimination is a spontaneous process.
31	A young tall thin male has ectopia lentis in both eyes. The most likely diagnosis is _____	Marfan's syndrome	Phenylketonuria	Homocystinuria	Marchesani's syndrome	Homocystinuria
32	Biotin is a coenzyme for reactions involving:	Decarboxylation	Carboxylation	Transamination	Deamination	Carboxylation
33	Folic acid is important for which of the following processes?	Fatty acid oxidation	Fatty acid synthesis	Gluconeogenesis	One carbon metabolism	One carbon metabolism

34	Which of the following is the coenzyme form of Thiamine?	TPP (Thiamine pyrophosphate)	TMP (Thiamine mono phosphate)	TTP (Thiamine triphosphate)	Free thiamine	TPP (Thiamine pyrophosphate)
35	Which of the following is a TPP dependent enzyme?	Lactate dehydrogenase	Glucokinase	Transketolase	Glutathione reductase	Transketolase
36	Which of the following is required as a coenzymes in the conversion of Histidine to Histamine?	TPP	NAD+	Vitamin C	Pyridoxal phosphate	Pyridoxal phosphate
37	Vitamin useful in the treatment of Hartnup's disease is	Biotin	Niacin	Folic Acid	Thiamine	Niacin
38	Ketogenic amino acid	Leucine	Valine	Alanine	Tryptophan	Leucine
39	Maple Syrup Urine Disease is due to defect in the metabolism of	Unbranched aminoacid	Phenyl alanine	Branched Chain Amino Acid	Tyrosine	Branched Chain Amino Acid
40	The main role of Vitamin K is	Carboxylation	Formatioun of active succinate	Heme systhesis	Synthesis of Fatty acid	Carboxylation
41	A child has pellagra like symptoms, amino acids in urine and family history of 2 siblings affected and 2 siblings normal. Parents are not affected. The diagnosis is ?	Alkaptonuria	Hartnup disease	Phenylketonuria	Maple syrup disease	Hartnup disease
42	Which amino acid, among the 20 standard protein coding amino acids, is most abundantly occurs in proteins?	Glycine	Methionine	Serine	Leucine	Leucine
43	Majority of enzyme's active site usually contain one or more _____ residues.	Glycine	Tryptophan	Histidine	Arginine	Histidine
44	Amino acid acting as a defensive molecule in plants:	Canavanine	Con-canavalin	Proline	All of these	Canavanine

45	Which amino acid act as the precursor of dopamine?	Glycine	Aspartate	Valine	Tyrosine	Tyrosine
46	Amino acid which act as the precursor of IAA (indole 3-acetic acid) biosynthesis in plants is_____.	Tyrosine	Phenylalanine	Tryptophan	Methionine	Tryptophan
47	Amino acid which act as the precursor of epinephrine synthesis is_____.	Glycine	Aspartate	Tyrosine	Valine	Tyrosine
48	Which of the following is an essential amino acid?	Aspartic acid	Alanine	Leucine	Asparagine	Leucine
49	Which of the following is a non-essential amino acid?	Alanine	Histidine	Lysine	Methionine	Alanine
50	First discovered amino acid is	Asparagine	Aspartate	Glutamate	Glutamine	Aspartate
51	Choose the correct category for milk protein casein out of the followings	Nucleoprotein	Phospho protein	Lipoprotein	Glycoprotein	Phospho protein
52	Hartnup's disease is associated with	Increased plasma tryptophan	Decreased plasma tryptophan	Increased neutral amino acids	Reduced plasma tryptophan and neutral amino acids	Reduced plasma tryptophan and neutral amino acids
53	Nonessential amino acids:	Are amino acids other than those required for protein synthesis.	Are not utilized in mammalian proteins.	Are synthesized by plants and bacteria, but not by humans.	Can be synthesized in humans as well as in bacteria	Can be synthesized in humans as well as in bacteria
54	An amino acid that does not derive its carbon skeleton, at least in part, from α -ketoglutarate is:	Arginine.	Glutamate.	Glutamine.	Threonine	Threonine

55	Glutamine, arginine, and proline:	Do not have a common precursor.	May all be derived from a citric acid cycle intermediate.	May all be derived from a Cori cycle intermediate.	May all be derived from a glycolytic intermediate.	May all be derived from a citric acid cycle intermediate
56	In which group are all the amino acids closely interrelated metabolically?	Arginine, hydroxyproline, and histidine	Arginine, tyrosine, and glutamate	Glycine, valine, glutamine, and aspartate	Ornithine, proline, arginine, and glutamate	Ornithine, proline, arginine, and glutamate
57	Which one of the following is semiessential amino acid for humans?	Valine	Arginine	Lysine	Tyrosine	Arginine
58	An essential amino acid in man is	Aspartate	Tyrosine	Methionine	Serine	Methionine
59	Casein, the milk protein is	Nucleoprotein	Chromoprotein	Phosphoprotein	Glycoprotein	Phosphoprotein
60	Pepsin acts on denatured proteins to produce	Proteoses and peptones	Polypeptides	Peptides	Dipeptides	Proteoses and peptones

Precursor functions of amino acids

Biosynthesis of creatine and creatinine, polyamines (putresine, spermine, spermidine), catecholamines (dopamine, epinephrine, norepinephrine) and neurotransmitters (serotonin, GABA). Porphyrin biosynthesis, catabolism and disorders of porphyrin metabolism.

Biosynthesis of creatine and creatinine

Occurrence of Creatine and Creatinine:

Creatine is widely distributed in animal tissues. It is present in muscle, brain and blood as phospho-creatine and also in the free state. Skeletal muscle contains about 0.5 per cent creatine and heart muscle about half that amount. 98 per cent of the total creatine in the body is in the muscles.

Creatinine is formed largely in the muscle by the irreversible and non-enzymic removal of water from creatine phosphate. Traces of creatine are also normally present in urine. Creatinine formation is a preliminary step required for the excretion of most of the creatine.

Biosynthesis of Creatine and Creatinine:

- Three amino acids—Glycine, arginine, and methionine—are directly involved.
- The first reaction is that of transamidation from arginine to glycine to form guanidoacetic acid (Glycocyamine). This reaction takes place in the kidney but not in the liver or in heart muscle. Recently, evidence has shown that nephrectomized rats can still synthesize creatine. The interpretation is that there is the existence of an external site or sites of transamidation in this animal.
- The synthesis of creatine is completed in the liver by the methylation of glyco-cyamine. “Active” methionine is the methyl donor. Other methyl donors betaine or choline after oxidation to betaine—serve indirectly by producing methionine through the methylation of homocysteine.

The methylation of glyco-cyamine is not reversible. Creatine or creatinine cannot methylate homocysteine to methionine. In the methylation of creatine, ATP and oxygen are required.

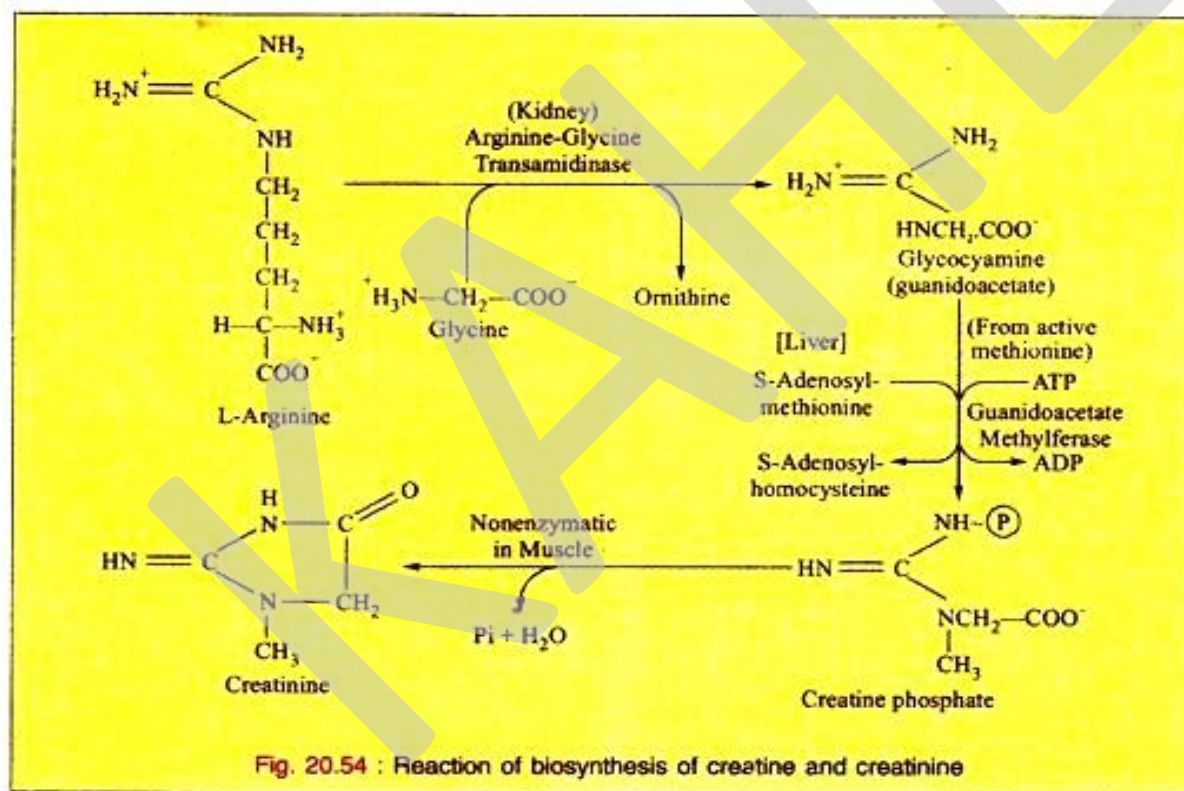
The enzymatic mechanisms for the methylation of glyco-cyamine involves first the formation of active methionine (S-adenosylmethionine) which requires ATP, Mg^{++} and glutathione as well as a methionine activating enzyme.

The methylation of glycocyamine by active methionine is catalyzed by guanidoacetate methylferase found in the liver of mammals. Glutathione or other reducing substances are required for the optimal activity of the enzyme. There is no evidence for the requirement of metal ions or other cofactors.

It has also been found that the pancreas can synthesize glycocyamine. Therefore, the pancreas may play an important role in the synthesis of creatine within the body of mammals. Dietary creatine or high blood creatine has no effect on the rate of synthesis of creatine in the liver.

The rate of creatine biosynthesis is dependent on kidney transamidinase activity. Hyperthyroidism is associated with reduced kidney transamidinase activity. The effect of hyperthyroidism on kidney transamidinase is mediated by the increased levels of blood creatine.

d. Creatinine is the anhydride of creatine and is formed by the non-enzymatic means in muscle.

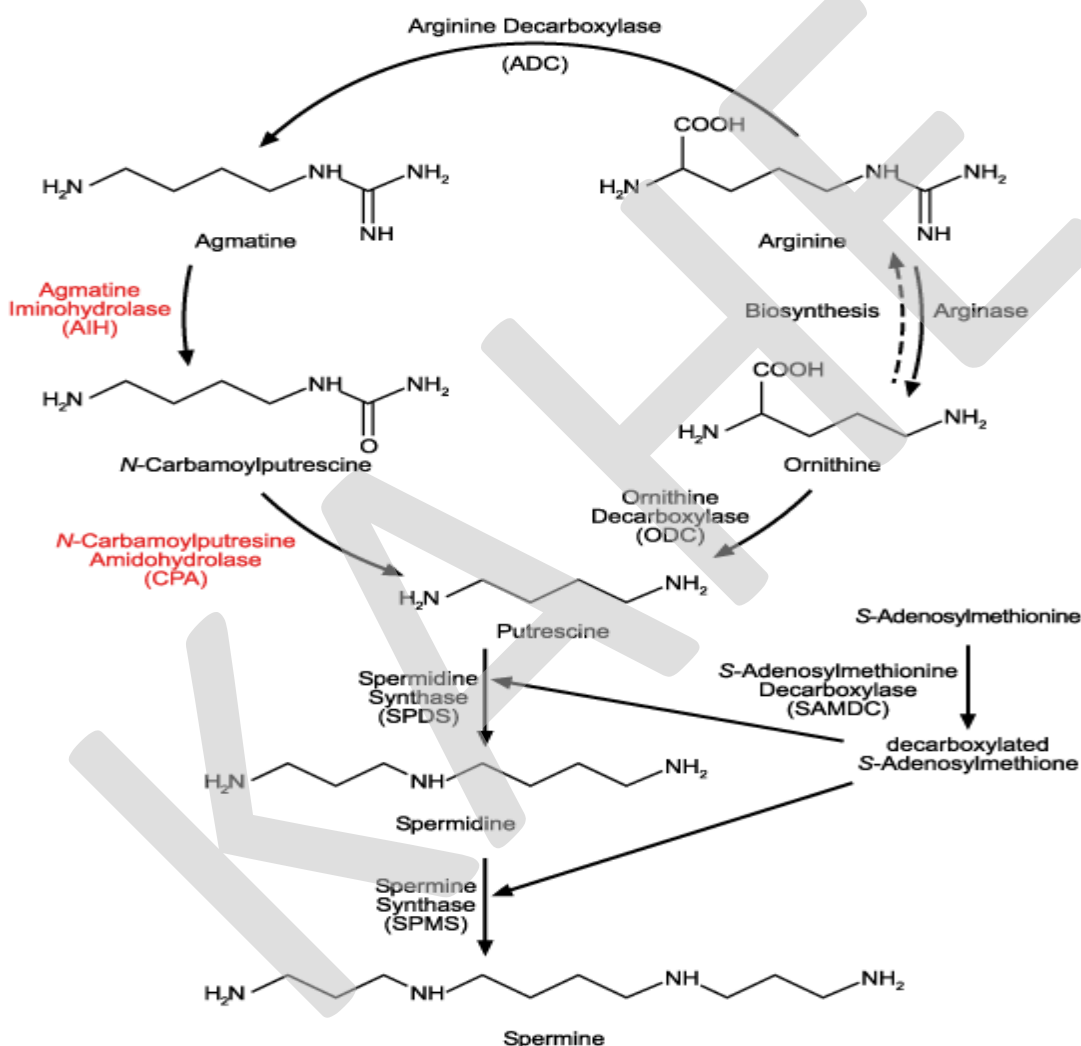


Biosynthesis of polyamines

Putrescine

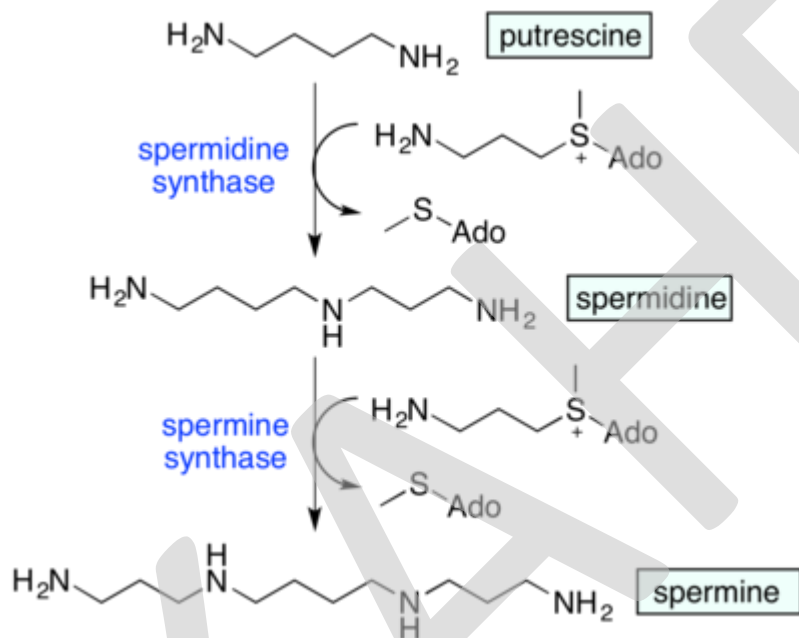
Putrescine is synthesized biologically via two different pathways, both starting from arginine.

