1

Carbohydrate Chemistry and Metabolism of Carbohydrates

DEFINITION

Carbohydrates are **aldehyde or ketone derivative of polyhydroxy alcohols**[Q] or substances which yield such compound on hydrolysis. Glycerol having 3 hydroxyl group is the parent alcohol from which carbohydrates are derived.

Classification

Carbohydrates are **classified on the basis of number of individual monosaccharide units**[Q] derived from complete hydrolysis of the carbohydrate compound.

Accordingly they are classified into following **4 major groups:**[Q]

1. ***Monosaccharides*** $[C_n(H_2O)_n]$: They are carbohydrates which cannot be further hydrolyzed into simpler carbohydrates. Monosaccharides are subdivided further depending on: (i) No. of carbon atoms, (ii) Aldehyde/ketone group present (Table 1.1).

Table 1.1: Monosaccharides

General formula	*Aldosugar*	*Ketosugar*
Trioses	Glyceraldehyde	Dihydroxyacetone
Tetroses	Erythrose	Erythrulose
Pentoses	Ribose	Ribulose
Hexoses	Glucose	Fructose
Heptoses	Glucoheptose	Sedoheptulose
Nanoses	Sialic acid (NANA)	

2. ***Disaccharides*** **$[C_n(H_2O)_{n-1}]$:** Yield two molecules of same/different monosaccharide on hydrolysis (Table 1.2).
3. ***Oligosaccharides*****:** Yield **3–10* molecules of monosaccharides**[Q] units on hydrolysis.

   *(According to Harper's 28th ed) (Vasudevan 6th ed. Oligosaccharides have monosaccharide units between 2 and 9). Let's go with what Harper says.

4. ***Polysaccharides*****:** Yield **more than 10 molecules of monosaccharides**[Q] on hydrolysis. Polysaccharide may be classified as **homopolysaccharide** or **heteropolysaccharide** depending on whether the same or different individual monosaccharides are produced on complete hydrolysis of the compound.

Table 1.2: List of disaccharides[Q]

Disaccharides	*Reducing or non-reducing*[Q]	*Individual monosaccharide units*[Q]	*Bonds*[Q]
Sucrose	NR	Glucose + Fructose	α-D-glucopyranosyl β-D-fructofuranoside
Trehalose	NR	Glucose + Glucose	α-1,1-glycosidic bond
Maltose	R	Glucose + Glucose	α-1,4-glycosidic
Isomaltose	R	Glucose + Glucose	α-1,6-glycosidic
Lactose	R	Glucose + Galactose	β-1,4-glycosidic bond (glu is β, gal is α)[Q*]
Lactulose	R	Fructose + Galactose	β-1,4-glycosidic bond (fructose is β, gal is α)[Q*]

*Many books and guides have given this wrong. Kindly refer Harper 30th ed, Table 15.4, p-157

a. *Homopolysaccharides (homoglycans):* Polymers of the same monosaccharides unit, e.g. starch, glycogen, inulin, cellulose, etc. (Table 1.3).

Table 1.3: List of homopolysaccharides

Homopolysaccharides	*Units of monosaccharide*	*Bond*
Starch	Glucose	α-1,4 and α-1,6
Glycogen	Glucose	α-1,4 and α-1,6
Cellulose	Glucose	β-1,4
Inulin	Fructose	β-1,2
Dextran	Glucose	α-1,6 α-1,4 α-1,3
Chitin	N-acetyl D-glucosamine[Q]	β-1,4

b. *Heteropolysaccharides:* Mucopolysaccharides are important examples of HPS. They are also known as glycosaminoglycans (GAG). Examples of heteropolysaccharides are:

1. Heparin*
2. Heparan sulfate*
3. Chondroitin sulfate
4. Dermatan sulfate*
5. Keratin sulfate I** and II**
6. Hyaluronic acid#

*Presence of iduronic acid
**No uronic acid
#No sulfation and non-covalent bond when attached to proteoglycan structure

Role of various glycosaminoglycans

1. Hyaluronic acid: Cell migration
2. Keratin sulfate I and II and dermatan sulfate: Corneal transparency.
3. Dermatan sulfate: Scleral structure

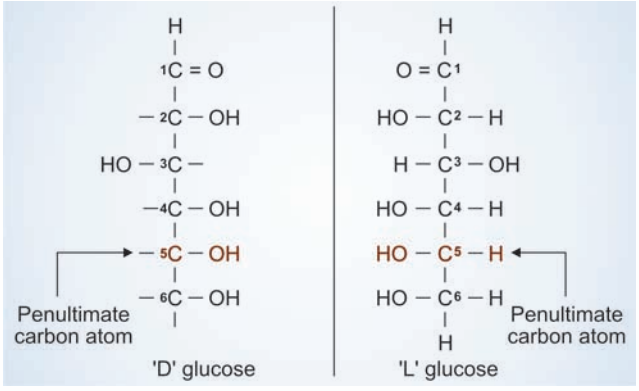
4. Heparin: Anticoagulant
5. Heparan sulfate: Cell adhesion and cell to cell interaction.

Isomerism

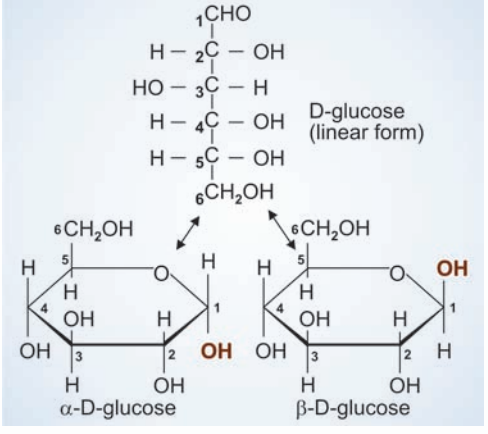
Compounds which **have same structural formula but differ in their spatial configuration are known as stereoisomers**.Q Number of possible isomers depends on number of asymmetric carbon atoms (n). If a compound has 'n' number of asymmetric C-atom, it will have total n^2 stereoisomers.

Types of Isomers

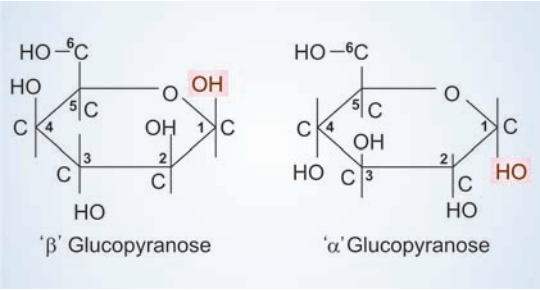
1. ***D and L isomers:***Q In this type of isomers the difference in the structure is in the orientation of H and OH groups on Penultimate carbon/reference carbon atoms. If –OH group on this carbon atom is towards right, carbohydrate is called D-isomer, when –OH group is on left, it is a member of L-series (*see* the diagram).



2. ***Aldo-keto isomers:***Q If the reactive group of the carbohydrate is aldehyde, it is an aldose and if the reactive group of the carbohydrate is ketone, it is a ketose.
3. ***Pyranose and furanose ring structure:***Q **Pyranose is heterocyclic, hexacyclic ring structure and furanose ring is heterocyclic pentacyclic ring structure**.Q In physiological state, 99% of the glucose is in pyranose form, and 99% of the fructose is in furanose form (*see* the diagram).

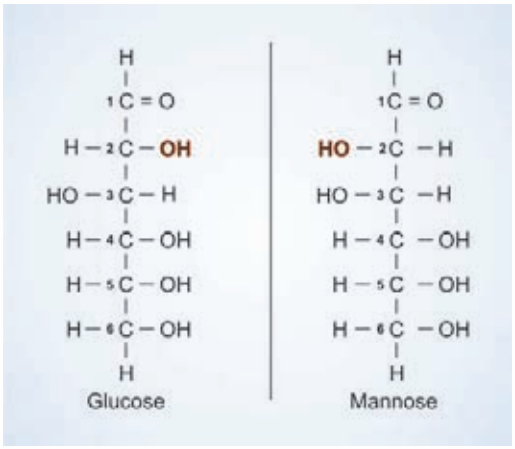


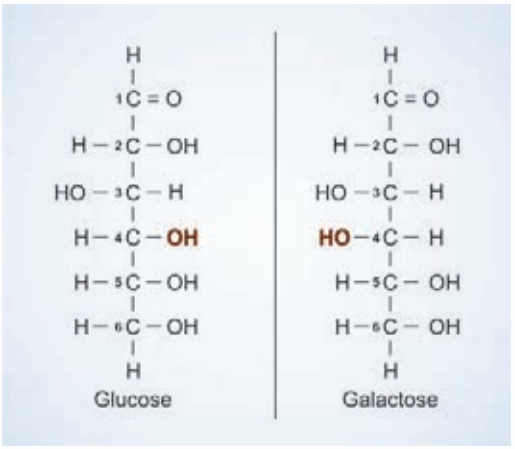
4. ***Alpha and beta anomers:*** Q In the ring structure form if –OH group on anomeric carbon atom is **above the plane of ring, the anomeric form is β** and if –OH group on anomeric carbon atom is **below the plane of ring, the anomeric form is α**. Anomeric carbon atom is the carbon at which hemiacetal or hemiketal group is present (*see* the diagram).



Mutarotation: Q Interconversion of α and β form of D-glucose in aqueous medium is known as mutarotation. Fresh solution of glucose has optical activity of + 112° and after mutarotation the solution shows optical activity of + 52.5° (it is due to conversion of α-glucose to β-glucose).

5. ***Epimers:*** Q Isomers differing as a result of variation in configuration of the –OH and –H on only one of the carbon atoms (2, 3 or 4) of glucose are known as epimers. Glucose and mannose are C_2 epimers and glucose and galactose are C_4 epimers (*see* the diagram).





Aldonic acid: Q Oxidation of carbonyl (aldehyde) carbon of the glucose produces carboxyl group at that position. This new structure is now known as gluconic acid.

Uronic acid: Q Oxidation of the last carbon atom of the chain (C_6 in case of glucose and other hexoses) produces uronic acid, e.g. glucuronic acid, etc.

Invert sugar: Sucrose is known as invert sugar. Sucrose has got specific rotation of +66.5°. On hydrolysis sucrose solution yields equimolar mixture of D-glucose (specific rotation of +52.5°) and D-fructose (specific rotation of –92°), this results in net levorotation, that is why sucrose is known as invert sugar.

In other words, fructose is strongly levorotatory and changes (inverts) the weaker dextrorotatory action of sucrose.

GLYCOLYSIS

Also known as **Embden-Meyerhof Pathway (EMP).**

Definition

Glycolysis is a process by which glucose molecules are metabolised through a series of enzymatic reactions into 2 molecules of pyruvate (Diagram 1.1).

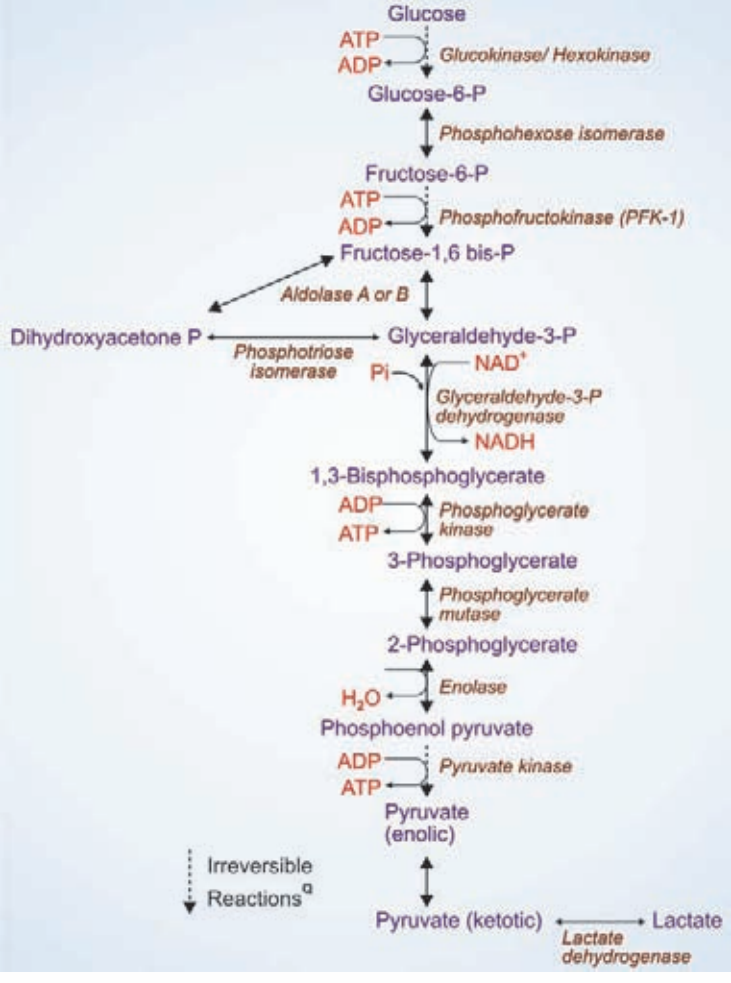


Diagram 1.1: Steps of glycolysis

Site of glycolysis: Cytosol

Purpose

1. Aerobic glycolysis produces **total 9 and net 7 moles of ATP**[Q] per mole of glucose.
2. Anerobic glycolysis produces **total 4 and net 2 moles of ATP**[Q] per mole of glucose.