- In one pathway, arginine is converted into agmatine, with a reaction catalyzed by the enzyme arginine decarboxylase (ADC); then agmatine is transformed into N-carbamoylputrescine by agmatine imino hydroxylase (AIH). Finally, N-carbamoylputrescine is converted into putrescine.^[10]
- In the second pathway, arginine is converted into ornithine and then ornithine is converted into putrescine by ornithine decarboxylase (ODC).



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Spermidine and spermine



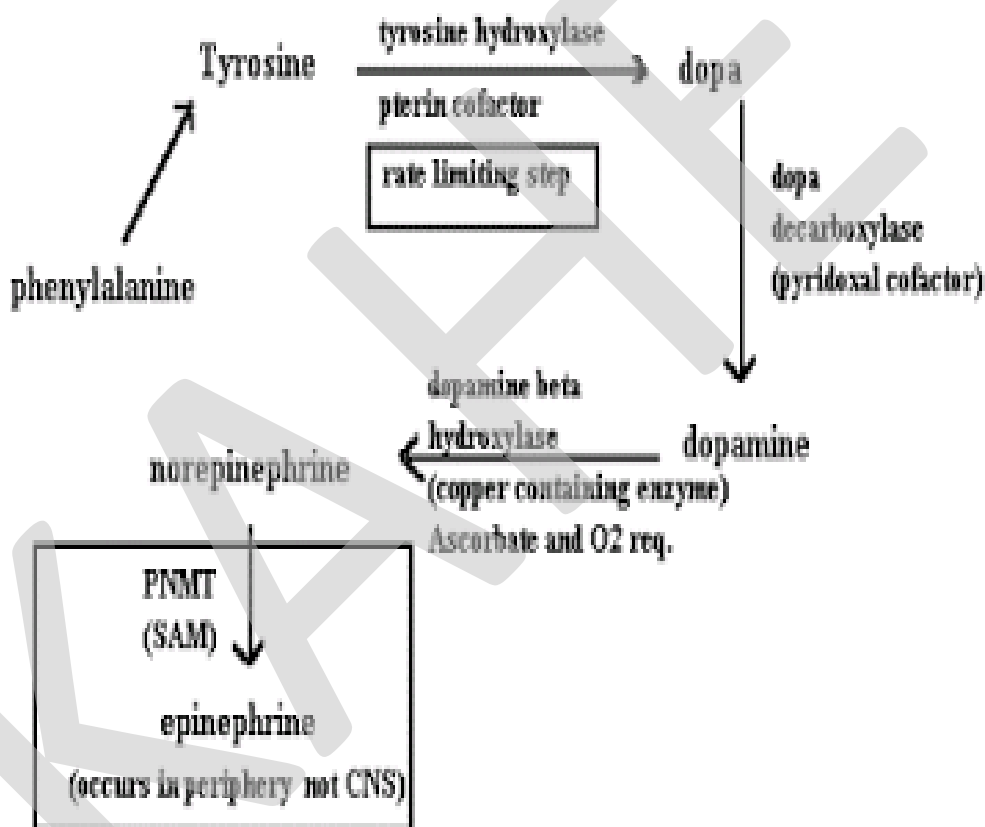
Biosynthesis of spermidine and spermine from putrescine. Ado = 5'-adenosyl.

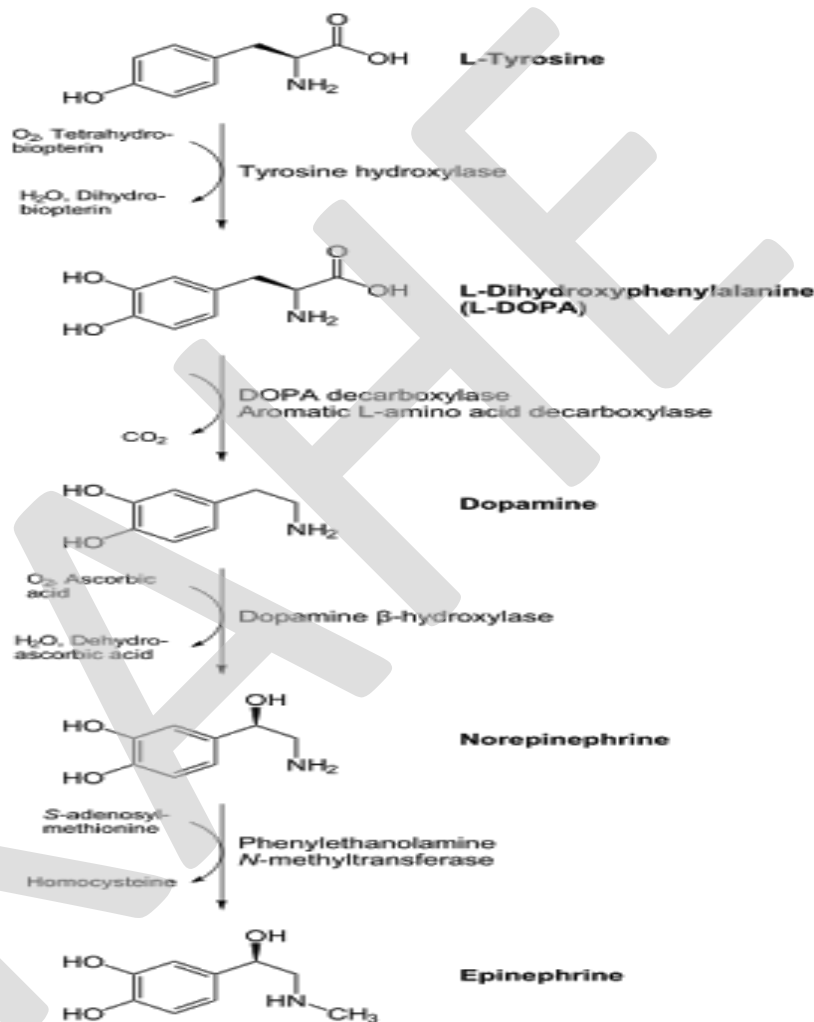
Spermidine is synthesized from putrescine, using an aminopropyl group from decarboxylated *S*-adenosyl-L-methionine (SAM). The reaction is catalyzed by spermidine synthase.

Spermine is synthesized from the reaction of spermidine with SAM in the presence of the enzyme spermine synthase.

Catecholamines (dopamine and norepinephrine)

synthesis and metabolism

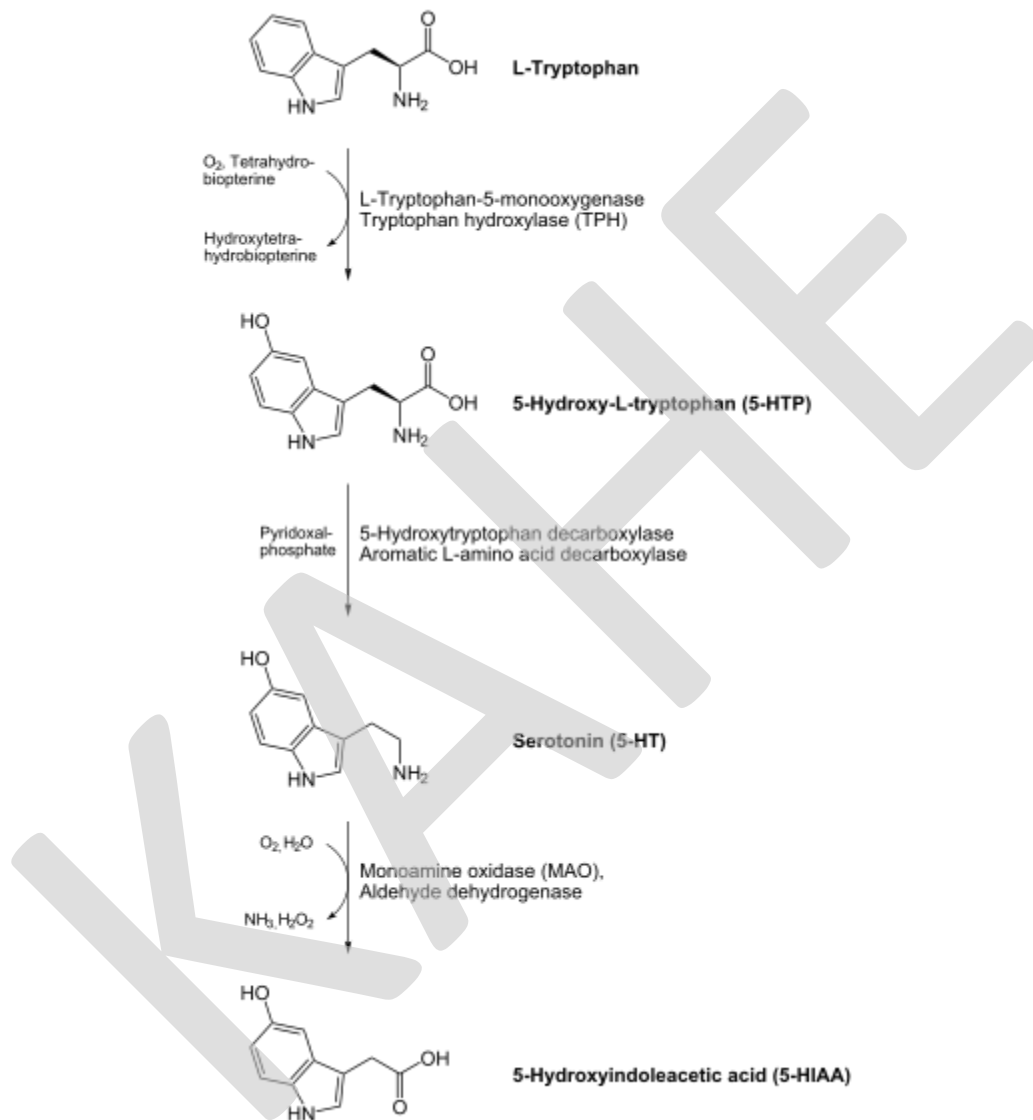




Biosynthesis of neurotransmitters

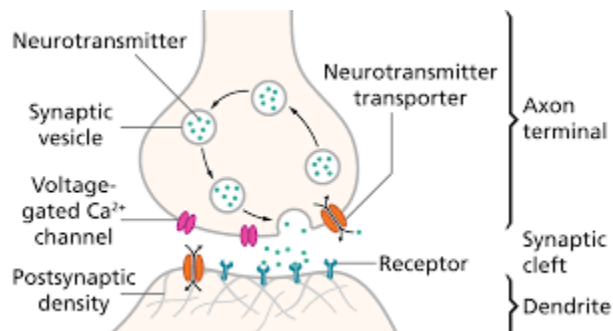
In animals including humans, **serotonin** is synthesized from the amino acid L-tryptophan by a short metabolic pathway consisting of three enzymes: tryptophan hydroxylase (TPH), aromatic amino acid decarboxylase (DDC) and pyridoxal phosphate. The TPH-mediated reaction is the rate-limiting step in the pathway.

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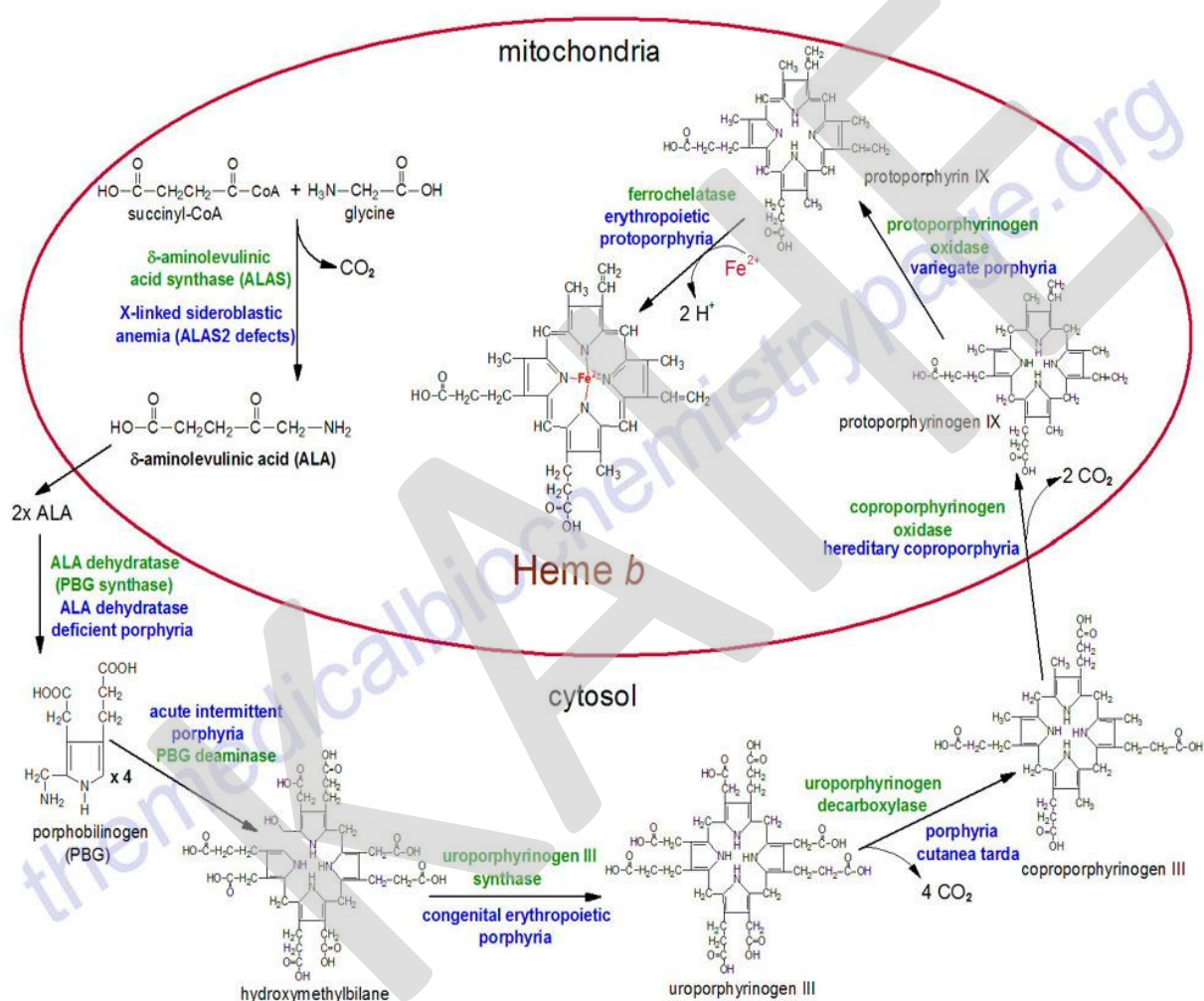