Irreversible Reactions of Glycolysis

Following 3 reactions are irreversible in the glycolysis:

1. Glucose $\xrightarrow{\text{HK/GK}}$ Glucose-6-phosphate
2. Fructose-6-phosphate $\xrightarrow{\text{Phosphofructokinase-1}}$ Fructose-1,6-bisphosphate
3. Phosphoenol pyruvate $\xrightarrow{\text{Pyruvate kinase}}$ Pyruvate

Important aspects of enzymes of glycolysis are:

Table 1.4: Difference between hexokinase and glucokinase[Q]

	Hexokinase	*Glucokinase*
Site	All tissues except liver	Only in liver, beta cell of pancreas
Substrate	Glucose, fructose or galactose	Only glucose
Induction	Non-inducible	Inducible
K_m for glucose	Low (0.05 mmol/L or 0.9 mg/dl)	High (10 mmol/L or 180 mg/dl)
Inhibition by glucose-6-phosphate	Inhibited	Not inhibited
Effect of feeding and insulin	No change in activity	Increased activity as well as rate of synthesis

1. **Difference between hexokinase and glucokinase**[Q] (Table 1.4).
2. **Phosphofructokinase:** Major regulatory enzyme of glycolysis. It is under both allosteric and hormonal control.

Allosteric Control of PFK-1[Q]

- Positive allosteric modifier of PFK: AMP, fructose-2,6-bisphosphate.
- Negative allosteric modifier of PFK: ATP, citrate, H^+ (Diagram 1.2).

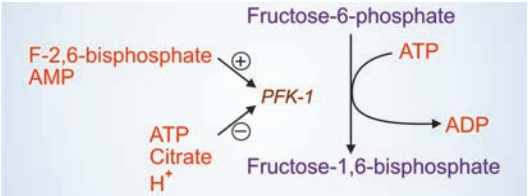


Diagram 1.2: Positive and negative allosteric modifier of phosphofructokinase enzyme

Hormonal Control[Q]

Fructose-2,6-bisphosphate plays an important role for hormonal control of the hepatic glycolysis. Fructose-2,6-bisphosphate is synthesized as a side product of the glycolysis.

A **bifunctional enzyme** named PFK-2/fructose-2,6-bisphosphatase is responsible for regulating the level of fructose-2,6-bisphosphate in the liver (Diagram 1.3).

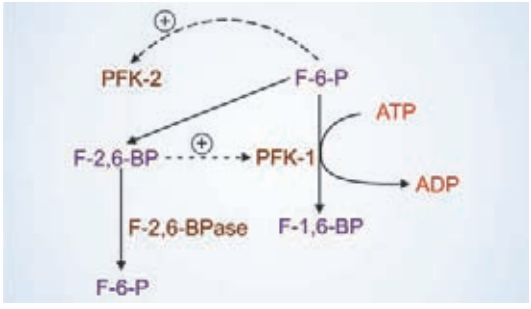


Diagram 1.3: Synthesis and degradation of F-2,6-BP

cAMP activates phosphatase and inactivates kinase moiety of this bifunctional enzyme.

Inhibitors of Glycolysis[Q]

1. *Fluoride*: Inhibiting enolase enzyme via forming ionic complex with Mg^{++} and Pi. This is an example of irreversible inhibition.[Q]
2. *Sulfhydryl reagents* (Mercury containing compounds/alkylating compounds, e.g. iodoacetate).
3. *Arsenate*: **Not a true inhibitor of glycolysis**,[Q] it acts via competition with inorganic Pi needed at glyceraldehyde-3-phosphate dehydrogenase reaction. In the presence of arsenic, glycolysis continues but the net ATP production does not occur. Arsenic prevents formation of 1,3-bisphosphoglycerate and thus the ATP production in subsequent step of *BPG kinase* is also bypassed in the presence of arsenic (Diagram 1.4).

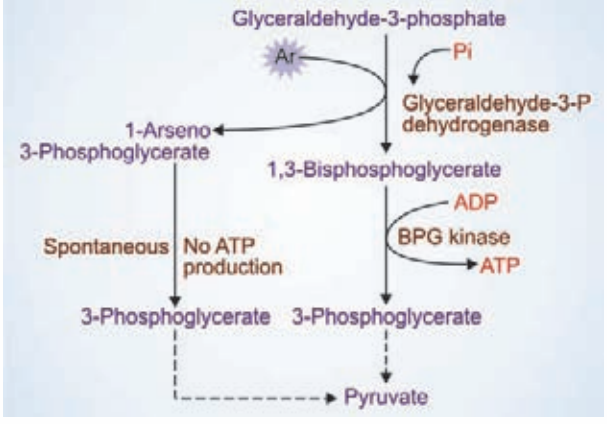


Diagram 1.4: To show how arsenic affects ATP production in glycolysis (it bypasses BPG kinase step)

Energetics of Glycolysis (Table 1.5)[Q]

Glucose-6-phosphate is an allosteric inhibitor of hexokinases. Glucokinase is not regulated by glucose-6-phosphate, rather glucokinase is regulated by *fructose-6-phosphate* by a special mechanism which is explained as follows:

Table 1.5: Energetics of glycolysis[Q]

Pathway	*Reaction catalyzed by*	*Method of ATP formation*	*No. of ATP per mol of glucose*[Q]
Glycolysis	Glyceraldehyde 3-phosphate dehydrogenase	Respiratory chain oxidation of 2 NADH	5 or 3*
	Phosphoglycerate kinase	Substrate level phosphorylation	2
	Pyruvate kinase	Substrate level phosphorylation	2
Total ATP from one glucose during glycolysis in cytosol (aerobic)			**9 or 7***
	Consumption of 1 ATP each for reactions of HK/GK and phosphofructokinase		–2
Net ATP from one glucose during glycolysis in cytosol (aerobic)			**Net 7 or 5***

(*if **malate aspartate shuttle** is used for NADH transfer across mitochondrial membrane, 1 NADH produces **2.5 ATP**; and if **glycerophosphate shuttle** is used for NADH transfer across the mitochondrial membrane, 1 NADH produces **1.5 ATP**)[Q]

Note: Glucokinase is also called hexokinase D or type IV.

Mechanism by which Glucokinase Activity is Influenced by Fructose-6-phosphate[Q]

Fructose-6-phosphate affects compartmentalization of glucokinase enzyme and has got inhibitory effect on its activity.

Glucokinase is present in the nucleus in the bound state to the glucokinase regulatory protein (GKRP). Whenever glucose enters in the cell, glucokinase is released from this bound protein and is freed into the cytosol. In the presence of fructose-6-phosphate in the cell, glucokinase is translocated back to the nucleus where it binds again with the glucokinase regulatory protein (GKRP), which makes enzyme inactive (Diagram 1.5).

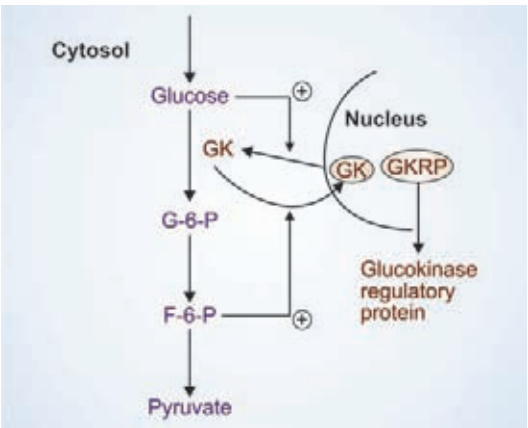
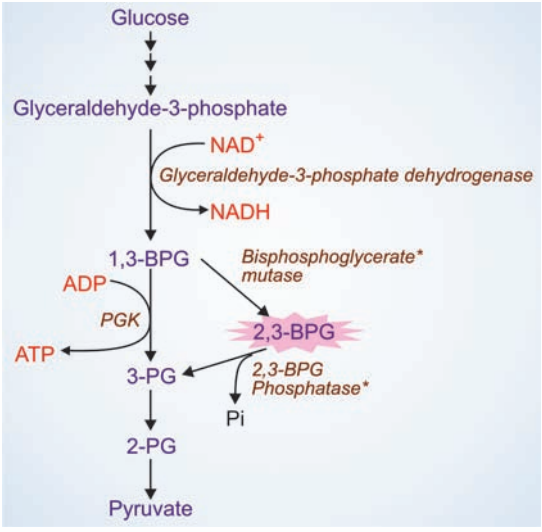


Diagram 1.5: To show how glucokinase is mobilised in and out of the nucleus

Rapoport-Luebering Cycle[Q]/BPG Shunt (Bisphosphoglycerate Shunt)

This pathway occurs **predominantly in the RBCs**[Q]. In this cycle shunting of the glycolytic intermediate 1,3-bisphosphoglycerate occurs for the production of 2,3-BPG (Diagram 1.6).

- In RBC 15–25% of glucose converted to lactate goes by way of BPG shunt.
- BPG shunt bypasses the PGK (phosphoglycerate kinase) step, therefore no net ATP production occurs when glucose is converted to lactate via BPG shunt.



*BPG mutase and BPG phosphatase are bifunctional enzyme

Diagram 1.6: Rapoport-Luebering cycle

2,3-Bisphosphate Glycerate (2,3-BPG)

2,3-BPG is an important allosteric modifier of oxygenation of hemoglobin.

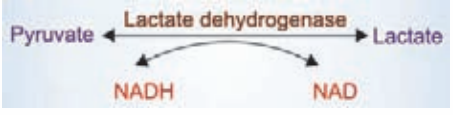
- Whenever Hb is in the deoxygenated form, **one molecule**[Q] **of 2,3-BPG is bound per Hb** tetramer in the central cavity, this helps **stabilization of deoxy form of haemoglobin.**[Q] It thus helps in unloading of O_2. In hypoxic conditions the concentration of 2,3-BPG in the RBC increases which helps unload the O_2 at the peripheral tissue.
- 2,3-BPG, which is present in high concentration in tissues, combines with Hb and causes a **decrease in the affinity for oxygen** thus helping oxyhemoglobin to unload oxygen and **displacing O_2 dissociation curve to the right**.[Q]
- BPG binds more weakly to fetal Hb than to adult Hb. Thus, BPG has a less profound effect on HbF and is responsible for HbF appearing to have a higher affinity for O_2 than does HbA.

Pasteur effect:[Q] Inhibitory effect of O_2 on glycolysis is called Pasteur effect.[Q]
- It is due to decreased AMP/ATP ratio.
- AMP has positive effect on PFK and so decreased level of AMP causes inhibition of glycolysis.

Crabtree effect:[Q] Relative anaerobiosis produced when glucose concentration is increased in constant supply of oxygen.

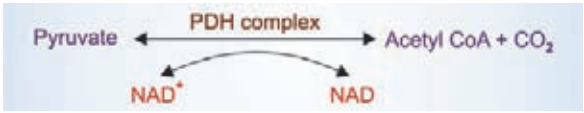
Fates of Pyruvate

a. Pyruvate to lactate (in anaerobic condition)



Lactate is produced under hypoxic condition in tissues, e.g. skeletal muscle white fibres, smooth muscles, renal medulla, retina, brain, GIT cell and skin.

b. Pyruvate to acetyl CoA (in aerobic condition)



- PDH reaction which is an oxidative decarboxylation takes place within mitochondrial matrix.
- Pyruvate dehydrogenase complex: It catalyses irreversible reaction.
- It is a multienzyme complex and contains 3 enzymes and 5 co-enzymes (Diagram 1.7).

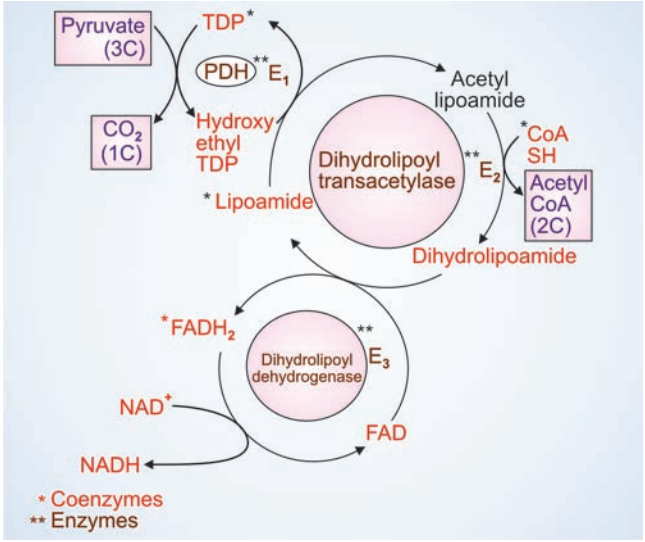


Diagram 1.7: PDH complex

Enzymes of PDH complex:[Q]

a. Pyruvate dehydrogenase (E_1): Also known as pyruvate decarboxylase[Q]
b. Dihydrolipoyl transacetylase (E_2)
c. Dihydrolipoyl dehydrogenase (E_3)

Co-enzymes of PDH complex:[Q]

TDP, lipoate, CoASH, FAD, NAD

***Energetics*:** One molecule of pyruvate produces one NADH, while undergoing PDH reaction and thus 2.5 ATP is produced from one pyruvate molecule.

One glucose produces 2 molecules of pyruvate which produces 5 ATP at this step.

PDH complex is active in dephosphorylated form[Q] (Diagram 1.8).

Three ratios[Q] are important for converting the PDH to the phosphorylated form (Diagram 1.8). These ratios are acetyl CoA/CoA, ATP/ADP, NADH/NAD^+.