GABA

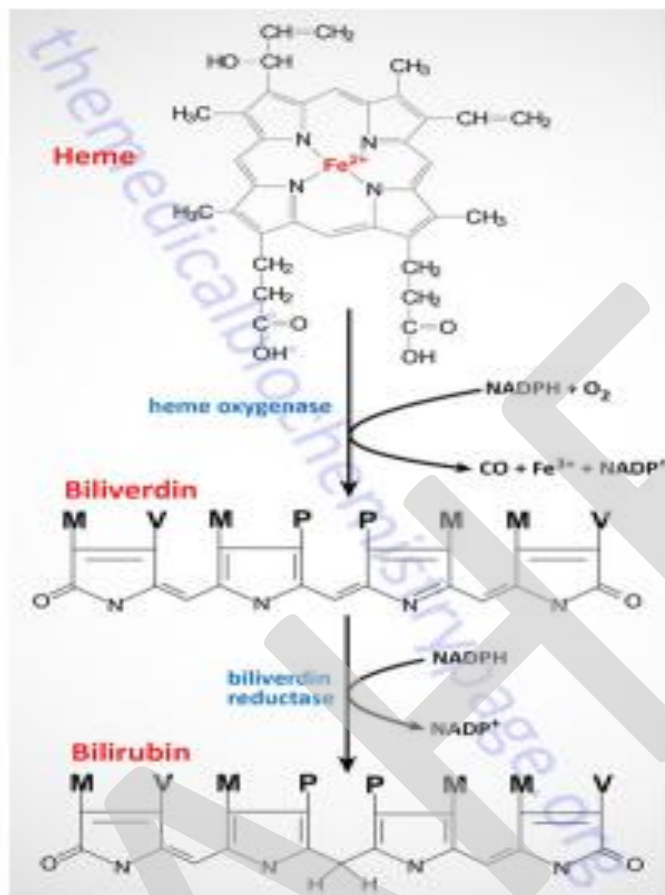
Exogenous GABA does not penetrate the blood–brain barrier; it is synthesized in the brain. It is synthesized from glutamate using the enzyme glutamate decarboxylase (GAD) and pyridoxal phosphate (which is the active form of vitamin B6) as a cofactor.



Biosynthesis of porphyrin



Catabolism of heme



Pathway for the degradation of heme to bilirubin. The ring of heme is opened through the action of heme oxygenase which also results in the release of the iron as the ferric form (Fe^{3+}) and also releases carbon monoxide, CO. The product of the heme oxygenase reaction is biliverdin. Biliverdin is converted to bilirubin via the action of biliverdin reductase. The various substituents on the pentameric rings of biliverdin and bilirubins are M: methyl, P: propyl, V: vinyl.

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METABOLISM OF AMINOACIDS AND NUCLEIC ACIDS (18BCU302)
MULTIPLE CHOICE QUESTIONS

UNIT III

S.No	Questions	Option A	Option B	Option C	Option D	Answer
1	Tryptophan could be considered as precursor of	Melanotonin	Thyroid hormones	Melanin	Epinephrine	Melanotonin
2	The rate limiting step in the biosynthesis of catecholamines is	Decarboxylation of dihydroxyphenylalanine	Hydroxylation of phenylalanine	Hydroxylation of tyrosine	Oxidation of dopamine	Hydroxylation of tyrosine
3	The enzyme carbamoyl phosphate synthetase requires	Mg ⁺⁺	Ca ⁺⁺	Na ⁺	K ⁺	Mg ⁺⁺
4	The enzyme dopamine β-oxidase which catalyses conversion of dopamine to norepinephrine requires	Vitamin A	Vitamin C	Vitamin E	Vitamin B12	Vitamin C
5	The amino acids involved in the synthesis of creatine are	Arginine, glycine, active methionine	Arginine, alanine, glycine	Glycine, lysine, methionine	Arginine, lysine, methionine	Arginine, glycine, active methionine
6	The amino acid which detoxicated benzoic acid to form hippuric acid is	Glycine	Alanine	Serine	Glutamic acid	Glycine
7	A limiting amino acid is an essential amino acid	That is most deficient in proteins	That is most excess in proteins	That which increases the growth	That which increases the weight gain	That is most deficient in proteins
8	Which of the following is not an amino acid?	Glutamic acid	Aspartic acid	Glutamine	Palmitic acid	Palmitic acid
9	What type of covalent bonds link the amino acids in a protein?	Peptide bonds	Hydrogen bonds	Ionic bonds	Glycosidic bonds	Peptide bonds

10	Kinase reactions:	inhibit ATP breakdown	involve the addition or removal of a phosphate group	involve the addition or removal of a ketone group	involve the addition or removal of an amino acid to a polypeptide chain	involve the addition or removal of a phosphate group
11	The energy for all forms of muscle contraction is provided by:	ATP	ADP	phosphocreatine	oxidative phosphorylation	ATP
12	The most rapid method to resynthesise ATP during exercise is through:	glycolysis	phosphocreatine breakdown	tricarboxylic acid cycle (Krebs' cycle)	glycogenolysis	phosphocreatine breakdown
13	When branched chain amino acids are deaminated in muscle, the ammonia produced is mostly:	converted into arginine and released from the muscle	converted into alanine and glutamine and released from the muscle	converted into urea and released from the muscle	used to synthesise purines and pyrimidines in the muscle	converted into alanine and glutamine and released from the muscle
14	Nonselective alpha-adrenergic receptor antagonist(s)	phentolamine (Regitine)	prazosin (Minipress)	yohimbine (Yocon)	DOPA	phentolamine (Regitine)
15	"Epinephrine reversal" could occur if epinephrine is administered in the presence of:	cocaine	imipramine (Tofranil)	propranolol (Inderal)	phentolamine (Regitine)	phentolamine (Regitine)
16	Enzyme(s) that degrade catecholamines:	MAO (monoamine oxidase)	dopamine beta-hydroxylase	tyrosine hydroxylase	dopa decarboxylase	MAO (monoamine oxidase)
17	Enzyme catalyzing the conversion of norepinephrine to epinephrine:	dopamine beta-hydroxylase	phenylethanolamine N-methyltransferase	tyrosine hydroxylase	dopa decarboxylase	phenylethanolamine N-methyltransferase
18	Which of the following is an inhibitory neurotransmitter	Acetyl choline	Glutamate	Norepinephrine	GABA	GABA
19	The main excitatory neurotransmitter of the central nervous system	Acetylcholine	Gamma-aminobutyric acid	Glycine	Glutamate	Glutamate
20	The neurotransmitter whose abundance is increased by fluoxetine	Anandamide	Dopamine	Glutamate	Serotonin	Serotonin
21	pH below pI amino acids will be___.	Anionic	Cationic	Net charge zero	No charge	Cationic
22	Naturally occurring proteins are usually polymers of ____.	D-amino acids	L-amino acids	A mixture of D and L amino acids	Either D amino acids or L- amino acids	L-amino acids

23	At zwitterionic form, an amino acid will act as ____.	Proton donor	Proton acceptor	Proton donor and acceptor	None of these	Proton donor and acceptor
24	Which of the following amino acid is more likely to occupy the interior of a globular protein?	Methionine	Aspartate	Lysine	Arginine	Methionine
25	Selenocysteine is a rare amino acid which contain ____ -	Selenium	Selenium and Sulfur	Sulfur	Selenium and Nickel.	Selenium
26	Which among the following is the largest amino acid?	Phenylalanine	Tyrosine	Tryptophan	Histidine	Tryptophan
27	The side chain of Histidine contain ____.	Indole ring	Phenol group	Imidazole ring	Guanidino ring	Imidazole ring
28	Selenocysteine is a derived from ____.	Cysteine	Serine	Methionine	Cystine	Serine
29	Example for selenocysteine containing protein:	Glutathione peroxidase	Thioredoxin reductase	Glycine reductase	All of these	All of these
30	A fully protonated glycine (NH ₃ ⁺ – CH ₂ – COOH) can release ____ protons.	1	2	3	4	2
31	Which out of the following is not a haemo protein?	Tryptophan pyrrolase	Tyrosinase	Myoglobin	Cytochrome P450	Tyrosinase
32	Which out of the following enzymes catalyses a rate limiting step in the pathway of haem biosynthesis?	ALA synthase	ALA dehydratase	PBG deaminase	Coproporphrinogen oxidase	ALA synthase
33	High levels of lead can affect heme metabolism by combining with SH groups of which out the following enzymes?	ALA synthase	ALA dehydratase	PBG deaminase	Coproporphrinogen oxidase	ALA dehydratase
34	Pyridoxal phosphate is necessary in the pathway of Haem biosynthesis, which out of the following enzymes requires Pyridoxal –P as a coenzyme?	ALA synthase	ALA dehydratase	PBG deaminase	Ferrochelatase	ALA synthase
35	In general, the porphyrias are inherited in an autosomal dominant manner, with the exception of	Acute intermittent porphyria	Porphyria Cutanea Tarda	Variegate Porphyria	Congenital Erythropoietic porphyria	Congenital Erythropoietic porphyria

36	Choose the incorrect statement out of the following	Synthesis of ALA occurs in the mitochondria	Uroporphyrinogen formed is almost exclusively the III isomer	A porphyrin with symmetric substitution of side chains is classified as a type III porphyrin	Coproporphyrinogen oxidase is able to act only on type III isomers	A porphyrin with symmetric substitution of side chains is classified as a type III porphyrin
37	In which of the following porphyrias, cutaneous hypersensitivity is not observed?	Variegate porphyria	Acute intermittent porphyria	Congenital Erythropoietic porphyria	Hereditary Coproporphyria	Congenital Erythropoietic porphyria
38	Which out of the following conditions is not associated with excessive bilirubin formation from hemolysis –	Sickle cell anemia	Thalassemia	Malaria	Rotor syndrome	Rotor syndrome
39	Which serum enzyme elevation is most diagnostic in obstructive jaundice?	ALT(Alanine amino transferase)	AST (Aspartate amino transferase)	LDH (Lactate dehydrogenase)	ALP (Alkaline phosphatase).	ALP (Alkaline phosphatase).
40	Porphyrins are	heterocyclic compounds.	metalloproteins.	inorganic pigments.	modified proteins.	heterocyclic compounds.
41	Quantitatively, the major porphyrin in human body is	heme.	chlorophyll.	bile pigment.	cytochrome.	heme.
42	Porphyrins are synthesized from	glycine and succinyl CoA.	ammonia and carbon dioxide.	proline and iron.	aminoacids, with the help of folic acid.	glycine and succinyl CoA.
43	Porphyrins are synthesized in	mitochondria.	cytosol.	both (a) and (b) combined.	neither (a) nor (b).	both (a) and (b) combined.
44	The key enzyme of porphyrin synthesis is	delta-aminolevulinic acid (ALA) synthase (ALAS).	uroporphyrinogen I synthase.	uroporphyrinogen III cosynthase.	uroporphyrinogen III decarboxylase.	delta-aminolevulinic acid (ALA) synthase (ALAS).
45	Which of the following is not required in the δ -aminolevulinic acid synthase reaction?	Glycine.	Succinyl CoA.	Pyridoxal phosphate.	Iron.	Iron.
46	Aminolevulinic acid synthase is inhibited by	hemin (oxidized heme).	lead.	iron.	vitamin B6.	hemin (oxidized heme).

47	Aminolevulinic acid dehydratase reaction	takes place in the mitochondria.	condenses two molecules of ALA.	forms porphobilinogen.	b + c.	b + c.
48	Porphobilinogen	is a monopyrrole compound.	has acetate and propionate side chains.	is condensed by deaminase to form a linear tetrapyrrole (hydroxymethylbilane).	all the above.	all the above
49	Deficient δ -aminolevulinic acid synthase reaction leads to	iron deficiency anemia.	sideroblastic anemia.	megaloblastic anemia.	aplastic anemia.	sideroblastic anemia.
50	The sequence of heme synthesis from δ -aminolevulinic acid (ALA) is	ALA \rightarrow porphobilinogen \rightarrow uroporphyrinogen \rightarrow coproporphyrinogen \rightarrow protoporphyrin \rightarrow protoporphyrinogen \rightarrow heme.	ALA \rightarrow porphobilinogen \rightarrow coproporphyrinogen \rightarrow uroporphyrinogen \rightarrow protoporphyrinogen \rightarrow protoporphyrin \rightarrow heme.	ALA \rightarrow uroporphyrinogen \rightarrow porphobilinogen \rightarrow coproporphyrinogen \rightarrow protoporphyrinogen \rightarrow protoporphyrin \rightarrow heme.	ALA \rightarrow porphobilinogen \rightarrow uroporphyrinogen \rightarrow coproporphyrinogen \rightarrow protoporphyrinogen \rightarrow protoporphyrin \rightarrow heme.	ALA \rightarrow porphobilinogen \rightarrow uroporphyrinogen \rightarrow coproporphyrinogen \rightarrow protoporphyrinogen \rightarrow protoporphyrin \rightarrow heme.
51	Which of the following is a cytosolic enzyme whose substrate is formed in the mitochondria?	ALA dehydratase.	Porphobilinogen deaminase.	Uroporphyrinogen I synthase.	Coproporphyrinogen III oxidase.	ALA dehydratase
52	Which of the following is a mitochondrial enzyme whose substrate is formed in the cytosol?	ALA dehydratase.	Porphobilinogen deaminase.	Uroporphyrinogen I synthase.	Coproporphyrinogen III oxidase.	Coproporphyrinogen III oxidase.
53	Which of the following molecules is least expected to result from catabolism of heme?	Bilirubin.	Urobilinogen.	Stercobilin.	Porphobilinogen.	Porphobilinogen.
54	Hemoglobin is broken down by which cells?	Red blood cells.	Erythropoietic cells.	Liver cells.	phagocytic cells of reticuloendothelial system.	phagocytic cells of reticuloendothelial system.
55	_____ is a monoamine neurotransmitter.	Serotonin	Glutamate	GABA	Nitric oxide	Serotonin

56	Which neurotransmitter is coming under gasotransmitter	Serotonin	Hydrogen sulfide	Dopamine	Histamine	Hydrogen sulfide
57	_____ is the first neurotransmitter discovered in the peripheral and CNS	Acetyl choline	Dopamine	GABA	Epinephrine	Acetyl choline
58	What is the source of polyamines?	Glutamate	Histidine	Arginine	Lysine	Arginine
59	Which is the enzyme which converts agmatine to N-Carbomoyl putresisne	Agmatine iminohydrolase	Agmatine synthase	Arginase	Spermine synthase	Agmatine iminohydrolase
60	Normal value of creatinine in blood	2.5 - 7.3 mg/dl	0.6 – 1.2 mg/dl	4.2 – 5.6 mg/dl	8 – 9.6 mg/dl	0.6 – 1.2 mg/dl

Biosynthesis of purine and pyrimidine nucleotides

De novo synthesis of purine and pyrimidine nucleotides, regulation and salvage pathways.