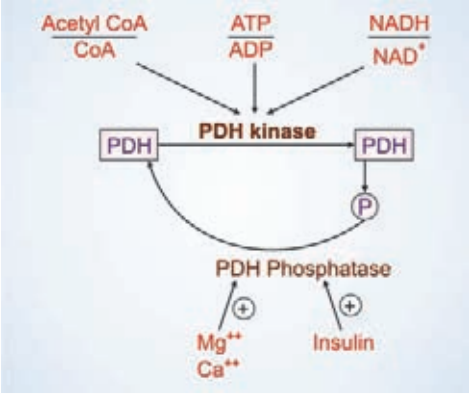


Diagram 1.8: Three ratios activate PDH kinase

Citric Acid Cycle (Krebs Cycle or TCA Cycle)

- ***Definition*:** It is a series of enzyme catalyzed reactions that form a common pathway for final oxidation of all metabolic fuels (carbohydrate, free fatty acids, ketone bodies and amino acids).
- ***Location*:** Mitochondrial matrix
- **Reactions of TCA cycle:** See Diagram 1.9

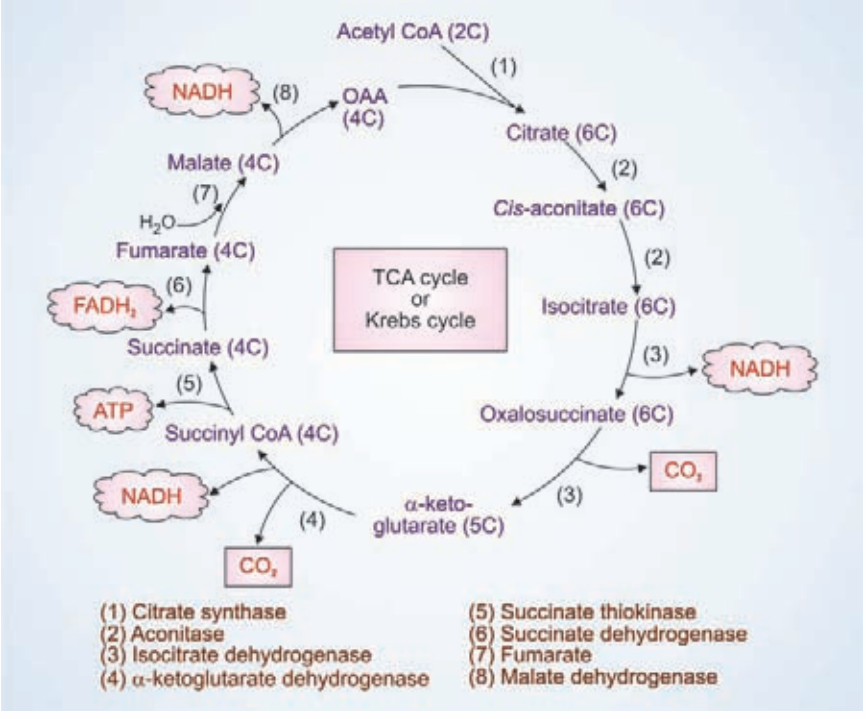


Diagram 1.9: Reactions of TCA cycle

- ***Bioenergetics*:** One molecule of acetyl CoA produces 10 ATP in a turn of citric acid cycle. One glucose molecule produces 2 pyruvate and thus 2 acetyl CoA produces 20 ATP in the TCA cycle (Table 1.6).

Table 1.6: ATP calculation in TCA cycle (one acetyl CoA produces 10 ATP in TCA cycle)Q

Step catalysed by	*Gain from 1 acetyl CoA*	*ATP*
Isocitrate dehydrogenase (ICD)	1 NADH	2.5 ATP
α-ketoglutarate dehydrogenase (α-KGD)	1 NADH	2.5 ATP
Succinate thiokinase	1 ATP	1 ATP
Succinate dehydrogenase (SCD)	1 $FADH_2$	1.5 ATP
Malate dehydrogenase	1 NADH	2.5 ATP
Total	–	**10 ATP**

***Anaplerotic reactions*Q:** Reactions providing the intermediates of the TCA cycle are known as anaplerotic reactions.

Gluconeogenesis

This is the process of formation of glucose from non-carbohydrate substances.

***Substrate of gluconeogenesis*:Q** Glucogenic amino acid, lactate, pyruvate, propionate, glycerol and fumaric acid.

***Site of synthesis*:Q** Liver, kidney, small intestine

This pathway of synthesis of glucose utilises reversible reactions of glycolysis and TCA cycle.

Irreversible steps of glycolysis are bypassed by **exclusive reactions of gluconeogenesis**.

- ***Synthesis of glucose from pyruvate*:** Three irreversible/nonequilibrium reactions in glycolysis, catalyzed by hexokinase, phosphofructokinase and pyruvate kinase, prevent simple reversal of glycolysis for glucose synthesis. They are circumvented as follows (Diagrams 1.10 to 1.12 and 1.16).

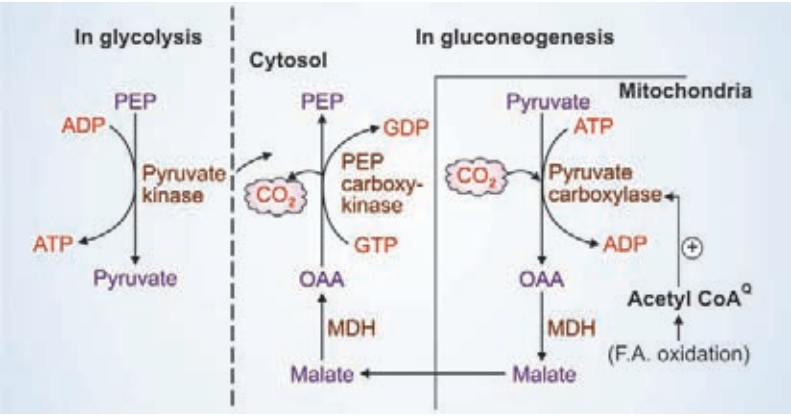


Diagram 1.10: Reversal of pyruvate kinase reaction

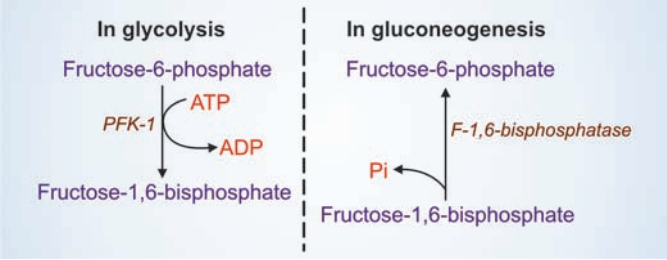


Diagram 1.11: Reversal of PFK-1 reaction

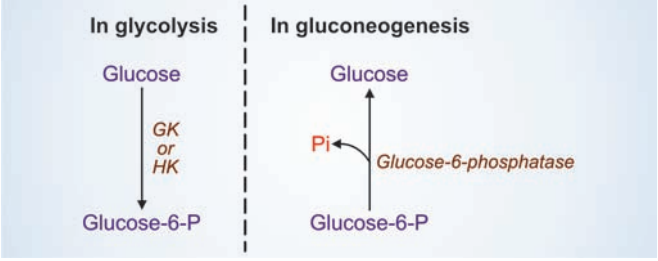


Diagram 1.12: Reversal of glucokinase/hexokinase reaction

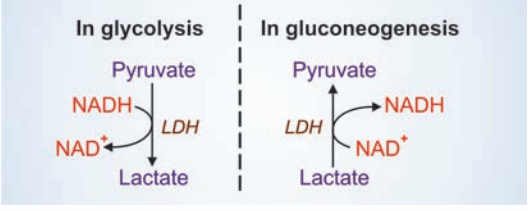


Diagram 1.13: Formation of pyruvate from lactate

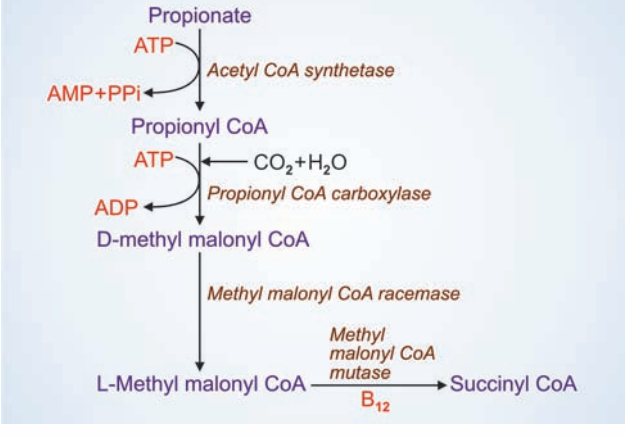


Diagram 1.14: Conversion of propionyl CoA to succinyl CoA

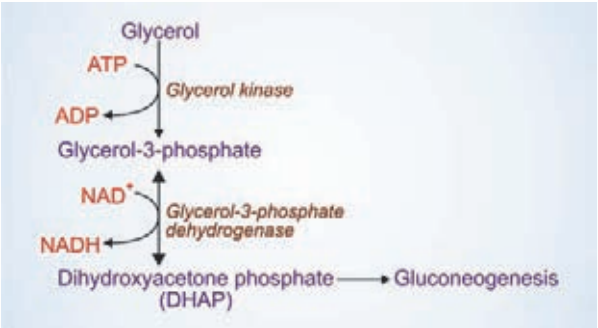


Diagram 1.15: Synthesis of DHAP from glycerol

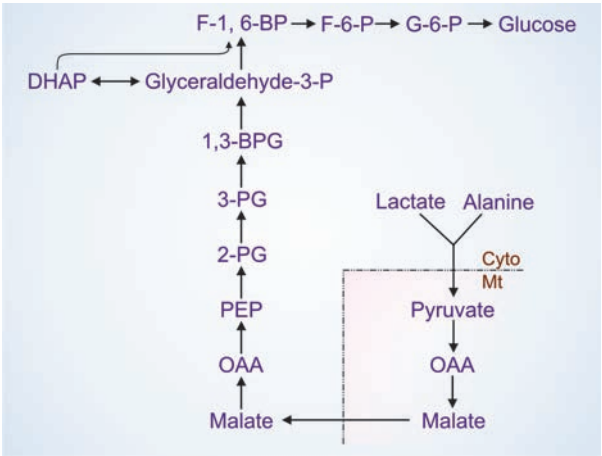


Diagram 1.16: Gluconeogenesis (representing how pyruvate is converted to glucose)

- ***Synthesis of glucose from lactate*:** LDH converts lactate to pyruvate after dehydrogenation (Diagram 1.13).
- ***Synthesis of glucose from propionate*:** Propionyl CoA is converted to succinyl CoA in the following reaction (Diagram 1.14).
- ***Synthesis of glucose from glycerol*:**Q After synthesizing DHAP (dihydroxyacetone phosphate) glycerol enters gluconeogenic pathway (Diagram 1.15).

Glycerol kinase enzyme is found in liver, kidney and gastrointestinal cell. (Not found in adipose cell.Q)

Regulation of gluconeogenesis: It occurs in the following ways:

A. Glucagon: Glucagon stimulates gluconeogenesis by the following three mechanisms:

1. Decreasing level of fructose-2,6-bisphosphate which is an inhibitor of fructose-1,6-bisphosphatase enzyme, so decreased level of fructose-2,6-bisphosphate in turn stimulates fructose-1,6-bisphosphatase enzyme stimulating the gluconeogenesis.
2. Glucagon elevates the level of cAMP, which phosphorylates pyruvate kinase and thus inactivates it, shunting PEP to gluconeogenesis.

3. Glucagon increases the transcription of PEP carboxykinase gene and thus stimulates gluconeogenesis.

B. Substrate availability

C. Allosteric activation by acetyl CoA: Acetyl CoA derived from fatty acid oxidation inhibits PDH enzyme and simultaneously stimulates pyruvate carboxylase, thus shunting pyruvate to gluconeogenesis.

D. Allosteric activation by AMP: AMP stimulates fructose-1,6-bisphosphatase enzyme and thus stimulates gluconeogenesis.

Energetics of Gluconeogenesis

Conversion of 2 moles of pyruvate into 1 mole of glucose requires 4 moles of ATP, 2 moles of GTP and 2 moles of NADH.Q

Glycogen Metabolism

Glycogen is storage form of carbohydrate in animals. It occurs mainly in liver (6%). In muscle it rarely exceeds 1%, but because of greater muscle mass, muscle represents 3–4 times as much glycogen as stored in liver.

Glycogen is a large branched polymer of glucose molecules linked by α-1,4-glycosidic linkages. **Branches arise by α-1,6-glycosidic linkage**Q at approximately every tenth residue (Diagram 1.17).

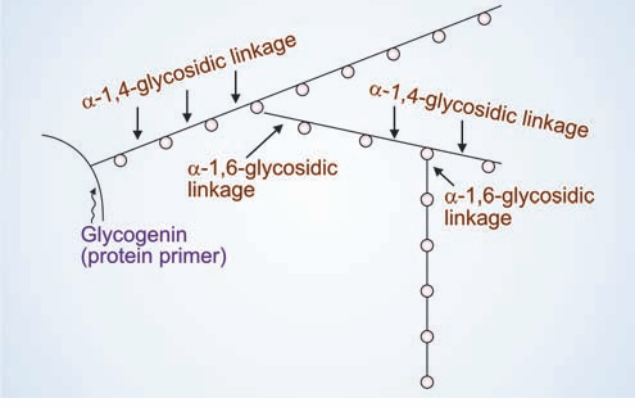


Diagram 1.17: Glycogen structure

After 12–18 hrs of fasting: Liver glycogen is depleted almost totally. Muscle glycogen is depleted significantly only after prolonged vigorous exercise.

***Glycogenin*:** It is a protein primer on which a few molecules of glucose are attached to form a glycogen primer.Q

Glycogenin gets glycosylated at a specific tyrosine residue.Q Further glucose residues are attached in 1 → 4 position to make a short chain of 7-glucose residue, that is further acted upon by glycogen synthase.

Glycogenesis: Glycogen Synthesis (Diagram 1.18)

1. Glucose is phosphorylated to glucose-6-phosphate by glucokinase enzyme.
2. Glucose-6-phosphate is then converted to glucose-1-phosphate by **phosphoglucomutase**[Q] (phosphoglucomutase enzyme is the common enzyme of glycogenesis as well as glycogenolysis).[Q]
3. Glucose-1-phosphate reacts with uridine triphosphate to form the active nucleotide diphosphate glucose (UDPGlu).
4. Glycogen synthase enzyme catalyses the transfer of glucose units of UDPGlu to pre-existing glycogen chain **till 11 residues are added together**.[Q] It is the rate limiting enzyme of glycogenesis.[Q]
5. A branching enzyme transfers 6 units of glucose residue together from this chain after breaking α-1,4-glycosidic bond and forming an α-1,6-linkage, thus establishing the branching points in the molecule.

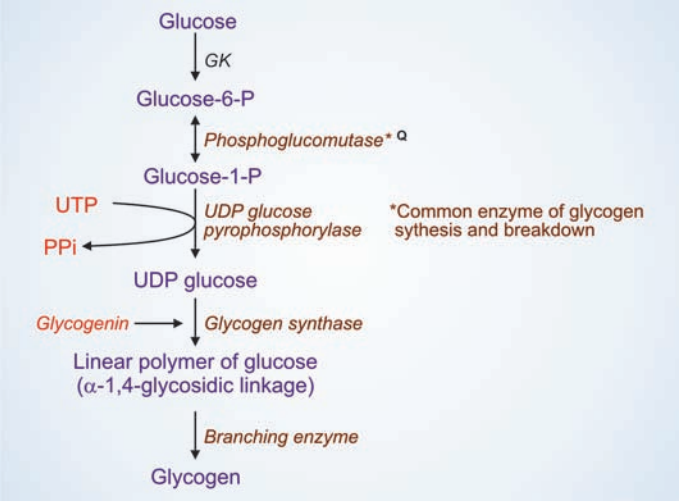


Diagram 1.18: Glycogen synthesis

Glycogenolysis: Glycogen Breakdown (Diagram 1.19)

1. **Phosphorylase enzyme** specifically acts on the terminal α-1,4-glycosidic bonds of glycogen molecules resulting in liberation of glucose units as ***glucose-1-phosphate***[Q] until four glucose residue remain on either side of branch point. This activity of phosphorylase utilises Pi, which is incorporated in the glucose-1-phosphate.
2. **A specific glucan transferase** (α-1,4 → α-1,4-glucan tranferase) will then transfer a trisaccharide unit from one side to the other, thus exposing the branch point.
3. **A debranching enzyme (α-1,6-glucosidase)**[Q] will act on α-1,6-linkage to liberate a ***free glucose residue*** (and not glucose-1-phosphate).[Q]

Note: Glucan transferase (α-1,4 to α-1,4-glucan transferase) and debranching enzyme (α-1,6-glucosidase) are examples of bifunctional enzyme.[Q]

4. Glucose-1-phosphate produced by phosphorylase enzyme is converted to glucose-6-phosphate by phosphoglucomutase enzyme.

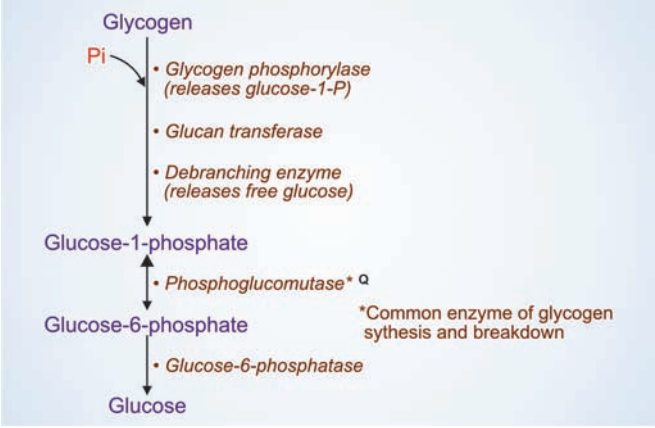


Diagram 1.19: Glycogen degradation

5. Glycogenolysis in liver produces free glucose as it has endoplasmic reticulum glucose-6-phosphatase enzyme which converts glucose-6-phosphate to free glucose.
6. In muscle there is no glucose-6-phosphatase enzyme, so end-product of glycogenolysis is glucose-6-phosphate (not the free glucose).
7. Glucose-6-phosphatase produced in muscle cell after glycogenolysis is utilized *de novo*.

Regulatory Enzymes

- **Phosphorylase** enzyme is the **rate limiting** enzyme in the process of **glycogenolysis**.Q
- Active phosphorylase in both tissues is allosterically inhibited by ATP and glucose-6-phosphate. In addition, free glucose is also an inhibitor in liver but not in the muscle.
- Muscle phosphorylase differs from the liver isoenzyme in having a binding site for 5′AMP, which acts as an allosteric activator of the (inactive) dephosphorylated β-form of the enzyme.
- Muscle phosphorylase kinase, which activates glycogen phosphorylase, is a tetramer of four different subunits, α, β, γ and δ. The α and β subunits contain serine residues that are phosphorylated by cAMP-dependent protein kinase. The **δ subunit is identical to the Ca^{++} binding protein calmodulin and binds four Ca^{++}.**Q The binding of Ca^{++} **activates the catalytic site of the γ subunit**Q even while the enzyme is in the dephosphorylated β-state; the phosphorylated α-form is only fully activated in the presence of high concentration of Ca^{++}.

Glycogen storage diseases are caused by genetic defects that results in deficiency in certain enzymes of glycogen metabolism. The causes and characteristics of several glycogen storage diseases are listed in Table 1.7.

*Hexose Monophosphate Shunt/Also known as Pentose Phosphate Pathway (PPP)/ Dickens-Horecker Pathway/Phosphogluconate Oxidative Pathway*Q

It is a multicyclic process in which 3 molecules of glucose-6-phosphate give rise to 3 molecules of CO_2 and 3 five carbon residues, the latter are rearranged to generate 2 molecules of glucose-6-phosphate and 1 molecule of glycolytic intermediate glyceraldehyde-3-phosphate.

Table 1.7: Glycogen storage disorder[QQ] (modified from table 1/Lehninger 5th ed/page 599)

Glycogenesis	*Name*	*Cause of disorder*	*Characteristics*
Type 0	–	Glycogen synthase	Hypoglycemia; hyperketonemia; early death
Type Ia	von Gierke disease	Deficiency of glucose-6-phosphatase	Hypoglycemia, lactic acidemia, ketosis, hyperlipemia
Type Ib	–	Endoplasmic reticulum glucose-6-phosphate transporter	As type Ia; neutropenia and impaired neutrophil function leading to recurrent infections
Type II*	Pompe's disease	Deficiency of lysosomal α-1,4 and α-1,6-glucosidase	Fatal, accumulation of glycogen in lysosomes. Skeletal and cardiac muscle involved. Liver spared
Type IIIa	**C**ori's/Forbes' disease/ limit dextrinosis	Absence of **D**ebranching enzyme in muscle and liver	Accumulation of characteristic branched polysaccharide in both liver and muscle
Type IIIb	Limit dextrinosis	Liver debranching enzyme is deficient	Accumulation of characteristic branched polysaccharide in liver alone.
Type IV	**A**ndersen's disease Amylopectinosis	Absence of **B**ranching enzyme	Death due to cardiac or liver failure in the first year of life
Type V*	**M**cArdle's syndrome	Absence of **M**uscle phosphorylase	Diminished exercise tolerance; muscles have abnormally high glycogen content
Type VI	**H**ers' disease	Deficiency of liver (**H**epatic) phosphorylase	High glycogen content in liver, tendency towards hypoglycemia
Type VII*	Tarui's disease	Deficiency of muscle and RBC phosphofructokinase	As in type V
Type VIII		Liver phosphorylase kinase	Hepatomegaly
Type IX		Liver and muscle phosphorylase kinase	Hepatomegaly
Type X		cAMP-dependent protein kinase A	Hepatomegaly
Type XI	Fanconi-Bickel disease	GLUT-2 in liver is affected	

**Liver spared in:* GSD type II, V, VII
Muscle spared in: GSD type 0, Ia, Ib, IIIb, VI, VIII, IX, X

Functions of HMP Shunt Pathway

1. Generation of NADPH for reductive biosynthesis.
   a. Fatty acid synthesis
   b. Steroid hormones synthesis
   c. Erythrocytes depend on PPP for NADPH which is required to maintain glutathione in reduced state, which is essential to maintain integrity of RBC membrane.
2. Provides ribose-5-phosphate for nucleic acid biosynthesis.

***Location*:** Q Erythrocytes, liver, lactating mammary gland, adipose tissue, adrenal cortex (cytosol).

Reactions of pentose phosphate pathway

Reactions of HMP shunt consist of 2 phases:

1. Oxidative/irreversible phase
2. Non-oxidative/reversible phase.

Oxidative phase generates NADPH and non-oxidative phase generates various intermediates, namely glyceraldehyde-3-phosphate, erythrose-4-phosphate, ribulose-5-phosphate, xylulose-5-phosphate, ribose-5-phosphate, fructose-6-phosphate, sedoheptulose-7-phosphate.

***Transketolase*:** Transfers a 2-carbon unit from ketose to aldose sugar. The reaction requires thiamine as TPP along with Mg^{++}. Q

***Transaldolase*:** Transfers a 3-carbon unit from aldose to ketose (Diagram 1.20).

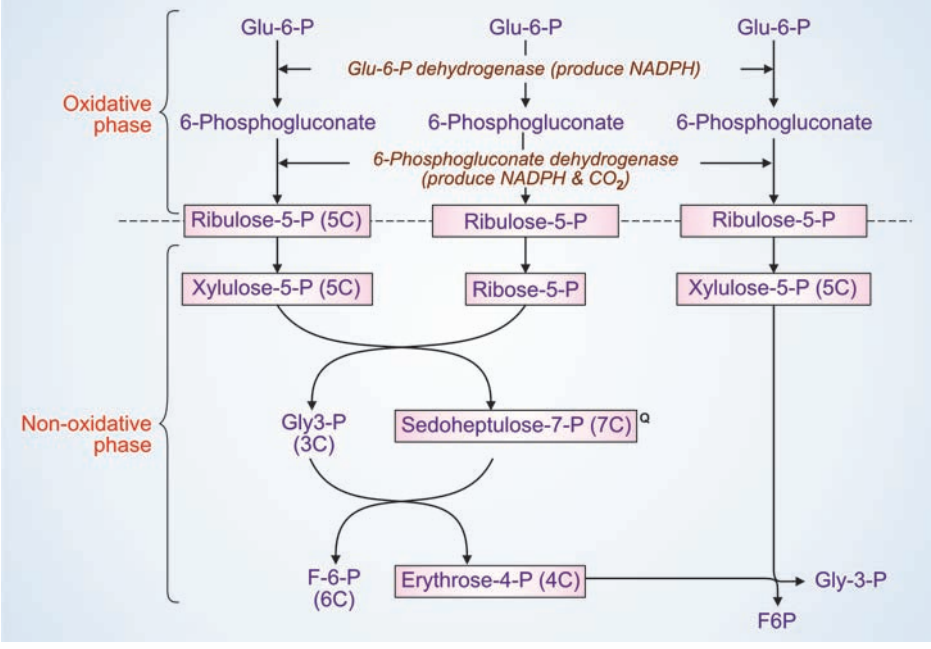


Diagram 1.20: HMP shunt pathway

Rate limiting enzyme of HMP shunt pathway is ***glucose-6-phosphate dehydrogenase (G6PD)***Q. Insulin induces it.

List of intermediate produced in HMP shunt pathway

1. Glyceraldehyde-3-phosphate
2. Erythrose-4-phosphate
3. Ribose-5-phosphate
4. Ribulose-5-phosphate
5. Xylulose-5-phosphate

6. Fructose-6-phosphate
7. Sedoheptulose-7-phosphate

Role of Pentose Phosphate in Protecting Erythrocytes Against Haemolysis

The pentose phosphate pathway in erythrocytes provides NADPH for reduction of oxidised glutathione to reduced glutathione catalyzed by glutathione reductase. In turn, reduced glutathione removes H_2O_2 from erythrocyte in a reaction catalyzed by glutathione peroxidase, an enzyme that contains the trace element ***selenium***[Q]. This reaction is important as GSH removes H_2O_2 from RBC. Accumulation of H_2O_2 may decrease the lifespan of RBC by increasing the rate of oxidation of Hb to MetHb (Diagram 1.21).

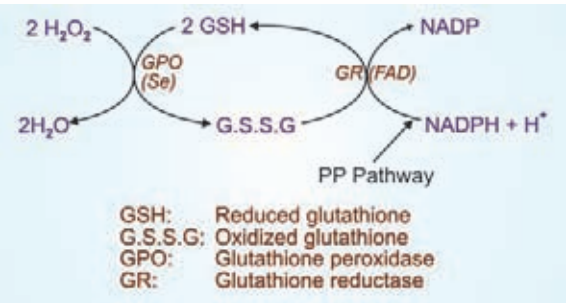


Diagram 1.21: Role of NADPH in maintaining integrity of cell membrane by supplying reduced glutathione (GSH)

Uronic Acid Pathway

Significance of uronic acid pathway:

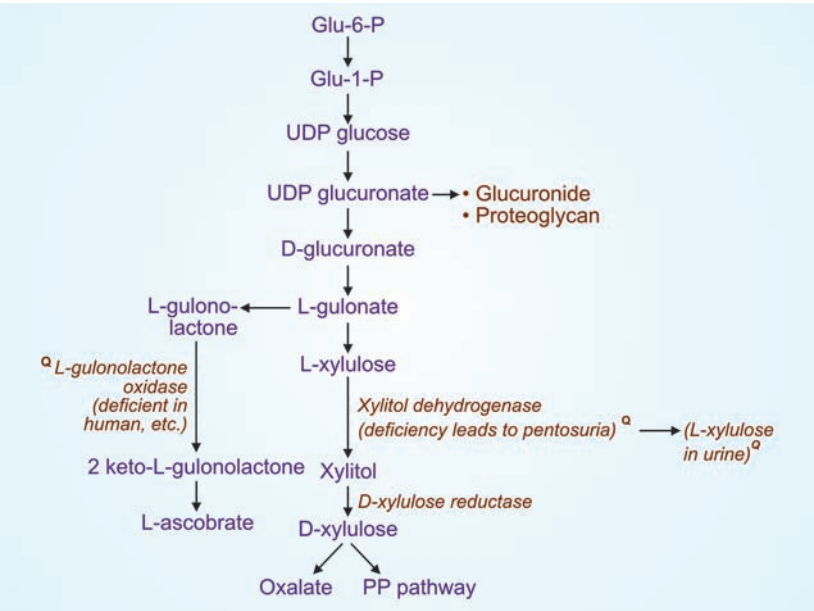


Diagram 1.22: Uronic acid pathway

1. Source of UDP glucose that is used for glycogen formation.
2. Formation of glucuronides for bilirubin, steroid hormone and drugs.
3. Pathway integral to formation of ascorbic acid in most animals.