Deoxyribonucleotides and synthesis of nucleotide triphosphate

Biosynthesis of deoxyribonucleotides and its regulation, conversion to triphosphates, biosynthesis of coenzyme nucleotides.

Nucleotide Biosynthesis (De-novo & Salvage Synthesis of Purine & Pyrimidine Nucleotides in the Cells)

Pathways for the biosynthesis of nucleotides

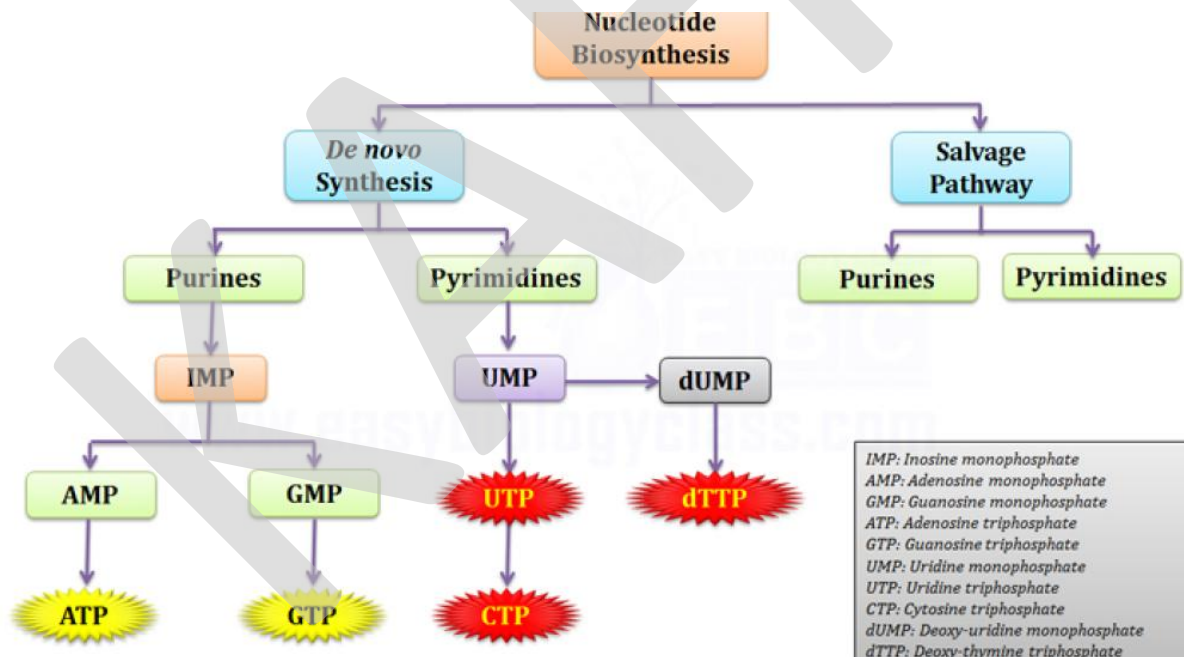
Nucleotide biosynthesis in the cell can be grouped into two broad classes.

(1) de-novo synthesis and

(2) synthesis by salvage pathways.

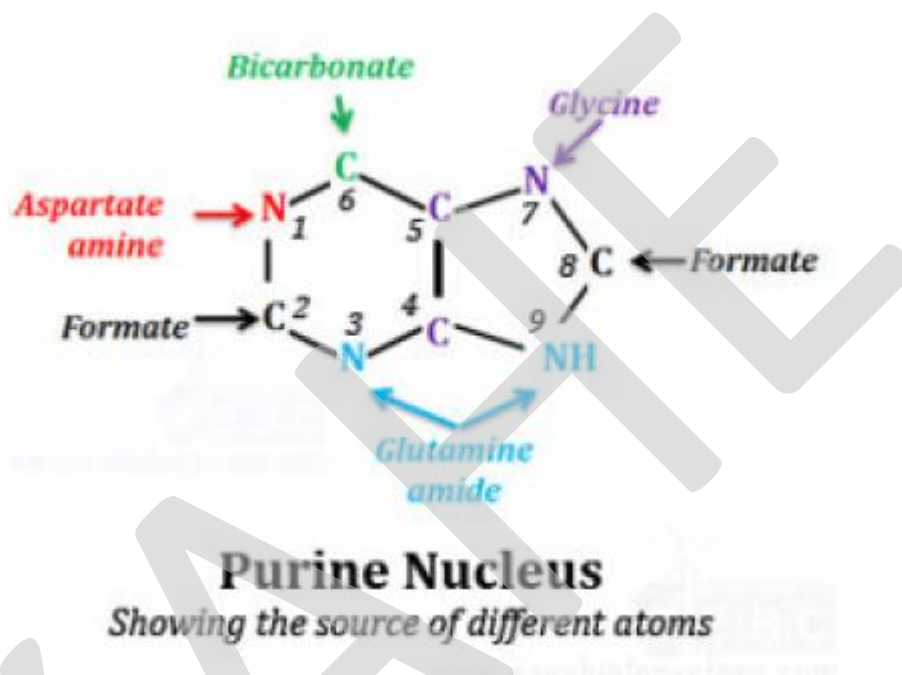
I. De-novo synthesis (synthesis from scratch): it is a biochemical pathway in which nucleotides are synthesized new from simple precursor molecules.

II. Salvage pathway (recycle pathway): used to recover bases and nucleosides formed during the degradation of RNA and DNA



The purine nucleotides of nucleic acids are adenosine 5-monophosphate (AMP; adenylate) and guanosine 5-monophosphate (GMP; guanylate), containing the purine bases adenine and guanine respectively. The first idea about purine nucleotide biosynthesis in the cell was come from the

study of John Buchanan (1948) by radioactive tracer studies in birds by analyzing the biochemistry of uric acid (a purine present in the excreta of birds). The detailed biosynthetic pathways of the purine biosynthesis came latter in 1950 primarily by the works of Buchanan and G. Robert Greenberg.



The image shows the source of different atoms in a purine skeleton identified by radio labeling studies

N1 is derived from amino group of Aspartate

C2 & C8 is derived from Formate

N3 & N9 is derived from amide group of Glutamine

C4, C5 & N7 is derived from Glycine

C6 is derived from HCO_3^- (bicarbonate)

Formation of IMP

Once the commitment step has produced the 5-phosphoribosyl amine, the rest of the molecule is formed by a series of additions to make first the 5- and then the 6-membered ring. (Note: the

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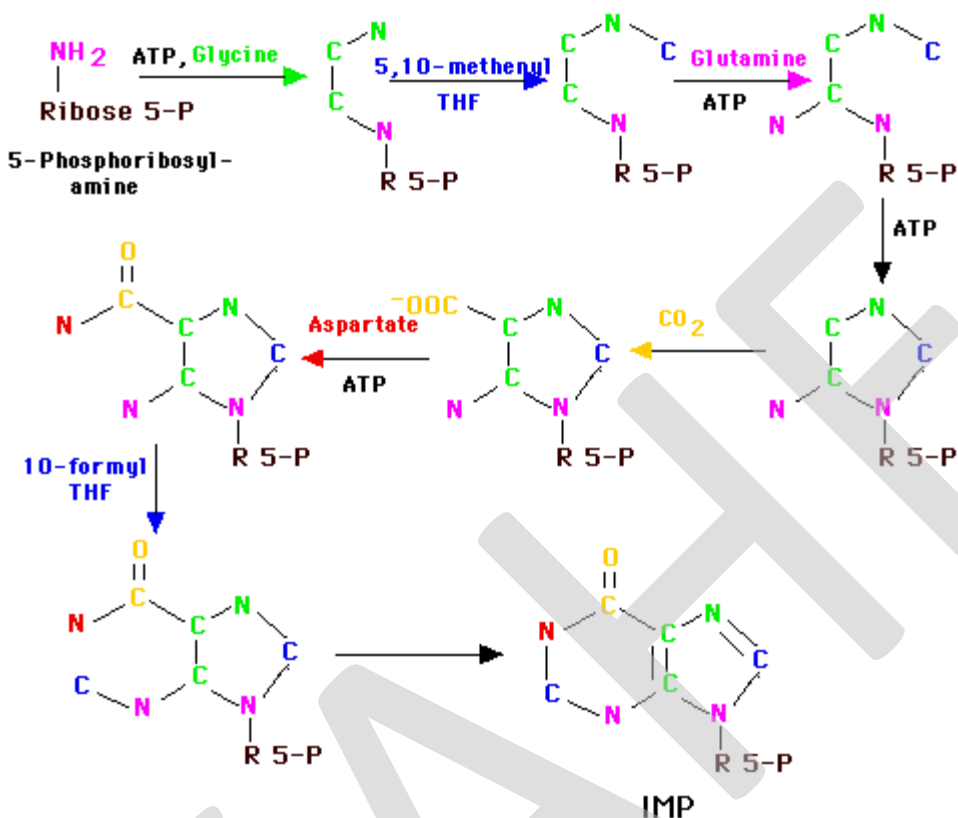
numbers given to the atoms are those of the completed purine ring and names, etc. of the intermediate compounds are not given.) The whole glycine molecule, at the expense of ATP adds to the amino group to provide what will eventually be atoms 4, 5, and 7 of the purine ring (The amino group of 5-phosphoribosyl amine becomes nitrogen N of the purine ring.) One more atom is needed to complete the five-membered ring portion and that is supplied as 5, 10-Methenyl tetrahydrofolate.

Before ring closure occurs, however, the amide of glutamine adds to carbon 4 to start the six-membered ring portion (becomes nitrogen 3). This addition requires ATP. Another ATP is required to join carbon 8 and nitrogen 9 to form the five-membered ring.

The next step is the addition of carbon dioxide (as a carboxyl group) to form carbon 6 of the ring. The amine group of aspartate adds to the carboxyl group with a subsequent removal of fumarate. The amino group is now nitrogen 1 of the final ring. This process, which is typical for the use of the amino group of aspartate, requires ATP. The final atom of the purine ring, carbon 2, is supplied by 10-Formyl tetrahydrofolate. Ring closure produces the purine nucleotide, IMP.

Note that at least 4 ATPs are required in this part of the process. At no time do we have either a free base or a nucleotide.

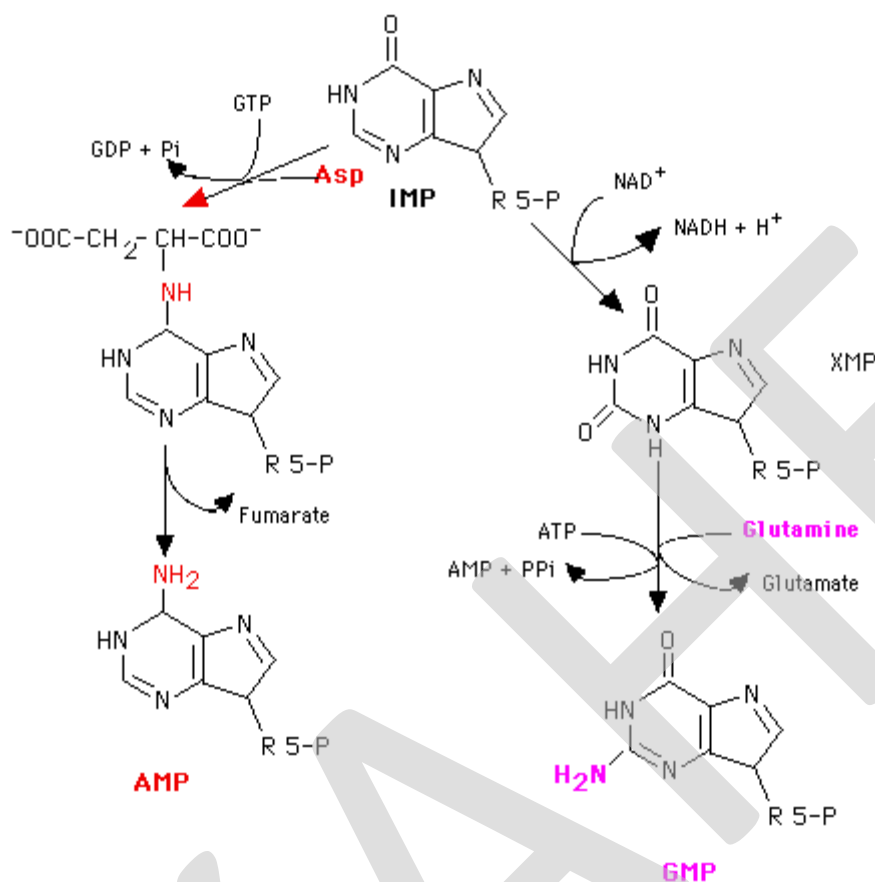
Schematic Representation of Purine Nucleotide Synthesis



Formation of AMP and GMP

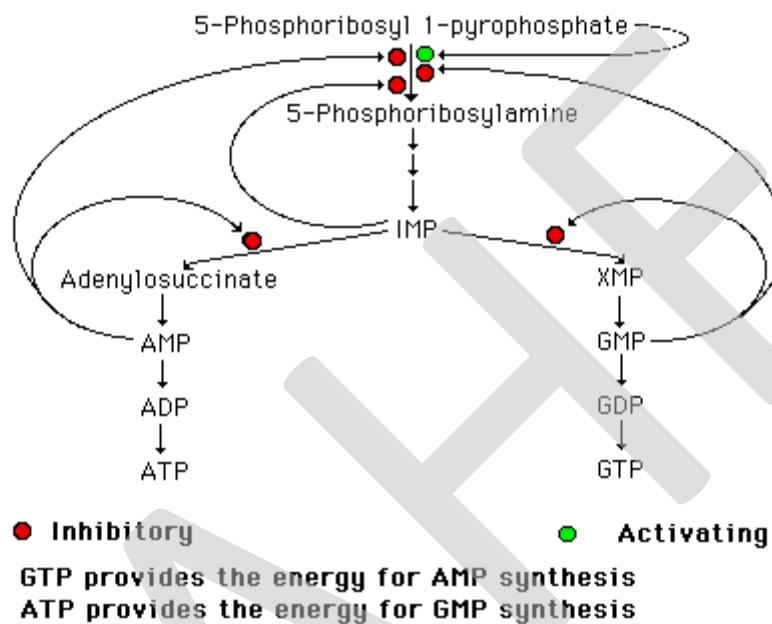
IMP can then become **either** AMP or GMP. **GMP** formation requires that IMP be first oxidized to XMP using NAD. The oxygen at position 2 is substituted by the amide N of glutamine at the expense of ATP. Similarly, GTP provides the energy to convert IMP to **AMP**. The amino group is provided by aspartate in a mechanism similar to that used in forming nitrogen 1 of the ring. Removal of the carbons of aspartate as fumarate leaves the nitrogen behind as the 6-amino group of the adenine ring. The monophosphates are readily converted to the di- and tri-phosphates.

Conversion of IMP to either AMP or GMP



Control of De Novo Synthesis

Control of purine nucleotide synthesis has two phases. Control of the **synthesis as a whole** occurs at the amidotransferase step by nucleotide inhibition and/or [PRPP]. The second phase of control is involved with **maintaining an appropriate balance (not equality) between ATP and GTP**. Each one stimulates the synthesis of the other by providing the energy. Feedback inhibition also controls the branched portion as GMP inhibits the conversion of IMP to XMP and AMP inhibits the conversion of IMP to adenylosuccinate.