(Human, other primates, guinea pigs, bats, fishes and some birds cannot synthesise vitamin C due to absence of L-gulonolactone oxidase enzyme[Q]).

4. **Xylitol dehydrogenase** deficiency leads to excretion of L-xylulose in the urine, in the disorder known as **essential pentosuria.**[Q]
5. **Alimentary pentosuria:** Due to excessive consumption of pears (Diagram 1.22).

Metabolism of Fructose

- Fructose undergoes rapid metabolism in the liver than does glucose, because it bypasses the regulatory step catalysed by phosphofructokinase.
- Organs utilising fructose are liver, spleen, kidney, GIT cell, placenta, testis, sperm.
- **Essential fructosuria.**[Q] Defect in enzyme fructokinase (benign condition).
- **Hereditary fructose intolerance.**[Q] Genetic defect leading to aldolase B deficiency leading to accumulation of fructose-1-phosphate in cell and consequently liver and kidney damage (Diagram 1.23).

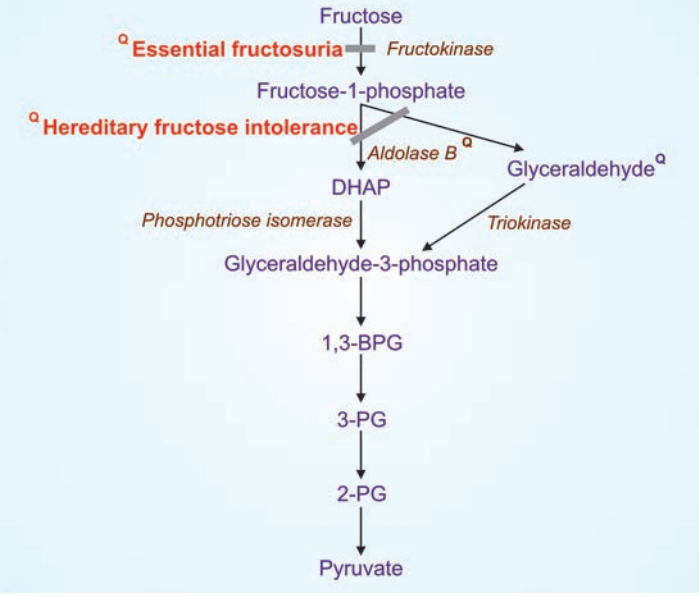


Diagram 1.23: Fructose metabolism

Metabolism of Galactose

- **Galactokinase catalyses** the phosphorylation of galactose, using ATP as phosphate donor.
- Galactose-1-phosphate reacts with uridinediphosphate glucose (UDP-Glc) to form uridine-diphosphate-galactose (UDP-Gal) and glucose-1-phosphate, in a reaction catalyzed by **galactose-1-phosphate uridyltransferase**.

- The conversion of UDP-Gal to UDP-Glc is catalyzed by **UDP-Gal 4-epimerase**. The reaction involves oxidation, then reduction, at carbon 4, with NAD^+ as coenzyme. The UDP-Glc is then incorporated into glycogen.

Since the epimerase reaction is freely reversible, glucose can be converted to galactose, making the **galactose dietary non-essential.**

Galactose is required in the body not only in the formation of lactose but also as a constituent of glycolipids (cerebrosides), proteoglycans, and glycoproteins. In the synthesis of lactose in the mammary gland, UDP-Gal condenses with glucose to yield lactose, catalyzed by lactose synthase.

- **Classical galactosemia** condition is characterised by inability to metabolise dietary galactose due to **deficiency of galactose-1-phosphate uridyl transferase**.Q This results in increased level of galactose in blood and urine leading to cataract, mental disturbance, lethargy, vomiting, liver enlargement.
- **Deficiency of galactokinase** leads to **benign galactosemia**Q where cataract is the only feature found, organomegaly or mental retardation is not found.
- **Deficiency of epimerase** if found in association with any of the above two enzymes described, the condition becomes very dangerous and non-treatableQ (Diagram 1.24).

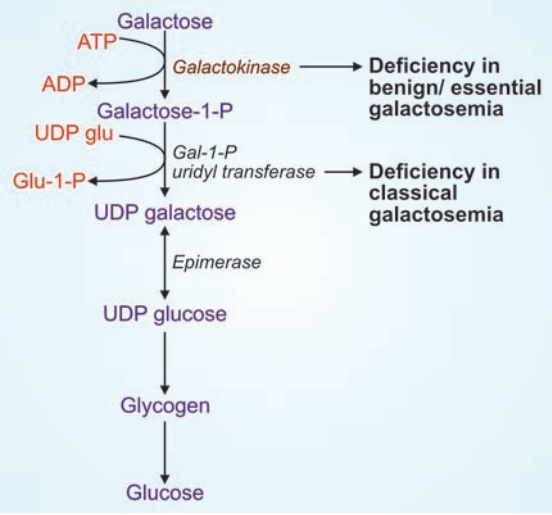


Diagram 1.24: Galactose metabolism

MULTIPLE CHOICE QUESTIONS

Q 1. The most effective for gluconeogenesis is ***(Nov 2016 AIIMS)***

a. Citrate stimulation of acetyl carboxylase
b. Acetyl CoA stimulation of pyruvate carboxylase
c. Fructose 2,6-bishosphate stimulation of phosphofructokinase
d. Citrate activating pyruvate carboxylase

Ans. b: Acetyl CoA stimulation of pyruvate carboxylase

Acetyl CoA is a very important positive allosteric modifier of pyruvate carboxylase enzyme. This acetyl CoA is produced during beta oxidation of fatty acid in the mitochondria. So, it is important to understand that for gluconeogenesis to occur in the liver, prior beta oxidation of fatty acid is must.

Ref. Harper's Illustrated Biochemistry, 30th ed, page 188

Q 2. Respiratory quotient after a heavy carbohydrate meal is: ***(Nov 2016 AIIMS)***

a. 1.2 b. 0.8
c. 1 d. 0.7

Ans. c: 1

Respiratory quotient of various food items

Carbohydrate	1.00
Protein	0.80
Lipid	0.70
Mixed diet	0.85
After exercise	1.20

Q 3. On urine examination of a patient by glucose strip method was negative but Benedict's test for reducing sugar was positive. Your probable diagnosis is: ***(Nov 2016 AIIMS)***

a. Fructosemia b. Galactosemia
c. Latent diabetes mellitus
d. Hyperaldosteronism

Ans. b: Galactosemia

Q 4. Which of the following is not a gluconeogenic substrate in humans? ***(November 2015 AIIMS)***

a. Lactate b. Pyruvate
c. Oxaloacetate d. Acetyl CoA

Ans. d: Acetyl CoA

Acetyl CoA is not capable of synthesizing glucose as it cannot form pyruvate.

PDH complex catalyses irreversible conversion of pyruvate to acetyl CoA .

Following substrate may be gluconeogenic

a. Pyruvate
b. Lactate
c. Oxaloacetate
d. Fumarate
e. Gluconeogenic amino acid
f. Glycerol
g. Propionic acid

Q 5. Activators of phosphofructokinase-1 of glycolysis include: ***(PGI)***

a. ATP
b. AMP
c. ADP
d. Frucose-1,6-biphosphate
e. Fructose 2,6-biphosphate

Ans. b, e

Explanation: Phosphofructokinase (also called PFK-1)

- Rate-limiting enzyme of glycolysis
- Allosteric activators include: Fructose 2,6-Biphosphate, AMP

- Allosteric inhibitor includes: Citrate, ATP and hydrogen ion
  Courtesy: Devlin 6th ed, page 599

Q 6. What is the total number of ATPs derived from one molecule of Acetyl CoA?

a. 8 b. 9
c. 10 d. 12

Ans. c: 10

- Energetics of TCA cycle : From 1 molecule of acetyl CoA

Enzyme	*Method of ATP formation*	*No. of ATPs*
Isocitrate dehydrogenase	1 NADH respiratory chain oxidation	2.5
Alpha ketoglutarate dehydrogenase	1 NADH respiratory chain oxidation	2.5
Succinate thiokinase	Substrate level phosphorylation	1
Succinate dehydrogenase	Respiratory chain oxidation of 1 FADH2	1.5
Malate dehydrogenase	Respiratory chain oxidation of 1 NADH	2.5
	Total	*10*

Q 7. All are true about glucuronic acid *except:*

a. It is a charged molecule at the physiological pH
b. As a UDP derivative, it can be decarboxylated to a component used in proteoglycan synthesis
c. It is a precursor of ascorbic acid in humans
d. It can ultimately be converted to xylulose-5-phosphate and thus enter in pentose phosphate pathway.

Ans. c: It is a precursor of ascorbic acid in humans

- Man does not make ascorbic acid.
- The charged acid group enhances water solubility, which is a major physiological role for glucuronic acid, for example bilirubin metabolism.
- Decarboxylation of UDP glucuronic acid gives rise to UDP xylose which is involved in proteoglycan synthesis.
- Reduction of d-glucuronic acid to/ gluconic acid leads to ascorbate as well as xylulose-5-phosphate for pentose phosphate pathway.

Q 8. Glycosaminoglycans:

a. Are the carbohydrate portion of the glycoprotein
b. Contain large segment of a repeating unit typically consisting of a hexosamine and a uronic acid
c. Always contain sulphate
d. Exist only in two forms

Ans. b: Contain large segment of a repeating unit typically consisting of a hexosamine and a uronic acid

- This is a major distinction from the glycoprotein, which by definition does not have repeating units of hexosamine and uronic acid.
- They are carbohydrate portions of the proteoglycan, not the glycoprotein.
- Hyaluronate does not contain sulphate.
- Exist in 6 different classes, e.g. heparin, heparan sulphate, keratan sulphate I and II, dermatan sulphate, chondroitin sulphate.

Q 9. Which of the following is not seen in low insulin/glucagon ratio:

(May 2017 AIIMS)

a. Gluconeogenesis
b. Glycogen storage

c. Glycogen breakdown
d. Ketogenesis

Ans. b: Glycogen storage

Low insulin/glucagon ratio—means low insulin levels and high glucagon levels.

Process	*Insulin*	*Glucagon*
Gluco-neogenesis	Inhibited (inhibition of: a. Pyruvate carboxylase b. Phosphoenol-pyruvate carboxy-kinase c. Glucose-6-phosphatase)	Increased (inhibition of: a. Pyruvate kinase b. Phosphofructo-kinase c. Activation of fructose 1,6-bisphosphatase)
Glyco-genolysis	Inhibited (inhibition of glycogen phosphorylase)	Increased (activation of glycogen phosphorylase)
Ketogenesis	inhibited [• Less substrate acetyl CoA formed • Inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG CoA) synthetase]	

Q 10. Which of the following is anaplerotic reaction? *(May 2017 AIIMS)*

a. Conversion of pyruvate to acetyl CoA
b. Conversion of pyruvate to acetaldehyde
c. Conversion of pyruvate to lactic acid
d. Conversion of pyruvate to oxaloacetate

Ans. d: Conversion of pyruvate to oxaloacetate

- Anaplerotic reactions are chemical reactions that form intermediates of a metabolic pathway.
- Anaplerotic flux must balance cataplerotic flux in order to retain homeostasis of cellular metabolism.

Q11. Thiamine deficiency results in decrease energy production, because TPP: *(May 2017 AIIMS)*

a. Interferes with alcohol metabolism
b. Interferes with transketolase activity
c. Interferes with energy production from amino acids
d. Is cofactor for pyruvate and alpha-ketoglutarate dehydrogenase

Ans. d: Is cofactor for pyruvate and alpha-ketoglutarate dehydrogenase

- Thiamine pyrophosphate (TPP) is a derivative of thiamine (vitamin B_1).
- Beriberi affects especially the brain, because TPP is required for carbohydrate metabolism, and the brain depends on glucose metabolism for energy.
- Nutritional deficiency of thiamine leads to the disease beriberi.
- Pyruvate carboxylase complex—energy metabolism.

Enzyme	*Abbreviated*	*Prosthetic group*
Pyruvate dehydrogenase	E_1	Thiamine pyrophosphate (TPP)
Dihydrolipoyl transacetylase	E_2	Lipoamide
Dihydrolipoyl dehydrogenase	E_3	FAD

Q 12. Which of the following yields 3 molecules of ATP under anaerobic metabolism? *(May 2017 AIIMS)*

a. Glucose
b. Galactose
c. Glycogen
d. Amino acid

Ans. c: Glycogen

Glycogen metabolism and energy production:

- One molecule of glycogen can yield a massive number of glucose-6-phosphate molecules.
- So, technically speaking the net yield of ATPs is large for one molecule of glycogen.
- But if we assume that the question tends to seek the number of ATPs from one glucose molecule extracted from one glycogen molecule then the answer is 3.
- If a free glucose is fermented it yields 2 ATPs.
- But glycogen releases glucose as glucose-6-phosphate due to the absence of glucose-6-phosphatase.

Q 13. Positive signals for glycogen breakdown include increase in all of the following *except*:

a. Cyclic AMP
b. Blood glucose
c. Epinephrine
d. Ca^{2+}

Ans. b: Blood glucose

- Rate-limiting enzyme in glycogenolysis is glycogen phosphorylase and in glycogenesis is glycogen synthetase. The two processes are reciprocally regulated.
- Phosphorylation makes the enzyme glycogen phosphorylase active whereas phsphorylation of glycogen synthetase results in its inactivation.
- Epipinephrine (in both muscle and liver) and glucagons (in liver only) acts in receptors to increase cAMP production.
- Cyclic AMP results in phosphorylation and thus stimulates glycogenolysis (remember that phosphorylated glycogen phosphorylase also known as phosphorylase is active) and inhibits glycogenesis (phosphoryl glycogen synthetase is inactive).
- ATP and glucose-6-phosphate act as inhibitors of phosphorylase enzyme.
- Since the two processes are reciprocally regulated, it functions like a negative feedback system where obviously increase in blood glucose will not cause breakdown of glycogen and increase blood glucose further.

Q14. Except for succinate dehydrogenase, all other enzymes of the tricarboxylic acid cycle are found in the:

a. Outer mitochondrial membrane
b. Inner mitochondrial membrane
c. Mitochondrial matrix
d. Cristae

Ans. c: Mitochondrial matrix

- The enzymes of the Krebs cycle are hydrophilic and occur within the mitochondrial matrix.
- Succinate dehydrogenase is embedded within the inner mitochondrial membrane, where it can transfer its electrons to other components (coenzyme Q) of the electron transport chain, also found in the inner mitochondrial membrane.

Q 15. Which of the following enzymes is not directly required in the sequence of reactions by which galactose is converted to UDP-glucose?

a. Galactokinase
b. An epimerase
c. Phosphoglucomutase
d. An uridyl transferase

Ans. c: Phosphoglucomutase

- Galactose is phosphorylated by galactokinase to galactose-l-phosphate, which reacts with UDP-glucose in a reaction catalyzed by uridyl transferase to form UDP-galactose and glucose-l-phosphate.
- An epimerase converts UDP-galactose to UDP-glucose.
- Phosphoglucomutase interconverts glucose-1-phosphate and glucose-6-phosphate.

Q 16. Hyperuricemia is caused by all *except*:

a. Von Gierke
b. Fructose intolerance
c. Galactosemia
d. Xanthine oxidase deficiency

Ans. d: Xanthine oxidase deficiency

- Uric acid is an end-product of purine catabolism.
- Xanthine oxidase is an enzyme of purine catabolism. Hence, when it is deficient, catabolism is defective causing hypo-uricemia.

Q 17. Synthesis of glycogen is inhibited in hepatocytes in response to glucagon stimulation primarily as a result of which of the following?

a. A decrease in the level of phospho-protein phosphatase
b. A decrease in the level of phosphory-lated phosphorylase kinase
c. An increase in the level of the dephos-phorylated form of glycogen synthase
d. An increase in the level of the phos-phorylated form of glycogen synthase

Ans. d: An increase in the level of the phosphorylated form of glycogen synthase

- Glucagon is released from the pancreas in response to low blood glucose and stimulates hepatocytes to synthesize glucose for delivery to the blood.
- Therefore, it would be counterproductive for hepatocytes to divert any of the gluconeogenically derived glucose into glycogen. This is accomplished by inhibition of glycogen synthase.
- Glucagon exerts its effects on the liver through the glucagon receptor. When glucagon binds, the receptor activates adenylate cyclase leading to increased production of cAMP.
- In turn, cAMP activates cAMP-dependent protein kinase, which then phosphorylates a number of substrates. Glucagon has no effect on the level of phosphoprotein phosphatase.
- Therefore, there is no increase in the level of dephosphorylated glycogen synthase. Phosphorylation inhibits glycogen synthase activity and activates phosphorylase.

Q 18. Which of the following steps is involved in the generation of glucose from lipolysis?

a. Glycerol from lipolysis is converted to triglycerides
b. Fatty acids from lipolysis are oxidized, producing NADH and stimulating gluconeogenesis
c. Glycerol from lipolysis is phosphorylated, converted to fructose-1,6-bisphosphate, and eventually converted to glucose
d. Fatty acids from lipolysis stimulate the citric acid cycle

Ans. c: Glycerol from lipolysis is phosphorylated, converted to fructose-1,6-bisphosphate, and eventually converted to glucose

- Lipolysis in adipose tissue leads to increased blood levels of fatty acids and glycerol.
- Since most tissues have a little glycerol kinase, the liver takes up most of the free glycerol, phosphorylates it using glycerol kinase, and oxidizes it to dihydroxyacetone phosphate (DHAP) using a dehydrogenase.
- Aldolase allows both of the triose phosphates DHAP and glyceraldehyde-3-phosphate to condense and form fructose-1,6-bisphosphate.
- In this manner, aldolase allows adipocyte glycerol to enter hepatic gluconeo-genesis.

Q 19. Which of the following reactions generates ATP?

a. Glucose-6-phosphate to fructose-6-phosphate
b. Glucose to glucose-6-phosphate
c. Fructose-6-phosphate to fructose-1,6-diphosphate
d. Phosphoenolpyruvate to pyruvate

Ans. d: Phosphoenolpyruvate to pyruvate

- ATP is synthesized by two reactions in glycolysis.
- The first molecule of ATP is generated by phosphoglycerate kinase, converting 1,3-diphosphoglycerate to 3-phosphoglycerate.
- The second molecule of ATP is generated by pyruvate kinase, converting phosphoenolpyruvate to pyruvate.

Q 20. The citric acid cycle is inhibited by which of the following:

a. Fluoroacetate
b. Fluorouracil
c. Aerobic conditions
d. Arsenic

Ans. a: Fluoroacetate

- Fluoroacetate can be converted to fluorocitrate, which is an inhibitor of aconitase.
- Arsenic is not a direct inhibitor, but arsenite is an inhibitor of lipoic acid-containing enzymes such as α-ketoglutarate dehydrogenase, PDH
- The citric acid cycle requires oxygen and would be inhibited by anaerobic, not aerobic, conditions.
- Fluorouracil is a suicide inhibitor of thymidylate synthase and blocks deoxythymidylate synthesis.

Q 21. During an overnight fast, the major source of blood glucose is:

a. Dietary glucose from the intestine
b. Hepatic glycogenolysis
c. Gluconeogenesis
d. Muscle glycogenolysis

Ans. b: Hepatic glycogenolysis

- During this period, the major source of blood glucose is hepatic glycogen. Through the effects of glycogenolysis, which are mediated by glucagon, hepatic glycogen is slowly parceled out as glucose to the bloodstream, keeping blood glucose levels normal.
- In contrast, muscle glycogenolysis has no effect on blood glucose levels because no glucose-6-phosphatase exists in muscle and hence phosphorylated glucose cannot be released from muscle into the bloodstream.
- Following a more prolonged fast or in the early stages of starvation, gluconeogenesis is needed to produce glucose from glucogenic amino acids and the glycerol released by lipolysis of triacylglycerides in adipocytes.

Q 22. Which one of the following inhibits hepatic gluconeogenesis?

a. Acidosis
b. Alcohol
c. Insulin
d. Glucagon

Ans. c: Insulin

- Glucagon, cortisol and adrenaline (epinephrine) all stimulate gluconeogenesis. Insulin inhibits gluconeogenesis.

Q 23. Which one of the following may result in a positive Clinitest reaction?

a. Hyperphosphaturia
b. Aminoaciduria
c. Rifampicin therapy
d. Salicylate therapy

Ans. d: Salicylate therapy

A positive Clinitest reaction (the apparent detection of glucose in the urine on dipstick testing) is associated with:

- Glycosuria
- Galactosaemia, hereditary fructosaemia, alkaptonuria
- Drugs—L-dopa, salicylates, vitamin C, isoniazid, tetracylines.

Q 24. Each of the following statements concerning pyruvate dehydrogenase is true *except*:

a. It is an example of a multienzyme complex
b. It requires thiamine pyrophosphate as a cofactor
c. It produces oxaloacetate from pyruvate
d. It is converted to an inactive form by phosphorylation

Ans. c: It produces oxaloacetate from pyruvate

- Pyruvate dehydrogenase converts pyruvate to acetyl CoA. The enzyme contains a dehydrogenase component that oxidatively decarboxylates pyruvate, a dihydrolipoyl transacetylase that transfers the acetyl group to coenzyme A, and a dihydrolipoyl dehydrogenase that reoxidizes lipoic acid.
- Thiamine pyrophosphate, lipoic acid, coenzyme A, NAD^+, and FAD serve as cofactors for these reactions.
- In addition, a kinase is present that phosphorylates and inactivates the decarboxylase component. Acetyl CoA and NADH activate this kinase, thereby inactivating pyruvate dehydrogenase.
- A phosphatase dephosphorylates the kinase, thereby reactivating pyruvate dehydrogenase.

Q 25. During exercise, stimulation of the TCA cycle results principally from:

a. Allosteric activation of isocitrate dehydrogenase by increased NADH
b. Allosteric activation of fumarase by increased ADP
c. A rapid decrease in the concentration of four-carbon intermediates
d. Stimulation of the flux through a number of enzymes by a decreased $NADH/NAD^+$ ratio

Ans. d: Stimulation of the flux through a number of enzymes by a decreased $NADH/NAD^+$ ratio

- NADH decreases during exercise (if it increased, it would slow the cycle). Fumarase is not activated by ADP.
- Four-carbon intermediates of the cycle are recycled. Their concentration does not decrease. Product inhibition of citrate synthase would slow the cycle.
- During exercise, the TCA cycle is stimulated because the $NADH/NAD^+$ ratio decreases and stimulates flux through isocitrate dehydrogenase, α-ketoglutarate dehydrogenase, and malate dehydrogenase.

Q 26. A patient has a genetic defect that causes intestinal epithelial cells to produce disaccharidases of much lower activity than normal. Compared to a normal person, after eating a bowl of milk and oatmeal, this patient will have higher levels of:

a. Maltose, sucrose, and lactose in the stool
b. Starch in the stool
c. Galactose and fructose in the blood
d. Glycogen in the muscles

Ans. a: Maltose, sucrose, and lactose in the stool

- Starch will be digested to small oligosaccharides and maltose, but a lower than normal amount of glucose will be

produced because of the deficiency of the brush border disaccharidases, which include sucrase and lactase.
- Sucrose and lactose will not be cleaved; hence, there will be more maltose, sucrose, and lactose in the stool and less monosaccharides in the blood and tissues.
- Insulin levels will be low.

Q 27. Which of the following statements about liver phosphorylase kinase is true?

a. It is present in an inactive form when epinephrine is elevated
b. It phosphorylates phosphorylase to an inactive form
c. It catalyzes a reaction that requires ATP
d. It is phosphorylated in response to elevated insulin

Ans. c: It catalyzes a reaction that requires ATP

- Glucagon in the liver and epinephrine in both the liver and muscle cause cAMP to rise, activating protein kinase A. Protein kinase A phosphorylates and activates phosphorylase kinase, which in turn phosphorylates and activates phosphorylase.
- These phosphorylation reactions require ATP.

The phosphorylase kinase-associated regulatory protein identified by the letter A in Diagram 1.25 is a calcium-binding protein.

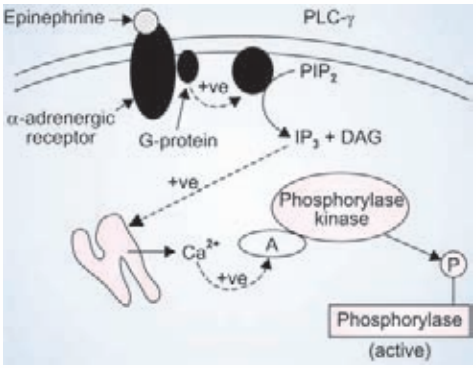


Diagram 1.25

Q 28. Which of the following proteins represents this regulatory subunit?

a. Calmodulin
b. Fructose-2,6-bisphosphate
c. Glycogen synthase kinase-3
d. Phosphoprotein phosphatase

Ans. a: Calmodulin

- Phosphorylase kinase (also referred to as phosphorylase/synthase kinase, because it can phosphorylate both glycogen phosphorylase and glycogen synthase) contains calmodulin as a subunit.
- The presence of calmodulin allows phosphorylase kinase to be activated in the absence of a cAMP-mediated phosphorylation cascade.
- This is important when muscle is stimulated by epinephrine binding to alpha-adrenergic receptors (this function is given in Diagram 1.25) or by acetylcholine release at the neuromuscular junction. Each of these events leads to increases in intracellular Ca^{2+}.

Q 29. The molecular basis for shock absorption within articular cartilage is which of the following?

a. Electrostatic interaction of proteoglycans with type IV collagen
b. Ability of glycosaminoglycans to bind anions
c. Noncovalent binding of glycosaminoglycans to protein cores
d. Hydration of glycosaminoglycans

Ans. d: Hydration of glycosaminoglycans (Alberts, page 1093–1094. Junqueira, page 113–114)

Hydration of the glycosaminoglycans plays an important role in shock absorption and enhances the resiliency of the cartilage. This role is particularly important in the articular cartilages, which receive pressure

during joint movement and are required to resist strong compressive forces.

- Proteoglycans are the major component of the ground substance of cartilage. They possess a large anionic charge because of the presence of sulfate, hydroxyl, and carboxyl groups within the glycosaminoglycans, which join to form proteoglycan subunits by linking with a core protein. The proteoglycan subunits (monomers) subsequently form an aggregate by linking noncovalently to hyaluronic acid.

Q 30. A 25-year-old Nigerian medical student in United States develops haemolytic anemia after taking the oxidizing antimalarial drug primaquine. Which of the following is most likely cause of this severe reaction?

a. Glucose-6-phosphate dehydrogenase deficiency
b. Concomitant scurvy
c. Vitamin C deficiency
d. Diabetes

Ans. a: Glucose-6-phosphate dehydrogenase (G6PD) deficiency

G6PD deficiency is commonest cause of enzyme deficient haemolytic anemia.

Hemolysis is precipitated by drugs like primaquine, sulfa drugs and flavonoids.