De Novo Synthesis of Pyrimidine Nucleotides

Since pyrimidine molecules are simpler than purines, so is their synthesis simpler but is still from readily available components. Glutamine's amide nitrogen and carbon dioxide provide atoms 2 and 3 of the pyrimidine ring. They do so, however, after first being converted to carbamoyl phosphate. The other four atoms of the ring are supplied by aspartate. As is true with purine nucleotides, the sugar phosphate portion of the molecule is supplied by PRPP.

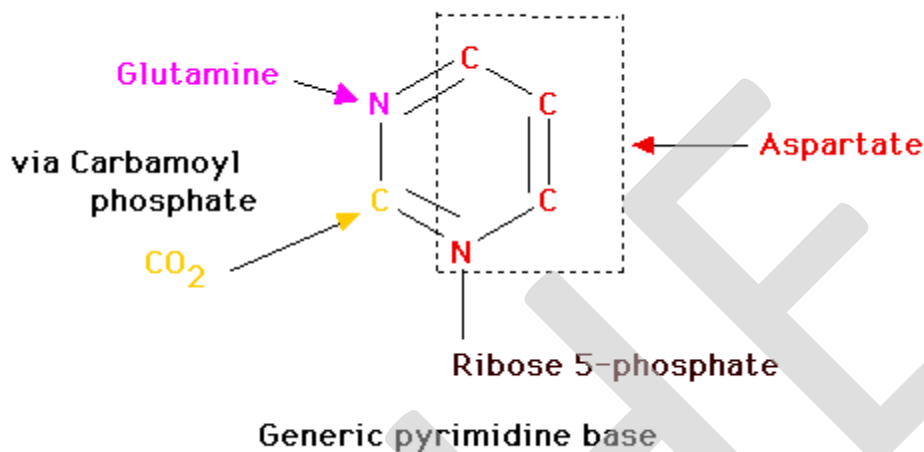
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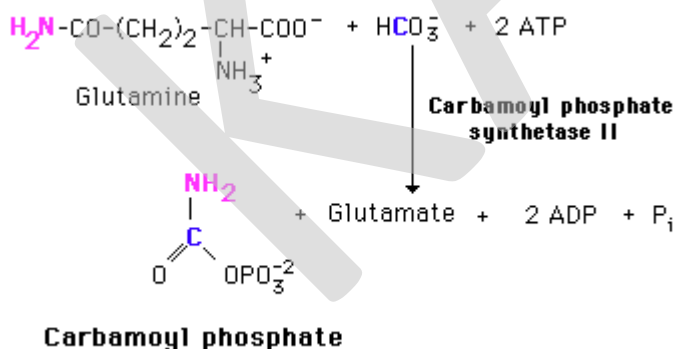
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Carbamoyl Phosphate

Pyrimidine synthesis begins with **carbamoyl phosphate** synthesized in the cytosol of those tissues capable of making pyrimidines (highest in spleen, thymus, GI tract and testes). This uses a different enzyme than the one involved in urea synthesis. **Carbamoyl phosphate synthetase II (CPS II)** prefers glutamine to free ammonia and has no requirement for N-Acetylglutamate.



Salvage of Bases

Salvaging of purine and pyrimidine bases is an exceedingly important process for most tissues. There are two distinct pathways possible for salvaging the bases.

Salvaging Purines

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The more important of the pathways for **salvaging purines** uses enzymes called **phosphoribosyltransferases (PRT)**:

PRTs catalyze the addition of ribose 5-phosphate to the base from PRPP to yield a nucleotide.:

Base + PRPP = Base-ribose-phosphate (BMP) + PPi

We have already seen one example of this type of enzyme as a normal part of *de novo* synthesis of the pyrimidine nucleotides, - O-PRT.

As a salvage process though, we are dealing with purines. There are two enzymes, A-PRT and HG-PRT. **A-PRT** is not very important because we generate very little adenine. (Remember that the catabolism of adenine nucleotides and nucleosides is through inosine). **HG-PRT**, though, is exceptionally important and it is inhibited by both IMP and GMP. This enzyme salvages guanine directly and adenine indirectly. Remember that AMP is generated primarily from IMP, not from free adenine.

Salvaging Pyrimidines

A second type of salvage pathway involves two steps and is the major pathway for the pyrimidines, uracil and thymine.

Base + Ribose 1-phosphate = Nucleoside + Pi (nucleoside phosphorylase)

Nucleoside + ATP - Nucleotide + ADP (nucleoside kinase - irreversible)

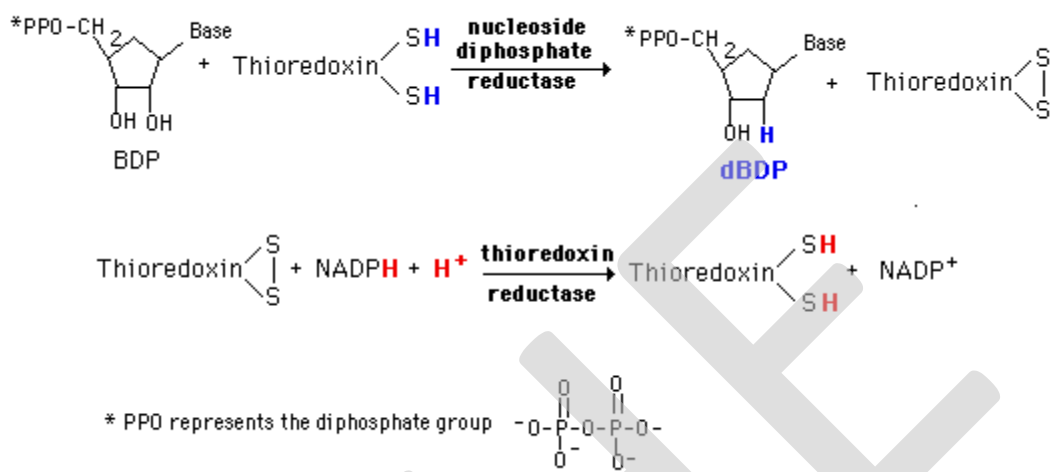
There is a uridine phosphorylase and kinase and a deoxythymidine phosphorylase and a thymidine kinase which can salvage some thymine in the presence of dR 1-P.

Formation of Deoxyribonucleotides

De novo synthesis and most of the salvage pathways involve the ribonucleotides. (Exception is the small amount of salvage of thymine indicated above.) Deoxyribonucleotides for DNA synthesis are formed from the ribonucleotide diphosphates (in mammals and *E. coli*).

A base diphosphate (BDP) is reduced at the 2' position of the ribose portion using the protein, **thioredoxin** and the enzyme **nucleoside diphosphate reductase**. Thioredoxin has two sulfhydryl groups which are oxidized to a disulfide bond during the process. In order to restore

the thioredoxin to its reduced form so that it can be reused, **thioredoxin reductase** and **NADPH** are required.

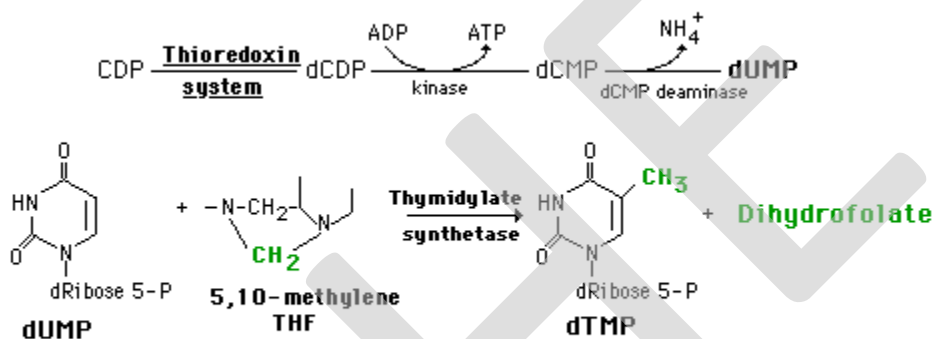


This system is very tightly controlled by a variety of allosteric effectors. dATP is a general inhibitor for all substrates and ATP an activator. Each substrate then has a specific positive effector (a BTP or dBTP). The result is a maintenance of an appropriate balance of the deoxynucleotides for DNA synthesis.

Synthesis of dTMP

DNA synthesis also requires dTMP (dTTP). This is not synthesized in the *de novo* pathway and salvage is not adequate to maintain the necessary amount. dTMP is generated from dUMP using the folate-dependent one-carbon pool.

Since the nucleoside diphosphate reductase is not very active toward UDP, CDP is reduced to dCDP which is converted to dCMP. This is then deaminated to form dUMP. In the presence of **5,10-Methylene tetrahydrofolate** and the enzyme **thymidylate synthetase**, the carbon group is both transferred to the pyrimidine ring and further reduced to a methyl group. The other product is **dihydrofolate** which is subsequently reduced to the tetrahydrofolate by dihydrofolate reductase.

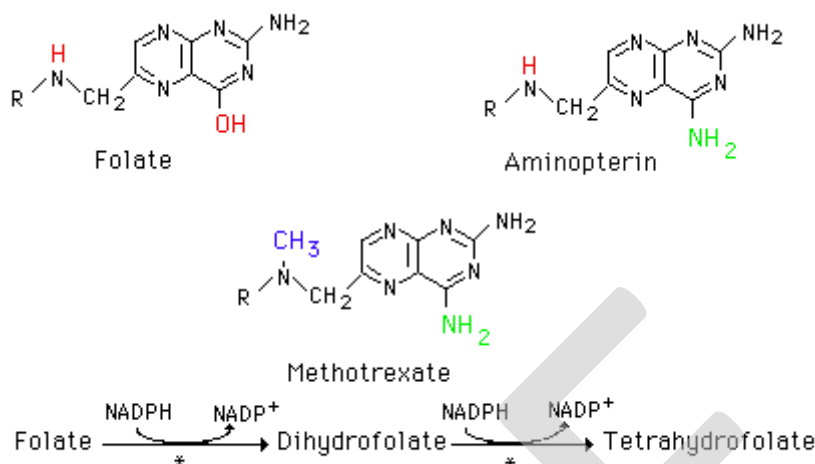


Dihydrofolate must be subsequently reduced to the tetrahydro form.

Chemotherapeutic Agents

Thymidylate synthetase is particularly sensitive to availability of the folate one-carbon pool. Some of the cancer chemotherapeutic agents interfere with this process as well as with the steps in purine nucleotide synthesis involving the pool.

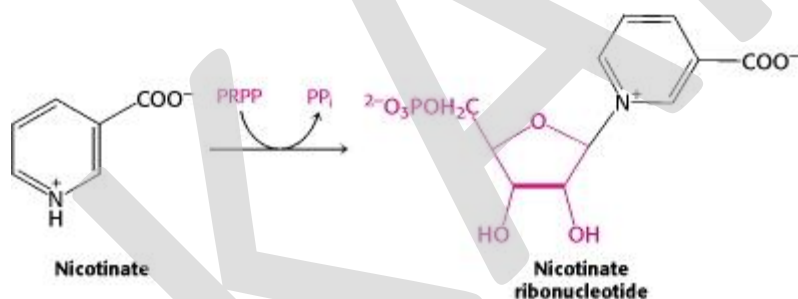
Cancer chemotherapeutic agents like **methotrexate** (4-amino, 10-methyl folic acid) and **aminopterin** (4-amino, folic acid) are structural analogs of folic acid and inhibit dihydrofolate reductase. This interferes with maintenance of the folate pool and thus of *de novo* synthesis of purine nucleotides and of dTMP synthesis. Such agents are highly toxic and administered under careful control.



* Aminopterin and Methotrexate are inhibitors of dihydrofolate reductase

NAD⁺, FAD, and Coenzyme A Are Formed from ATP

Nucleotides are important constituents not only of RNA and DNA, but also of a number of key biomolecules considered many times in our study of biochemistry. NAD⁺ and NADP⁺, coenzymes that function in oxidation-reduction reactions, are metabolites of ATP. The first step in the synthesis of *nicotinamide adenine dinucleotide* (NAD⁺) is the formation of *nicotinate ribonucleotide* from nicotinate and PRPP.

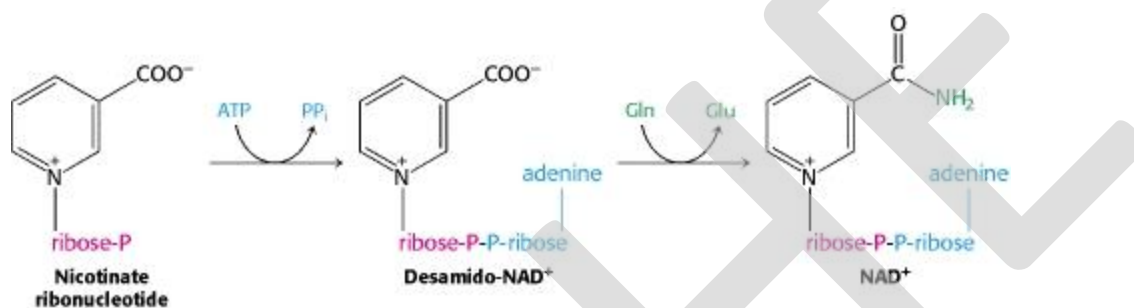


Nicotinate (also called niacin or vitamin B₆) is derived from tryptophan. Human beings can synthesize the required amount of nicotinate if the supply of tryptophan in the diet is adequate. However, nicotinate must be obtained directly if the dietary intake of tryptophan is low. A dietary deficiency of tryptophan and nicotinate can lead to pellagra, a disease characterized by dermatitis, diarrhea, and dementia. An endocrine tumor that consumes large

amounts of tryptophan in synthesizing the hormone and neurotransmitter serotonin (5-hydroxytryptamine) can lead to pellagra-like symptoms.

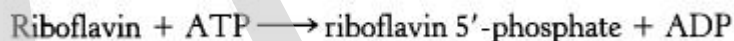
An AMP moiety is transferred from ATP to nicotinate ribonucleotide to form *desamido-NAD⁺*.

The final step is the transfer of the ammonia generated from the amide group of glutamine to the nicotinate carboxyl group to form *NAD⁺*.



NADP⁺ is derived from *NAD⁺* by phosphorylation of the 2'-hydroxyl group of the adenine ribose moiety. This transfer of a phosphoryl group from ATP is catalyzed by *NAD⁺ kinase*.

Flavin adenine dinucleotide (FAD) is synthesized from riboflavin and two molecules of ATP. Riboflavin is phosphorylated by ATP to give *riboflavin 5'-phosphate* (also called flavin mononucleotide, FMN). FAD is then formed from FMN by the transfer of an AMP moiety from a second molecule of ATP.