Q 31. A newborn Caucasian girl presents with poor feeding, vomiting, jaundice, and enlarged liver. The urine tests positive for reducing substances, indicating the presence of sugars with aldehyde groups. Which of following processes is most likely to be abnormal?

a. Conversion of glucose to galactose
b. Conversion of lactose to galactose
c. Conversion of activated galactose to activated glucose
d. Excretion of glucose by the kidney

Ans. c: Conversion of activated galactose to activated glucose

This infant may have classical galactosemia, a deficiency of GALT (galactose-1-phosphate uridyl transferase).

During its metabolism, galactose is converted to galactose-1-phosphate by galactokinase and is then converted to UDP galactose by GALT (galactose-1-phosphate uridyl transferase) enzyme. An epimerase enzyme then converts UDP galactose to UDP glucose which then is utilized. Interruption of this normal pathway either due to deficiency of GALT enzyme, galactokinase or epimerase leads to accumulation of galactose metabolite and liver toxicity. Urine also shows reducing substances due to excretion of some galactose in it.

Q 32. Total number of dehydrogenases in Krebs cycle:

a. 3 b. 2
c. 4 d. 5

Ans. c: 4

Q 33. Thiamine deficiency causes lactic acidosis due to dysfunction of which enzyme? *(May 2015 AIIMS)*

a. PEPcarboxykinase
b. Pyruvate dehydrogenase
c. Pyruvate carboxylase
d. Phosphofructokinase

Ans. b: Pyruvate dehydrogenase

Due to lack of thiamine pyruvate is not converted to acetyl CoA, rather it is reduced to lactate.

Q 34. Which of the following enzyme is involved in both glycogenesis and glycogenolysis pathways? *(May 2015 AIIMS)*

a. Glycogen synthase
b. Phosphoglucomutase
c. Glucan transferase
d. Glycogen phosphorylase

Ans. b: Phosphoglucomutase.

Phosphoglucomutase is the enzyme which catalyse following reaction in a reversible fashion.

Glucose-6-phosphate ↔ Glucose-1-phosphate

During glycogen synthesis the equilibrium of reaction is towards the formation of glucose-1-phosphate, and during glycogenolysis, equilibrium of reaction is towards the formation of glucose-6-phosphate.

Q 35. During fasting state for metabolism red blood cells can use: *(May 2015 AIIMS)*

a. Glucose
b. Alanine
c. Ketone body
d. Fatty acid

Ans. a: Glucose

Due to lack of mitochondria RBC does not use fatty acid or ketone body. Only fuel which the RBC uses is glucose (in well fed as well as in starved state).

Q 36. A child to emergency with accidental ingestion of cyanide. It blocks citric acid cycle by blocking: *(May AIIMS 2016)*

a. Acetyl-CoA production
b. Aconitase
c. NAD^+
d. Citrate

Ans. c: NAD^+

Ref: Harper's Illustrated Biochemistry, 30/e, p 132

NAD^+ is important coenzyme which is needed for many of the enzyme of the TCA cycle. For example

- Isocitarte dehydrogenase
- Alpha-ketoglutarate dehydrogenase
- Malate dehydrogenase

In deficiency of NAD^+ the TCA cycle will not run (Diagram 1.26).

Q 37. Baby is having hypoglycaemia, specially early morning hypoglycaemia. Glucagon raises blood glucose when given in fed state but same glucagon does not raise blood glucose when given during fasting state. Liver biopsy shows accumulation of glycogen in the liver. What is the enzyme deficiency?

(May AIIMS 2016)

a. Muscle phosphorylase
b. Glucose 6 phosphorylase
c. Branching enzyme
d. Debranching enzyme

And. d: Debranching enzyme

- This baby is suffering from Cori's disease (Type IIIa) where both liver and muscle are affected. Here debranching enzyme is deficient.
- Phosphorylase enzyme is normal in this baby so fasting of shorter duration is well managed by glycogenolysis.
- In well fed state when complete glycogen is present that time glugacon stimulates phosphorylase enzyme which cleaves the glycogen releasing glucose to the blood.
- During fasting state there is limit dextrin and there is no effect of glucagon on debranching enzyme. Hence, the glucagon is not able to raise the blood glucose in fasting state.

Q 38. During exercise the most rapid way of resynthesis of ATP *(Nov 2016 AIIMS)*

a. Glycolysis
b. Glycogenolysis
c. Phosphocreatine breakdown
d. Citric acid cycle

Ans. c: Phosphocreatine breakdown

During exercise existing ATP in the skeletal muscle last only for 2 seconds. In case of continued exercise rapid resynthesis of

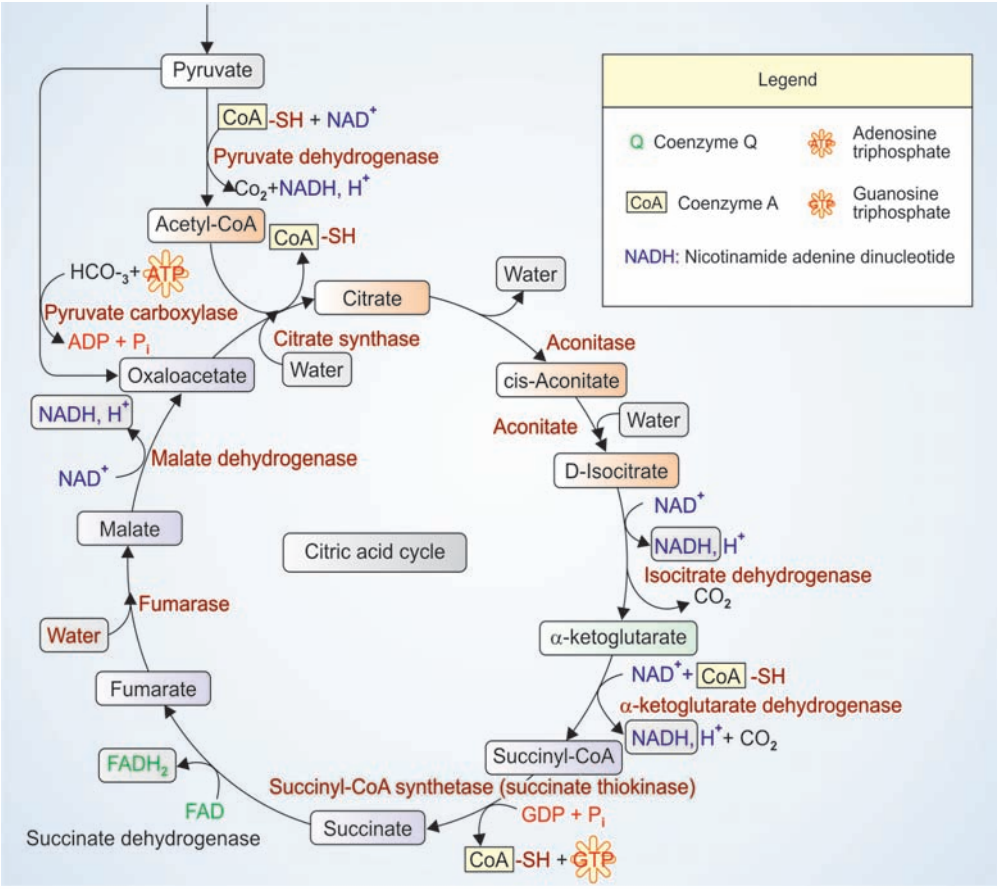


Diagram 1.26

muscle ATP is required for which phosphocreatine is cleaved rapidly to resynthesize the ATP. Role of glycolysis to provide the ATP comes only next followed by TCA cycle.

[Ref. Harper's Illustrated Biochemistry, 28th ed, Chapter 11; page 95]

[Voet and Voet Biochemistry, Chapter 27, page 1092]

Q 39. Decreased glucose concentration in hepatic cells triggers all of the following *except:* ***(AI 2012)***

a. Increased glucagon levels in blood
b. Activation of fructose-2,6-biphosphatase
c. Inhibition of phosphofructokinase-2
d. Increased fructose-2,6-biphosphate levels

Ans. d: Increased fructose-2,6-biphosphate levels

Decreased glucose level leads to increased level of glucagon. (So, option A is the right statement.)

Glucagon inhibits activity of PFK-2, and stimulates the activity of fructose-2,6-biphosphatase. (So, options B and C are right statements.)

Activation of fructose-2,6-biphosphatase leads to **decreased** level of fructose-2,6-biphosphate levels.

Q 40. Acetyl CoA can be converted into all of the following *except*:

(AI 2009, AIIMS Nov 2011)

a. Glucose
b. Fatty acids
c. Cholesterol
d. Ketone bodies

Ans. a: Glucose

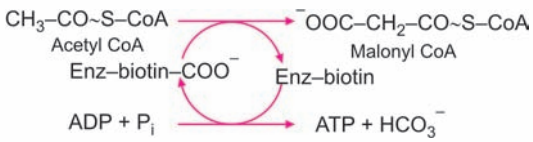
Acetyl CoA cannot synthesize glucose as conversion of acetyl CoA to pyruvate is not possible, due to irreversible nature of the enzyme pyruvate dehydrogenase.

Acetyl CoA is the precursor molecule for the synthesis of fatty acid, cholesterol, and ketone bodies.

a. Formation of Fatty Acid from Acetyl CoA

Initial reaction is the carboxylation of acetyl CoA to **malonyl CoA** in the presence of ATP and **acetyl CoA carboxylase.** Bicarbonate as a source of CO_2 is required in the initial reaction for the carboxylation.

Malonyl CoA now acts as a precursor molecule for cyclical reaction of fatty acid synthesis on fatty acid synthase complex occurring in the cytosol.

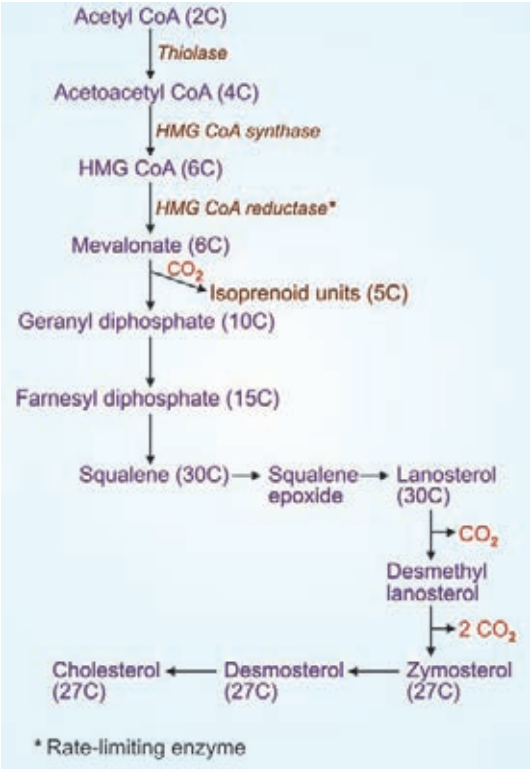


b. Formation of Cholesterol from Acetyl CoA

Acetyl CoA is the precursor molecule for the synthesis of cholesterol.

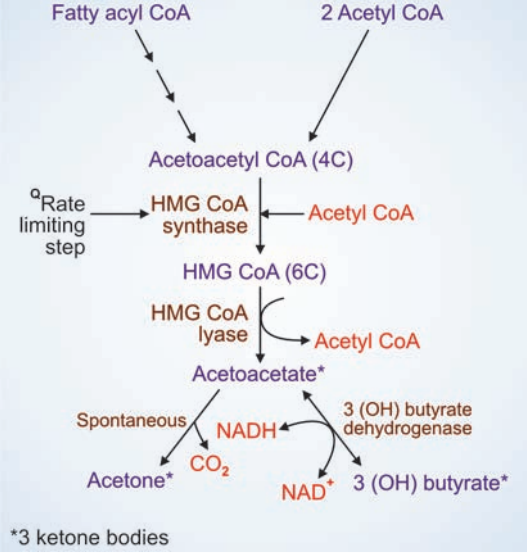
The biosynthesis of cholesterol may be divided into five steps:

1. Synthesis of mevalonate occurs from acetyl CoA.
2. Isoprenoid units are formed from mevalonate by loss of CO_2.
3. Six isoprenoid units condense to form squalene.
4. Squalene cyclizes to give rise to the parent steroid, lanosterol.
5. Cholesterol is formed from lanosterol
   - Initially, two molecules of acetyl CoA condense to form acetoacetyl CoA catalyzed by cytosolic **thiolase.**
   - Acetoacetyl CoA condenses with a further molecule of acetyl CoA catalyzed by **HMG CoA synthase** to form HMG CoA
   - HMG CoA is further reduced to **mevalonate** by **HMG CoA reductase.**



c. Synthesis of Ketone Bodies from Acetyl CoA

Ketogenesis occurs when there is a high rate of fatty acid oxidation in the liver.



Q 41. Which of the following plant components is not fermented by gastrointestinal microorganisms? ***(AIIMS Nov 2011)***

a. Lignin
b. Cellulose
c. Hemicellulose
d. Pectin

Ans. a: Lignin

- Lignin resists attack by most microorganisms, and anaerobic processes tend not to attack the aromatic rings at all.
- Aerobic breakdown of lignin is slow and may take many days.
- Lignin is nature's cement along with hemicellulose to exploit the strength of cellulose while conferring flexibility.
- Lignin is found in all vascular plants, mostly between the cells, but also within the cells, and in the cell walls. It makes vegetables firm and crunchy, and gives us what we call "fiber" in our food.
- **Lignin is an insoluble fiber so it is not fermented**. Pectin is a soluble fiber. Soluble fiber is acted on by the microflora and fermented to produce short chain volatile fatty acid, which improves the colonic environment, regulates immune response, involved in synthesizing some vitamins, helps to lower down the colonization of pathogenic bacteria.