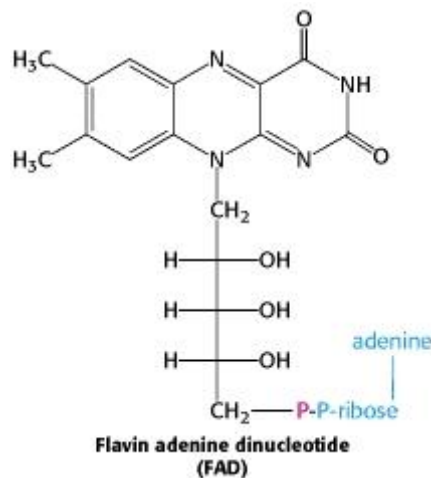
CLASS: II BSC BC

COURSE NAME: METABOLISM OF AMINOACIDS AND NUCLEIC ACIDS

UNIT: IV Biosynthesis of purine and pyrimidine nucleotides, Deoxyribonucleotides and synthesis of nucleotide triphosphate

COURSE CODE: 17BCU302

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The AMP moiety of coenzyme A also comes from ATP. A common feature of the biosyntheses of NAD^+ , FAD, and CoA is the transfer of the AMP moiety of ATP to the phosphate group of a phosphorylated intermediate. The pyrophosphate formed in these condensations is then hydrolyzed to orthophosphate. As in many other biosyntheses, much of the thermodynamic driving force comes from the hydrolysis of the released pyrophosphate.



KARPAGAM ACADEMY OF HIGHER EDUCATION
DEPARTMENT OF BIOCHEMISTRY
II-B.Sc., BIOCHEMISTRY
METABOLISM OF AMINOACIDS AND NUCLEIC ACIDS (17BCU302)
MULTIPLE CHOICE QUESTIONS

UNIT IV

S.No	Questions	Option A	Option B	Option C	Option D	Answer
1	Which of the following statements about the nomenclature of nucleosides is not true?	Cytosine is a nucleoside made up of the base cytidine attached to ribose.	Adenosine is a nucleoside made up of the base adenine attached to ribose.	Thymine is a nucleoside made up of the base thymidine attached to ribose.	Inosine is a nucleoside made up of the base hypoxanthine attached to L-ribose	Adenosine is a nucleoside made up of the base adenine attached to ribose.
2	Which of the following statements about the structure of nucleotides is correct?	The sugar component of a nucleotide is always ribose.	The sugar component of a nucleotide is always deoxyribose.	The bases in nucleotides are attached to the pentose sugar moieties by a glycosidic bond.	The sugar component of a nucleotide is in the L-configuration.	The bases in nucleotides are attached to the pentose sugar moieties by a glycosidic bond.
3	Which of the following statements about the de novo synthesis of purine nucleotides is correct?	AMP is the first purine nucleotide assembled from the de novo pathway.	The enzyme PRPP amidotransferase catalyses the committed step of the de novo synthesis pathway.	IMP is a competitive inhibitor of PRPP synthetase.	AMP is a competitive inhibitor of PRPP amidotransferase.	The enzyme PRPP amidotransferase catalyses the committed step of the de novo synthesis pathway.

4	Which of the following statements about the salvage pathway for the synthesis of purine nucleotides is correct?	Increased PRPP levels in cells inactivate hypoxanthine-guanine phosphoribosyl transferase (HGPRT).	Decreased PRPP levels in cells lead to the activation of hypoxanthine-guanine phosphoribosyltransferase (HGPRT).	Increased PRPP levels in cells lead to the activation of hypoxanthine-guanine phosphoribosyl transferase (HGPRT).	Purine nucleotides competitively inhibit hypoxanthine-guanine phosphoribosyl transferase (HGPRT).	Increased PRPP levels in cells lead to the activation of hypoxanthine-guanine phosphoribosyl transferase (HGPRT).
5	Which of the following statements about the formation of uric acid is correct?	Uric acid levels are reduced by a deficiency of hypoxanthine-guanine phosphoribosyl transferase (HGPRT).	Uric acid levels are increased by a deficiency of hypoxanthine-guanine phosphoribosyl transferase (HGPRT).	Uric acid levels are reduced by increasing the activity of the de novo pathway.	Uric acid levels are increased by increasing the activity of the salvage pathway.	Uric acid levels are increased by a deficiency of hypoxanthine-guanine phosphoribosyl transferase (HGPRT).
6	Which of the following statements about the salvage pathway for the synthesis of purine nucleotides is correct?	The salvage pathway for the synthesis of purine nucleotides is not energetically advantageous.	The salvage pathway for the synthesis of purine nucleotides is energetically advantageous.	Salvaged purines used in the salvage pathway are mainly from the diet.	The nucleotides produced from the salvage pathway do not decrease the de novo pathway.	The salvage pathway for the synthesis of purine nucleotides is energetically advantageous.
7	Which of the following statements about uric acid is correct?	Uric acid is readily soluble in the blood.	Overproduction of PRPP leads to the formation of excess uric acid.	Uric acid is the oxidised product of purines and pyrimidines	Allopurinol is a suicide inhibitor of PRPP amidotransferase.	Overproduction of PRPP leads to the formation of excess uric acid.
8	Which of the following statements about one-carbon transfers reactions in purine and pyrimidine nucleotide synthesis are correct? Please select all that apply.	FH4 (tetrahydrofolate) is used for the one-carbon transfer in purine nucleotide synthesis.	N10-formyltetrahydrofolate is used as the one-carbon donor in purine nucleotide synthesis.	Thymidylate synthase uses FH4 (tetrahydrofolate) for the synthesis of dTMP.	N5-methyl FH4 is used for the one-carbon transfer in purine nucleotide synthesis.	N10-formyltetrahydrofolate is used as the one-carbon donor in purine nucleotide synthesis.
9	A nucleoside consists of	Nitrogenous base	Purine or pyrimidine base + sugar	Purine or pyrimidine base + phosphorous	Purine + pyrimidine base + sugar + phosphorous	Purine or pyrimidine base + sugar

10	A nucleotide consists of	A nitrogenous base like choline	Purine + pyrimidine base + sugar + phosphorous	Purine or pyrimidine base + sugar	Purine or pyrimidine base + phosphorous	Purine + pyrimidine base + sugar + phosphorous
11	A purine nucleotide is	AMP	UMP	CMP	TMP	AMP
12	A pyrimidine nucleotide is	GMP	AMP	CMP	IMP	CMP
13	The chemical name of guanine is	2,4-Dioxy-5-methylpyrimidine	2-Amino-6-oxypurine	2-Oxy-4-aminopyrimidine	2, 4-Dioxypyrimidine	2-Amino-6-oxypurine
14	The pyrimidine nucleotide acting as the high energy intermediate is	ATP	UTP	UDPG	CMP	UDPG
15	Uracil and ribose form	Uridine	Cytidine	Guanosine	Adenosine	Uridine
16	DNA does not contain	Thymine	Adenine	Uracil	Deoxyribose	Uracil
17	The sugar moiety present in DNA is	Deoxyribose	Ribose	Lyxose	Ribulose	Deoxyribose
18	DNA rich in G-C pairs have	1 Hydrogen bond	2 Hydrogen bonds	3 Hydrogen bonds	4 Hydrogen bonds	3 Hydrogen bonds
19	The key substance in the synthesis of purine, phosphoribosyl pyrophosphate is formed by	α -D-ribose 5-phosphate	5-phospho β -D-ribosylamine	D-ribose	Deoxyribose	α -D-ribose 5-phosphate
20	In purine biosynthesis ring closure in the molecule formyl glycineamide ribosyl-5- phosphate requires the cofactors:	ADP	NAD	FAD	ATP and Mg ⁺⁺	ATP and Mg ⁺⁺
21	Ring closure of formimidoimidazole carboxamide ribosyl-5-phosphate yields the first purine nucleotide:	AMP	IMP	XMP	GMP	IMP
22	Conversion of inosine monophosphate to xanthine monophosphate is catalysed by	IMP dehydrogenase	Formyl transferase	Xanthine-guanine phosphoribosyl transferase	Adenine phosphoribosyl transferase	IMP dehydrogenase
23	Phosphorylation of adenosine to AMP is catalysed by	Adenosine kinase	Deoxycytidine kinase	Adenylosuccinase	Adenylosuccinate synthetase	Adenosine kinase
24	The major determinant of the overall rate of denovo purine nucleotide biosynthesis is the concentration of	5-phosphoribosyl 1-pyrophosphate	5-phospho β -D-ribosylamine	Glycinamide ribosyl-5-phosphate	Formylglycinamide ribosyl-5-phosphate	5-phosphoribosyl 1-pyrophosphate
25	An enzyme which acts as allosteric regulator and sensitive to both phosphate concentration and the purine nucleotides is	PRPP synthetase	PRPP glutamyl midotransferase	HGPR Tase	Formyl transferase	PRPP synthetase

26	PRPP glutamyl amidotransferase, the first enzyme uniquely committed to purine synthesis is feed back inhibited by	AMP	IMP	XMP	CMP	AMP
27	In the biosynthesis of purine nucleotides the AMP feed back regulates	Adenylosuccinase	Adenylosuccinate synthetase	IMP dehydrogenase	HGPR Tase	Adenylosuccinate synthetase
28	6-Mercapto purine inhibits the conversion of	IMP→ XMP	Ribose 5 phosphate → PRPP	PRPP → 5-phospho → β -D-ribosylamine	Glycinamide ribosyl 5-phosphate → formylglycinamide ribosyl-5-phosphate	IMP→ XMP
29	Purine biosynthesis is inhibited by	Aminopterin	Tetracyclin	Methotrexate	Chloramphenicol	Aminopterin
30	Pyrimidine and purine nucleoside biosynthesis share a common precursor:	PRPP	Glycine	Fumarate	Alanine	PRPP
31	Pyrimidine biosynthesis begins with the formation from glutamine, ATP and CO ₂ , of	Carbamoyl aspartate	Orotate	Carbamoyl phosphate	Dihydroorotate	Carbamoyl phosphate
32	The two nitrogen of the pyrimidine ring are contributed by	Ammonia and glycine	Asparate and carbamoyl phosphate	Glutamine and ammonia	Aspartate and ammonia	Asparate and carbamoyl phosphate
33	The first true pyrimidine ribonucleotide synthesized is	UMP	UDP	TMP	CTP	UMP
34	UDP and UTP are formed by phosphorylation from	AMP	ADP	ATP	GTP	ATP
35	Conversion of deoxyuridine monophosphate to thymidine monophosphate is catalysed by the enzyme:	Ribonucleotide reductase	Thymidylate synthetase	CTP synthetase	Orotidylic acid decarboxylase	Thymidylate synthetase
36	d-UMP is converted to TMP by	Methylation	Decarboxylation	Reduction	Deamination	Methylation
37	UTP is converted to CTP by	Methylation	Isomerisation	Amination	Reduction	Amination
38	A substrate for enzymes of pyrimidine nucleotide biosynthesis is	Allopurinol	Tetracylin	Chloramphenicol	Puromycin	Allopurinol
39	The enzyme aspartate transcarbamoylase of pyrimidine biosynthesis is inhibited by	ATP	ADP	AMP	CTP	CTP
40	In humans end product of purine catabolism is	Uric acid	Urea	Allantoin	Xanthine	Uric acid
41	In humans purine are catabolised to uric acid due to lack of the enzyme:	Urease	Uricase	Xanthine oxidase	Guanase	Uricase

42	In mammals other than higher primates uric acid is converted by	Oxidation to allantoin	Reduction to ammonia	Hydrolysis to ammonia	Hydrolysis to allantoin	Oxidation to allantoin
43	Orotic aciduria type I reflects the deficiency of enzymes:	Orotate phosphoribosyl transferase and orotidylate decarboxylase	Dihydroorotate dehydrogenase	Dihydroorotase	Carbamoyl phosphate synthetase	Orotate phosphoribosyl transferase and orotidylate decarboxylase
44	Orotic aciduria type II reflects the deficiency of the enzyme:	Orotate phosphoribosyl transferase	Orotidylate decarboxylase	Dihydroorotase	Dihydroorotate dehydrogenase	Orotidylate decarboxylase
45	De novo synthesis of purine nucleotide occurs in	Mitochondria	Cytosol	Microsomes	Ribosomes	Cytosol
46	The nitrogen atoms for de novo synthesis of purine nucleotides are provided by	Aspartate and glutamate	Aspartate and glycine	Aspartate, glutamine and glycine	Aspartate, glutamate and glycine	Aspartate, glutamine and glycine
47	For de novo synthesis of purine nucleotides, glycine provides	One nitrogen atom	One nitrogen and one carbon atom	Two carbon atoms	One nitrogen and two carbon atoms	One nitrogen and two carbon atoms
48	For de novo synthesis of purine nucleotides, aspartate provides	Nitrogen 1	Nitrogen 3	Nitrogen 7	Nitrogen 9	Nitrogen 1
49	In the purine nucleus, carbon 6 is contributed by	Glycine	CO ₂	Aspartate	Glutamine	CO ₂
50	5-Phosphoribosyl-1-pyrophosphate is required for the synthesis of	Purine nucleotides	Pyrimidine nucleotides	Both (A) and (B)	None of these	Both (A) and (B)
51	Inosine monophosphate is an intermediate during the de novo synthesis of	AMP and GMP	CMP and UMP	CMP and TMP	All of these	AMP and GMP
52	All of the following enzymes are unique to purine nucleotide synthesis except	PRPP synthetase	PRPP glutamyl amido transferase	Adenylosuccinate synthetase	IMP dehydrogenase	PRPP synthetase
53	The first reaction unique to purine nucleotide synthesis is catalysed by	PRPP synthetase	PRPP glutamyl amido transferase	Phosphoribosyl glycinamide synthetase	Formyl transferase	PRPP glutamyl amido transferase
54	Free purine bases which can be salvaged are	Adenine and guanine	Adenine and hypoxanthine	Guanine and hypoxanthine	Adenine, guanine and hypoxanthine	Adenine, guanine and hypoxanthine
55	The enzyme required for salvage of free purine bases is	Adenine phosphoribosyl transferase	Hypoxanthine guanine phosphoribosyl transferase	Both (A) and (B)	None of these	Both (A) and (B)

56	Salvage of purine bases is regulated by	Adenosine phosphoribosyl transferase	Hypoxanthine guanine phosphoribosyl transferase	Availability of PRPP	None of these	Availability of PRPP
57	The enzyme common to catabolism of all the purines is	Adenosine deaminase	Purine nucleoside phosphorylase	Guanase	None of these	Purine nucleoside phosphorylase
58	Uric acid is the end product of purine as well as protein catabolism in	Man	Fish	Birds	None of these	None of these
59	Daily uric acid excretion in adult men is	2–6 mg	20–40 mg	150–250 mg	40–600 mg	40–600 mg
60	Dietary purines are catabolised in	Liver	Kidneys	Intesitnal mucosa	All of these	Intesitnal mucosa

Degradation of purine and pyrimidine nucleotides

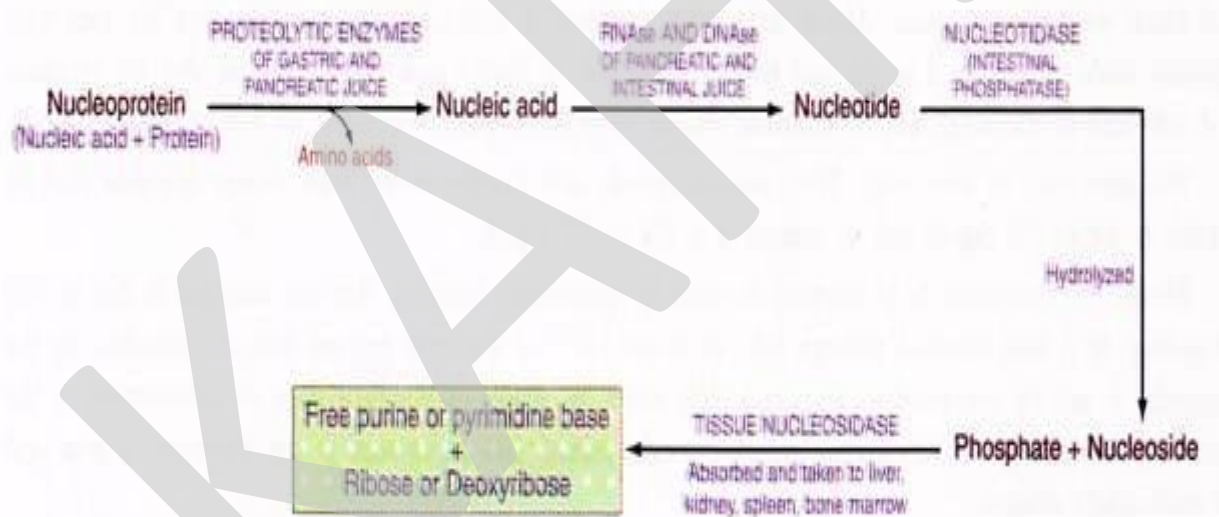
Digestion of nucleic acids, degradation of purine and pyrimidine nucleotides. Inhibitors of nucleotide metabolism. Disorders of purine and pyrimidine metabolism – Lesch-Nyhan syndrome, Gout, SCID, adenosine deaminase deficiency.

Integration of metabolism

Integration of metabolic pathways (carbohydrate, lipid and amino acid metabolic pathways), tissue specific metabolism (brain, muscle, and liver).

Digestion and Absorption of Nucleic Acid:

Nucleic acids are consumed in large quantities owing to their presence in all cells. These nucleic acids are not utilized by the body; instead they are digested, catabolized and excreted. They are taken in the form of nucleoproteins, which are conjugated proteins with amino acids constituting the protein part and nucleic acids constituting the prosthetic part.



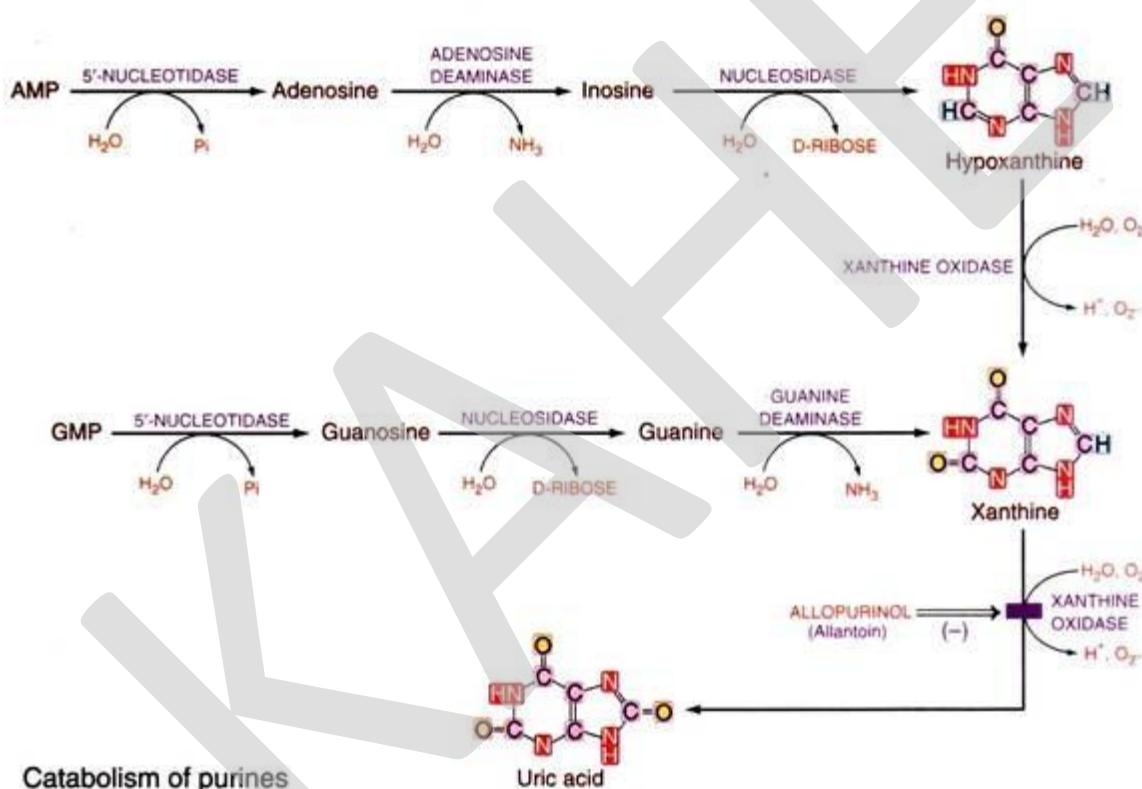
The protein part of nucleoprotein is acted upon by proteolytic enzymes of gastric and intestinal juices. Nucleic acids are acted upon by nucleases (ribonuclease and deoxyribonuclease) of pancreatic and intestinal juices to produce mononucleotides. Nucleotides are hydrolysed to nucleosides by nucleotidases (intestinal phosphatase). Nucleosides are absorbed by intestinal mucosa to portal blood and transported to the liver and supplied through systemic circulation to

other viscera. The enzyme nucleosides liberate the free purine and pyrimidine base and ribose or deoxyribose from the nucleosides.

Catabolism of Nucleosides:

1. Purine Nucleoside – Formation of Uric Acid:

End product of purine metabolism is uric acid (in primates including man and dog). In lower animals, birds and reptiles, uric acid is converted to allantoin by the action of enzyme uricase. Liver, spleen, kidney, intestinal mucosa contain enzymes capable of acting on the purine ring in the free or combined state.



Uric acid metabolism:

Uric acid exists as sodium ureate in plasma. Maximum amount of sodium ureate that can dissolve in the blood plasma is about 7 mg/100 ml. At this point there will be saturation of blood

with sodium ureate. Above this it gets precipitated. Uric acid concentration does not vary with greater intake of uric acid in the diet because on intake of higher concentration in the diet the synthesis of uric acid in the body will be inhibited. Hence there is a balanced amount of uric acid in the body.

Miscible pool of uric acid:

Total amount of uric acid present in the body in the dissolved state in males is 3.4 to 7.0 mg/dl and in females it is 2.4 to 5.7 mg/dl.

Modes of excretion:

It is excreted in urine by glomerular filtration. Amount excreted is 250 to 750 mgs/day. It is also excreted through bile, to about $1/5^{\text{th}}$ of the total amount into the intestine. In the intestine it will be converted to CO_2 and NH_3 either by action of intestinal flora or autoxidation of the uric acid. Estimation of blood uric acid in ureotelic animals has importance in the diagnosis of gout and Von-Gierke's disease.

Conditions varying the blood levels of uric acid:

Gout:

If the concentration of uric acid exceeds 7 mg/100 ml in the blood plasma, the uric acid gets precipitated as sodium ureate crystals that cannot be excreted hence gets deposited in the soft tissues. There is abnormal deposition in joints and tendons. This abnormal deposition of sodium ureate crystals in soft tissue is known as TOPHI. Because of this the tissue gets degraded or degenerated at the bone joints leading to degeneration of neighbouring tissues as well. Degeneration causes inflammation of the joint.

Gouty arthritis:

Generally the metacarpal phalangeal joints and metatarsal phalangeal joints are affected by this gout. Knee joint is also affected.

There are two types of gout:

1. Primary Gout:

Enzyme 'PRPP synthetase' shows altered kinetics leading to overproduction of PRPP and hence overproduction of purines.

2. Secondary gout:

This is due to—

- (i) Excess catabolism of purine as in polycythemia.
- (ii) Decreased excretion of uric acid as in renal failure.

Gout can be controlled by—

1. Uricosuric drugs like salicylates, cinchophen, adrenal cortical hormones, which cause increased excretion of uric acid in urine by decreasing its re-absorption.
2. Allopurinol (Allantoin) a structural analogue to hypoxanthine which competitively inhibits xanthine oxidase and decreases the production of uric acid.

Von-Gierke's disease:

In this disease there is an overproduction of uric acid. The HMP shunt pathway is overactive due to the deficiency of glucose-6-phosphatase thereby producing excessive amounts of ribose-5-phosphate. This leads to the overproduction of PRPP, hence the uric acid.

Methods of estimation:

Phosphotungstic acid method, Fehling's method and Auto analyzer.

Conditions varying the blood level of uric acids:

Whenever there is cell death, the nucleic acids are released and converted to purines and finally uric acid is formed.

The conditions where uric acid level increases in the blood are:

- (a) Excessive tissue destruction and
- (b) Gout.

Excessive tissue destruction:

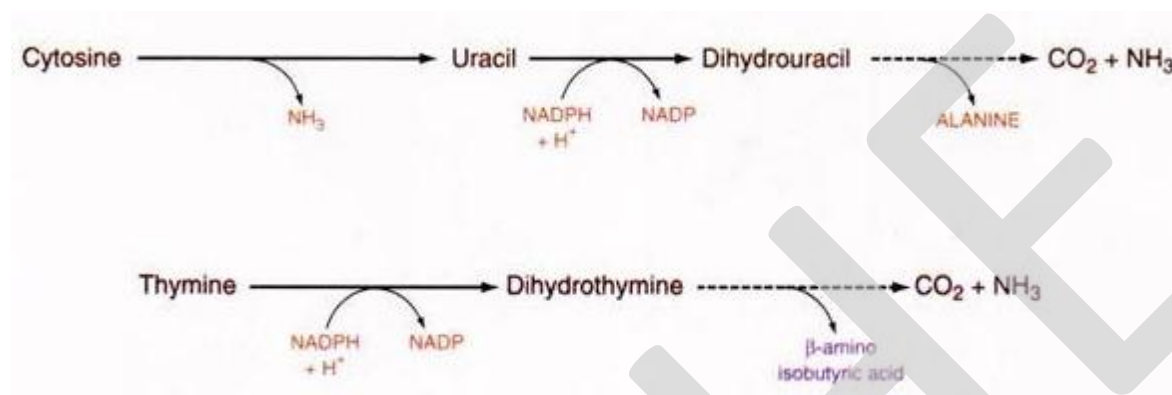
Is seen in—

1. Old age
2. Febrile diseases

3. Hypoxia
4. Trauma
5. Kidney dysfunction or total renal failure
6. High non-vegetarian diets

2. Pyrimidine Nucleoside:

Pyrimidine nucleosides are catabolized in the liver. The products of breakdown of pyrimidine ring are ammonia and CO_2 which are converted into urea for excretion.



Lesch-Nyhan syndrome

Lesch-Nyhan syndrome is a condition that occurs almost exclusively in males. It is characterized by neurological and behavioral abnormalities and the overproduction of uric acid. Uric acid is a waste product of normal chemical processes and is found in blood and urine. Excess uric acid can be released from the blood and build up under the skin and cause gouty arthritis (arthritis caused by an accumulation of uric acid in the joints). Uric acid accumulation can also cause kidney and bladder stones.

The nervous system and behavioral disturbances experienced by people with Lesch-Nyhan syndrome include abnormal involuntary muscle movements, such as tensing of various muscles (dystonia), jerking movements (chorea), and flailing of the limbs (ballismus). People with Lesch-Nyhan syndrome usually cannot walk, require assistance sitting, and generally use a wheelchair. Self-injury (including biting and head banging) is the most common and distinctive behavioral problem in individuals with Lesch-Nyhan syndrome. Frequency The prevalence of Lesch-Nyhan

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syndrome is approximately 1 in 380,000 individuals. This condition occurs with a similar frequency in all populations. Genetic Changes Mutations in the HPRT1 gene cause Lesch-Nyhan syndrome. The HPRT1 gene provides instructions for making an enzyme called hypoxanthine phosphoribosyltransferase 1.

This enzyme is responsible for recycling purines, a type of building block of DNA and its chemical cousin RNA. Recycling purines ensures that cells have a plentiful supply of building blocks for the production of DNA and RNA. HPRT1 gene mutations that cause Lesch-Nyhan syndrome result in a severe shortage (deficiency) or complete absence of hypoxanthine phosphoribosyltransferase 1. When this enzyme is lacking, purines are broken down but not recycled, producing abnormally high levels of uric acid. For unknown reasons, a deficiency of hypoxanthine phosphoribosyltransferase 1 is associated with low levels of a chemical messenger in the brain called dopamine. Dopamine transmits messages that help the brain control physical movement and emotional behavior, and its shortage may play a role in the movement problems and other features of this disorder. However, it is unclear how a shortage of hypoxanthine phosphoribosyltransferase 1 causes the neurological and behavioral problems characteristic of Lesch-Nyhan syndrome. Some people with HPRT1 gene mutations produce some functional enzyme. These individuals are said to have Lesch-Nyhan variant.

The signs and symptoms of Lesch-Nyhan variant are often milder than those of Lesch-Nyhan syndrome and do not include self-injury. **Inheritance Pattern** This condition is inherited in an X-linked recessive pattern. The gene associated with this condition is located on the X chromosome, which is one of the two sex chromosomes. In males (who have only one X chromosome), one altered copy of the gene in each cell is sufficient to cause the condition. In females (who have two X chromosomes), a mutation would have to occur in both copies of the gene to cause the disorder. Because it is unlikely that females will have two altered copies of this gene, males are affected by X-linked recessive disorders much more frequently than females. A characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons.

Severe combined immunodeficiency

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Severe combined immunodeficiency, SCID, also known as alymphocytosis, Glanzmann–Riniker syndrome, severe mixed immunodeficiency syndrome, and thymic alymphoplasia, is a rare genetic disorder characterized by the disturbed development of functional T cells and B cells caused by numerous genetic mutations that result in heterogeneous clinical presentations. SCID involves defective antibody response due to either direct involvement with B lymphocytes or through improper B lymphocyte activation due to non-functional T-helper cells. Consequently, both "arms" (B cells and T cells) of the adaptive immune system are impaired due to a defect in one of several possible genes. SCID is the most severe form of primary immunodeficiencies, and there are now at least nine different known genes in which mutations lead to a form of SCID. It is also known as the bubble boy disease and bubble baby disease because its victims are extremely vulnerable to infectious diseases and some of them, such as David Vetter, have become famous for living in a sterile environment. SCID is the result of an immune system so highly compromised that it is considered almost absent.

SCID patients are usually affected by severe bacterial, viral, or fungal infections early in life and often present with interstitial lung disease, chronic diarrhoea, and failure to thrive. Ear infections, recurrent *Pneumocystis jirovecii* (previously *carinii*) pneumonia, and profuse oral candidiasis commonly occur. These babies, if untreated, usually die within one year due to severe, recurrent infections unless they have undergone successful hematopoietic stem cell transplantation.

Adenosine deaminase deficiency (ADA) is an inherited condition that affects the immune system and typically leads to severe combined immunodeficiency (SCID). People with SCID have a reduced or absent immune response which leaves them vulnerable to frequent bacterial, viral, and fungal infections. Most people affected by ADA develop symptoms of the condition before 6 months of age. However, approximately 10-15% of affected people have a "delayed" onset of symptoms; diagnosis of these cases, which are often less severe, typically takes place later in childhood (often between age 1 and 10) or even into adulthood. Signs and symptoms of ADA include pneumonia, chronic diarrhea, widespread skin rashes, slowed growth

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and/or developmental delay. ADA is caused by changes (mutations) in the *ADA* gene and is inherited in an autosomal recessive manner. The most effective treatment is transplantation of blood-forming stem cells from the bone marrow of a healthy person.

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METABOLISM OF AMINOACIDS AND NUCLEIC ACIDS (17BCU302)
MULTIPLE CHOICE QUESTIONS

UNIT V

S.No	Questions	Option A	Option B	Option C	Option D	Answer
1	Enzymes involved in the digestion of nucleic acid	Proteases	Peptidases	Nucleases	Amylases	Nucleases
2	Ribonucleases cleave	Ribosomes	RNA	DNA	Protein	RNA
3	Deoxyribonuclease cleave	Ribosomes	RNA	DNA	Protein	DNA
4	End product of purine metabolism is	urea	uric acid	sulphuric acid	glucose	uric acid
5	Accumulation of uric acid is called	gout	stout	out	ouch	gout
6	hypoxanthine:guanine phosphoribosyltransferase	uric acid accumulation	gout	gout and uric acid accumulation	urea	gout and uric acid accumulation
7	Adenosine deaminase deficiency leads to	SCID	Hypersensitivity I	Hypersensitivity II	Hypersensitivity III	SCID
8	SCID is	Autosomal dominant	Autosomal recessive	Allosomal dominant	Allosomal recessive	Autosomal recessive
9	Adenosine deaminase deficiency leads to	accumulation of deoxy adenosine	accumulation of urea	accumulation of co2	accumulation of ammo	accumulation of deoxy adenosine
10	T cell development occur in	thymus	bone marrow	blood	plasma	thymus
11	Immature T cells are found in	cortex of thymus	medulla of thymus	cortex of kidney	medulla of kidney	cortex of thymus
12	Gout is a metabolic disorder of catabolism of	Pyrimidine	Purine	Alanine	Phenylalanine	Purine
13	Gout is characterized by increased plasma levels	Urea	Uric acid	Creatine	Creatinine	Uric acid
14	Lesch-Nyhan syndrome, the sex linked recessive disorder is due to the lack of the enzyme:	Hypoxanthine-guanine phosphoribosyl transferse	Xanthine oxidase	Adenine phosphoribosyl transferase	Adenosine deaminase	Hypoxanthine-guanine phosphoribosyl

15	Lesch-Nyhan syndrome, the sex linked, recessive absence of HGPRTase, may lead to	Compulsive self destructive behaviour with elevated levels of urate in serum	Hypouricemia due to liver damage	Failure to thrive and megaloblastic anemia	Protein intolerance and hepatic encephalopathy	Compulsive self destructive behaviour with elevated levels of
16	Which statement best describes Xanthine ?	It is a direct precursor of Guanine	It covalently binds to Allopurinol	It is oxidized to form Uric acid	It is oxidized to form Hypoxanthine	It is oxidized to form Uric acid
17	Feedback inhibition of pyrimidine nucleotide synthesis can occur by which of the following ?	Increased activity of Carbamoyl phosphate synthetase	Increased activity of Aspartate transcarbamoylase	CTP allosteric effects	UMP competitive inhibition	CTP allosteric effects
18	Which base derivative can serve as a precursor for the synthesis of two of the other pyrimidine base derivatives ?	Cytidine triphosphate	Uridine mono phosphate	Adenosine mono phosphate	deoxy thymidine mono phosphate	Uridine mono phosphate
19	Purine nucleotide biosynthesis can be inhibited by which of the followings ?	Guanosine triphosphate	Uridine mono phosphate	Adenosine mono phosphate	Adenosine tri phosphate	Adenosine mono phosphate
20	Which of the following contributes nitrogen atoms to both purine and pyrimidine rings ?	Aspartate	Carbamoyl phosphate	Carbon dioxide	Glutamate	Aspartate
21	Which out of the following conditions is associated with hypouricemia ?	Lesch Nyhan syndrome	Adenosine deaminase deficiency	Over activity of PRPP synthetase	Over activity of amido transferase	Adenosine deaminase
22	Which of the following is a required substrate for purine biosynthesis ?	5- methyl thymidine	Ara –C	Ribose phosphate	PRPP	PRPP
23	Which of the following is an analogue of hypoxanthine ?	Ara C	Allopurinol	Ribose phosphate	PRPP	Allopurinol
24	A Pentose with a 5' phosphate group, a 2' OH group and 1' pyrimidine group describes which of the following structures ?	Cytosine	Thymidine	Thymidylate	Cytidylate	Cytidylate
25	The conversion of Inosine mono phosphate	To Adenosine mono phosphate (AMP) is inhibited by Guanosine mono phosphate(GMP)	To AMP requires uridine mono phosphate (UMP)	To GMP requires GMP kinase	To GMP requires Glutamine	To GMP requires Glutamine
26	Which disease would be most similar to AIDS in its pathology?	DiGeorge Syndrome	Agammaglobulinemia	ADA deficiency	SCID	SCID
27	Tophus is the pathognomonic lesion of which of the following condition	Multiple myeloma	Cystinosis	Gout	Eale's disease	Gout

28	All of the following conditions are observed in Gout, except	Uric acid nephrolithiasis	Deficiency of enzyme xanthine oxidase	Increase in serum urate concentration	Renal disease involving interstitial	Deficiency of enzyme xanthine
29	Which of the following substrates derived from adipose tissues contributes to net gluconeogenesis in mammalian liver?	Alanine	Glutamate	Glycerol	Pyruvate	Glycerol
30	Which of the following statements is incorrect?	Aerobically, oxidative decarboxylation of pyruvate forms acetate that enters the citric acid cycle.	In anaerobic muscle, pyruvate is converted to lactate.	Reduction of pyruvate to lactate generates a coenzyme essential for Glycolysis.	Under anaerobic conditions pyruvate does not form because Glycolysis does not occur.	Under anaerobic conditions pyruvate does not form because Glycolysis does
31	The steps of Glycolysis between glyceraldehyde 3-phosphate and 3-phosphoglycerate involve all of the following except:	ATP synthesis.	Catalysis by phosphoglycerate kinase.	Oxidation of NADH to NAD+.	The formation of 1, 3-bisphosphoglycerate.	Oxidation of NADH to NAD+.
32	The oxidation of 3 mol of glucose by the pentose phosphate pathway may result in the production of:	2 mol of pentose, 4 mol of NADPH, and 8mol of CO ₂ .	3 mol of pentose, 4 mol of NADPH, and 3mol of CO ₂ .	3 mol of pentose, 6 mol of NADPH, and 3mol of CO ₂ .	4 mol of pentose, 3 mol of NADPH, and 3mol of CO ₂ .	3 mol of pentose, 6 mol of NADPH, and 3mol of CO ₂ .
33	How many ATP molecules can be derived from each molecule of acetyl CoA that enters the	6	12	18	38	12
34	All of the following vitamins except one participate in the TCA cycle	Pantothenic acid	Lipoic acid	Folic acid	Riboflavin	Folic acid
35	Why Phosphofructokinase rather than hexokinase is the pacemaker of Glycolysis?	Glucose 6-phosphate is not solely a glycolytic intermediate	Hexokinase has low km for glucose	Hexokinase is inhibited by feed back inhibition	None of the above	Glucose 6-phosphate is not solely a glycolytic
36	Which are correct about pyruvate dehydrogenase complex except one	a) The formation of acetyl CoA from pyruvate is an irreversible step	b) Pyruvate dehydrogenase is switched off when Acetyl co A is in excess	c)Phosphorylation switches off the activity of the complex.	d) Pyruvate as well as ADP (a signal of low energy charge) inhibits the complex.	d) Pyruvate as well as ADP (a signal of low energy charge) inhibits the
37	Cellular isozymes of pyruvate kinase are allosterically inhibited by:	High concentrations of AMP.	High concentrations of ATP.	High concentrations ofFr1,6 bisphosphate.	Low concentrations of acetyl-CoA.	High concentrations of
38	Which of the following is not an intermediate of the citric acid cycle?	Acetoacetate	Citrate	Oxalosuccinate	Succinyl-CoA	Acetoacetate

39	In an anaerobic system that is metabolizing glucose as a substrate, which of the following compounds would you expect to increase in concentration following the addition of fluoride?	2-phosphoglycerate	Glucose	Phosphoenolpyruvate	Pyruvate	2-phosphoglycerate
40	Which of the following is a coenzyme in the reaction catalyzed by glyceraldehyde 3-phosphate dehydrogenase?	NAD+	ATP	Cu ²⁺	Heme	NAD+
41	An enzyme used in both glycolysis and gluconeogenesis is:	3-phosphoglycerate kinase.	Glucose 6-phosphatase.	Hexokinase.	Phosphofructokinase-1.	3-phosphoglycerate
42	Which of the following statements about the pentose phosphate pathway is incorrect?	It generates 36 mol of ATP per mole of glucose consumed.	It generates 6 moles of CO ₂ for each mole of glucose consumed	It is a reductive pathway; it consumes NADH.	It provides precursors for the synthesis of nucleotides	It is a reductive pathway; it consumes NADH.
43	Which of the following enzymes catalyzes a reaction that involves a decarboxylation	Pyruvate dehydrogenase	Isocitrate dehydrogenase	α -keto glutarate dehydrogenase	All of the above	All of the above
44	Anaplerotic reactions are those that result in replenishing intermediates in the TCA cycle. Which of the following enzymes catalyzes an Anaplerotic reaction?	Malate dehydrogenase	Pyruvate carboxylase	Pyruvate kinase	Citrate synthase	Pyruvate carboxylase
45	Which statement BEST describes the fate of Propionyl-CoA in mammalian systems?	Propionyl-CoA is metabolized via are action sequence that involves vitamin B12 and biotin.	Propionyl-CoA is converted to acetyl CoA.	Propionyl-CoA and acetyl CoA condense to form a 5 carbon precursor of a TCA cycle intermediate.	Propionyl-CoA is oxidized to Malonate and CoA	Propionyl-CoA is metabolized via are action sequence that involves vitamin
46	It is very important to feed the baby very soon after birth, because during the first few hours after birth the enzyme Phosphoenolpyruvate carboxykinase is present in very low amounts, and this fact compromises:	Gluconeogenesis	Glucose phosphorylation	Glycogenesis	Glycogenolysis	Gluconeogenesis
47	The citric acid cycle is inhibited by which of the following?	Fluoroacetate	Aerobic conditions	Malic acid	Fluorouracil	Fluoroacetate
48	Which of the following enzymes is associated with Glycogen synthesis?	Amylo- (1, 4->1,6) – transglycosylase	Phosphorylase	Amylo-1,6-glucosidase	Glucose-6-phosphatase	Amylo- (1, 4->1,6) –

49	A medical student developed hemolytic anemia after taking the oxidizing Antimalarial drug primaquine. This severe reaction is most likely	Glucose-6- phosphate dehydrogenase deficiency	Concomitant Scurvy	Diabetes	Glycogen phosphorylase deficiency	Glucose-6- phosphate dehydrogenase
50	Which of the following explains why individuals with hyperlipidemia should minimize their intake of sucrose and high fructose syrup?	Fructose metabolism is faster than glucose	After initial modification fructose is cleaved by a specific Enolase	Fructose is ultimately converted to galactose	Fructose can be phosphorylated by hexokinase in adipose cells	Fructose metabolism is faster than glucose
51	The major glycolytic product produced under normal circumstances by erythrocytes required for unloading of oxygen to the peripheral tissues	2,3bisphosphoglycerate	1,3bisphosphoglycerate	Lactate	Pyruvate	2,3bisphosphoglyc erate
52	Poorly perfused areas exposed to chronic hypoxia have decreased metabolic energy for tissue maintenance and repair an important reason for this is	Increased hexokinase activity owing to increased oxidative phosphorylation	Decreased ATP production and increased glucose utilization due to an aerobic mode of lycolysis	Increased glucose utilization by HMP pathway on changing from anaerobic to aerobic glycolysis	Decreased respiratory quotient on changing from carbohydrates to fats as the major fuel	Decreased ATP production and increased glucose utilization due to an aerobic mode of lycolysis
53	Asians and Native Americans may flush and feel ill after drinking a small amount of ethanol in alcoholic beverages. This reaction is due to genetic variation in an enzyme that metabolizes the liver metabolite of alcohol, which is	Methanol	Acetone	Acetaldehyde	Glycerol	Acetaldehyde
54	Which one of the following enzymes catalyzes the phosphorylation of the substrate with the use of inorganic phosphate-?	Hexokinase	Phospho fructokinase	Glyceraldehyde-3- phosphate dehydrogenase	Phospho glycerate kinase	Glyceraldehyde-3- phosphate dehydrogenase
55	Which of the following statements about the regulation of a metabolic pathway is correct?	Most metabolic pathways are not regulated.	Regulation of metabolic pathways always involves changing the amount of enzymes.	Metabolic regulation always depends on control by hormones.	Most metabolic pathways are regulated.	Most metabolic pathways are regulated.

56	Which of the following correctly exhibits an example of metabolic control?	In cases where the direction of a metabolic pathway has to be reversed the pathway is controlled at an irreversible step.	Regulatory changes in a pathway always occur slowly over periods of several hours or more.	Enzymes which are controlled are always those which catalyse the first reaction of the pathway.	Most enzyme control mechanisms are irreversible.	In cases where the direction of a metabolic pathway has to be reversed the pathway is controlled at an
57	Which type of metabolic fuel is utilised for generating glucose under conditions of severe	Glycogen.	Fats.	Starch.	Amino acids.	Amino acids.
58	Which is true of brain metabolism in starvation?	The brain can only use glucose as fuel.	Up to a quarter of the energy requirement of the brain can come from fatty acids.	Up to half the energy requirement of the brain can be met by ketone bodies.	The brain can use glucogenic amino acids for energy.	The brain can use glucogenic amino acids for energy.
59	Which of the following statements about the control of enzyme activity by phosphorylation is correct?	Enzyme control by phosphorylation is irreversible.	Phosphorylation of enzymes is carried out by phosphoprotein phosphatases.	Phosphorylation of enzymes only occurs at specific tyrosine residues.	Phosphorylation of an enzyme results in a conformational change.	Phosphorylation of enzymes only occurs at specific tyrosine residues.
60	Which of the following statements about the control of muscle glycogen phosphorylase is correct?	Muscle glycogen phosphorylase is allosterically activated by cAMP.	Muscle glycogen phosphorylase is allosterically activated by ATP.	Muscle glycogen phosphorylase normally exists in the a form.	Muscle glycogen phosphorylase is activated by phosphorylation by an active phosphorylase	Muscle glycogen phosphorylase is activated by phosphorylation by an active phosphorylase