Q 42. During prolonged starvation, the rate of gluconeogenesis depends on: ***(AIIMS Nov 2011)***

a. Increased alanine levels in liver
b. Decreased cGMP in liver
c. ADP in liver
d. Decreased essential fatty acids in liver

Ans. a: Increased alanine levels in liver

- In the fasting state, there is a considerable output of alanine from skeletal muscle, far in excess of its concentration in the muscle proteins that are being catabolized.
- Source of this alanine is the pyruvate. It is formed by transamination of pyruvate produced by glycolysis of muscle glycogen, and is exported to the liver where after transamination back to pyruvate, it is a substrate for gluconeogenesis.
- This **glucose-alanine cycle** (*see* Diagram above) thus provides an indirect way of utilizing muscle glycogen to maintain blood glucose in the fasting state. The ATP required for the hepatic synthesis of glucose from pyruvate is derived from the oxidation of fatty acids.

Q 43. The 40 nm gap in-between adjacent tropocollagen molecule in collagen which serve as the site of bone formation is occupied by which of the following moieties? ***(AIIMS Nov 2011)***

a. Carbohydrate
b. Ligand moiety
c. Ca^{++}
d. Fe^{+++}

Ans. c: Ca^{++} as mineralization starts first in the gap between successive molecule of collagen.

The mechanisms involved in mineralization are not fully understood, but several factors

have been implicated. Alkaline phosphatase contributes to mineralization, but in itself is not sufficient. Small vesicles (matrix vesicles) containing calcium and phosphate have been described at sites of mineralization, but their role is not clear.

Type I: Collagen appears to be necessary, with mineralization being first evident in the gaps between successive molecules.

Recent interest has focused on **acidic phosphoproteins,** such as bone sialoprotein, acting as sites of nucleation. These proteins contain motifs (e.g. poly-Asp and poly-Glu stretches) that bind calcium and may provide an initial scaffold for mineralization. Some macromolecules, such as certain proteoglycans and glycoproteins, can also act as **inhibitors** of nucleation.

Q 44. A 6-month-old child with hepatomegaly cannot maintain a normal blood glucose either by glycogenolysis or gluconeogenesis. He is very likely suffering from a deficiency of which of the following enzymes? ***(AIIMS Nov 2012)***

a. Fructokinase
b. Glucose-6-phosphatase
c. Glucokinase
d. Transketolase

Ans. b: Glucose-6-phosphatase

Deficiency of glucose-6-phosphatase is affecting the conversion of glucose-6-phosphate to free glucose both during gluconeogenesis and glycogenolysis in the liver. This leads to frequent hypoglycemic episodes.

This deficiency of glucose-6-phosphatase enzyme is seen in von Gierke's disease (GSD Type I) .

Manifestations of von Gierke's disease are:

a. Hypoglycemia
b. Lactic acidosis
c. Ketosis
d. Hepatomegaly
e. Hyperuricemia

Q 45. Thiamine deficiency causes decreased energy production because: ***(AIIMS May 2008)***

a. It is required for the process of transamination
b. It is a cofactor for oxidative reduction
c. It is a coenzyme for transketolase in the pentose phosphate pathway.
d. It is a coenzyme for pyruvate dehydrogenase and alpha-ketoglutarate dehydrogenase in the TCA cycle

Ans. d: It is a coenzyme for pyruvate dehydrogenase and alpha-ketoglutarate dehydrogenase in the TCA cycle.

PDH complex enzyme, alpha-ketoglutarate dehydrogenase and branched chain alpha ketoacid decarboxylase, all of them require 5 coenzymes for activity:

a. Thiamine b. Lipoic acid
c. Coenzyme A d. FAD
e. NAD

Deficiency of thiamine impairs pyruvate oxidation as well as TCA cycle and hence decreases energy production.

Q 46. Which of the following statements is true? ***(AIIMS May 2008)***

a. Sulphonamide inhibits folate reductase irreversibly
b. Ethanol inhibits aldehyde dehydrogenase when used in methanol poisoning
c. Acetylcholinesterase inhibition by malathione can be reversed by increasing the level of acetylcholine
d. Fluoroacetate competitively inhibits aconitase.

Ans. d. Fluoroacetate competitively inhibits aconitase.

Q 47. Inulin-like fructosans are used as prebiotics as they are nondigestible resistance to digestion in upper GIT is due to: *(AI 2010)*

a. Absence of digestive enzyme in the upper GIT
b. Beta configuration of the anomeric C_2
c. Low pH of the stomach
d. Presence of alpha-glycosidic linkage

Ans. b: Beta configuration of the anomeric C_2.

Enzyme responsible to cleave beta bond is absent in human intestine and hence inulin and cellulose are not digestible in GIT lumen.

(**Inulin:** β-1,2-glycosidic bond; cellulose: β-1,4-glycosidic bond).

Q 48. Which of the following pathways is not producing ATP? *(AI 2009)*

a. Glycolysis
B. TCA cycle
c. Fatty acid oxidation
d. HMP shunt pathway

Ans. d: HMP shunt pathway

HMP shunt pathway is not responsible for ATP production. It is meant for NADPH and ribose production.

Glycolysis, TCA cycle and fatty acid oxidation all are responsible for ATP production.

Q 49. Within the RBC, hypoxia stimulates glycolysis by which of the following regulating pathways?

a. Hypoxia stimulates pyruvate dehydrogenase by increased 2,3-bisphosphoglycerate
b. Hypoxia inhibits hexokinase
c. Hypoxia stimulates release of all glycolytic enzyme from band 3 of RBC membrane
d. Activation of regulatory enzyme by high pH

Ans. c: Hypoxia stimulates release of all glycolytic enzyme from band 3 of RBC membrane.

In cancer cell during hypoxia cell releases HIF-1(hypoxia induced transcription factor-1) which increases transcription of glycolytic enzyme, GLUT-1, GLUT-3 and VEGF.

Q 50. All of the following pathways occur in mitochondria *except*:

a. TCA cycle
b. Glycogenolysis
c. Fatty acid oxidation
d. ETC

Ans. b: Glycogenolysis

Glycogenolysis is a cytosolic process.

- TCA cycle, fatty acid oxidation take place in mitochondrial matrix.
- Electron transport chain occurs at inner mitochondrial membrane.
- Gluconeogenesis, heme synthesis, urea synthesis are the pathways which are partly mitochondrial and partly cytosolic.

Q 51. Thiamine requirement increases in excessive intake of: *(AIIMS May 2009)*

a. Carbohydrate
b. Fat
c. Lecithin
d. Amino acid

Ans. a: Carbohydrate

Thiamine is required for oxidation of glucose, so excess consumption of the glucose leads to increased demand of the thiamine. In a similar fashion requirement of vitamin B_6 (pyridoxine) increases with increase in protein content of the food.

Q 52. Which of the following statements about thiamine is true? *(AIIMS Nov 2008)*

a. It is a coenzyme of lactate dehydrogenase
b. Its deficiency is associated with scurvy
c. Its coenzyme function is done by thiamine monophosphate
d. It is a coenzyme for pyruvate dehydrogenase and alpha-ketoglutarate

Ans. d: It is a coenzyme for pyruvate dehydrogenase and alpha-ketoglutarate.

Q 53. First substrate of TCA cycle is: *(AIIMS May 2007)*

a. Pyruvate b. Glycine
c. HCl d. Lipoprotein

Ans. a: Pyruvate

Best possible answer in the above question is pyruvate. Though strictly speaking pyruvate is not the substrate of the TCA cycle. First substrate of the TCA cycle is oxaloacetate.

Q 54. All take place in mitochondria *except*:

a. Fatty acid oxidation
b. EMP pathway
c. Electron transport chain
d. Citric acid cycle

Ans. b: EMP pathway

Embden-Meyerhof pathway is the other name of glycolysis. This is a cytosolic pathway.

Q 55. After overnight fasting, levels of glucose transporters reduced in: *(AIIMS Nov 2009)*

a. Brain b. RBC
c. Adipocytes d. Hepatocyte

Ans. c: Adipocytes

Q 56. Mucopolysaccharidoses are caused by:

a. An increased rate of synthesis of proteoglycans
b. Defects in the degradation of proteoglycans
c. The synthesis of polysaccharides with an altered structure
d. An insufficient amount of proteolytic enzymes

Ans. b: Defects in the degradation of proteoglycans

Q 57. Aggrecan is:

a. Meant for platelet aggregation
b. For adhesions of cells to basement membrane
c. For adhesion of fibrinogen receptors to plate
d. Proteoglycan found in cartilage

Ans. d: Proteoglycan found in cartilage

Q 58. Regarding HMP shunt, all of the following are true *except*: *(AI 2007)*

a. Occurs in the cytosol
b. No ATP is produced in the cycle
c. It is active in adipose tissues, liver, gonads
d. Oxidative phase generates NADPH and non-oxidative phase generates pyruvate

Ans. d: Oxidative phase generates NADPH and non-oxidative phase generates pyruvate.

- HMP shunt pathway occurs in the cytosol, in which glucose is oxidised. This is important for generation of ribose and NADPH.
- It occurs in all the cell of the body, but in certain organs where reductive biosynthesis occurs, this pathway occurs to larger

extent. Such organs are liver, adipose tissue, adrenal glands, gonads, lactating mammary gland, etc.

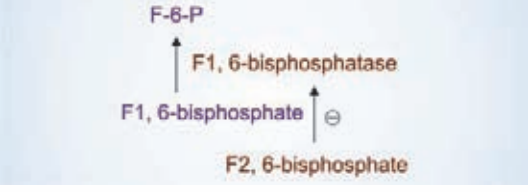
- It has got no energy value as it is not involved in ATP production.
- Oxidative phase of this pathway is responsible for production of **NADPH** and non-oxidative phase is responsible for various intermediate productions, most important of which is **ribose**, involved in purine and pyrimidine biosynthesis.

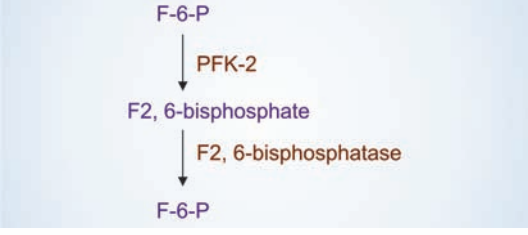
Q 59. A genetic disorder renders fructose-1,6-bisphosphatase in the liver less sensitive to regulation by fructose-2, 6-bisphosphate. All of the following metabolic changes are observed in this disorder *except:* ***(AI 2004)***

a. Level of fructose-1,6-bisphosphate is higher than normal
b. Level of fructose-1,6-bisphosphate is lower than normal
c. Less pyruvate will be formed
d. Less ATP will be generated

Ans. a: Level of fructose-1,6-bisphosphate is higher than normal

Refer to the following diagram





Fructose 2,6-bisphosphate has got inhibitory effect on fructose 1,6-bisphosphatase enzyme. If the genetic disease is rendering fructose 1,6-bisphosphatase enzyme less sensitive by fructose 2,6-bisphosphate, in that case fructose 1,6-bisphosphatase enzyme will act more, reducing level of fructose 1,6-bisphosphate molecule. So,

Option a: Will not be seen, and hence it is the answer of the question.

Option b: Fructose 1,6-bisphosphate level is going to be lower than normal.

Option c: Gluconeogenesis will be upregulated so, pyruvate will be less.

Option d: Gluconeogenesis is the energy consuming process and so ATP will be consumed in this case and level of ATP will be reduced.

Q 60. Decreased glycolytic activity impairs oxygen transport by hemoglobin. Reason is: ***(AI 2003)***

a. Reduced energy production
b. Decreased production of 2,3-bisphosphoglycerate
c. Reduced synthesis of hemoglobin
d. Low level of oxygen

Ans. b: Decreased production of 2,3-bisphosphoglycerate

2,3-Bisphosphoglycerate is produced during glycolysis within RBC in Rapoport-Luebering cycle. 2,3-Bisphosphoglycerate is an important allosteric modifier of hemoglobin O_2 saturation and desaturation. This shifts O_2 dissociation curve to the right. During decreased glycolytic activity, decreased production of 2,3-bisphosphoglycerate is responsible for increased O_2 affinity to the Hb and decreased dissociation from it leading to impaired O_2 delivery at the tissue level.

Q 61. Regarding conversion of pyruvate to acetyl CoA and CO_2, true statement is:

a. Reversible reaction
b. Lipoic acid is required
c. Activated when PDH complex is phosphorylated
d. Cytosolic reaction

Ans. b: Lipoic acid is required

PDH reaction is irreversible reaction. It is active in dephosphorylated form. This reaction takes place within the mitochondria.

Q 62. Decreased consumption of acetyl CoA in the TCA cycle occurs in which of the following?

a. A low ATP/ADP ratio
b. A low GTP/GDP ratio
c. A low NAD/NADH ratio
d. A low NADH/NAD ratio

Ans. c: A low NAD/NADH ratio

Low NAD/NADH ratio limits the rate of NAD requiring dehydrogenases.

A low ATP/ADP, GTP/GDP ratio stimulate the cycle.

Q 63. Enzyme involved in catabolism of fructose to pyruvate is:

a. Glyceraldehyde-3-phosphate dehydrogenase
b. Phosphoglucomutase
c. Lactate dehydrogenase
d. Glucokinase

Ans. a: Glyceraldehyde-3-phosphate dehydrogenase

- This enzyme is very important for converting glyceraldehyde-3-phosphate to 1,3-bisphosphoglycerate during first step of oxidoreduction phase of glycolysis.
- Phosphoglucomutase is involved in glycogenesis and glycogenolysis for interconversion of glucose-6-phosphate and glucose-1-phosphate.
- Lactate dehydrogenase is involved in interconversion of pyruvate and lactate.
- Glucokinase is needed to metabolise glucose. This enzyme is not needed for metabolising fructose.

Q 64. True statement about glucokinase is:

a. K_m value is higher than normal blood sugar
b. Found exclusively in liver
c. G-6-P inhibits it
d. Has both G-6-phosphatase and pyruvate kinase activity

Ans. a: K_m value is higher than the normal blood sugar

Glucokinase is an isoenzyme of hexokinase and is found in liver and β cell of the pancreas. It has got low affinity (high K_m) for glucose and so is able to remove glucose from blood only when glucose is more than 100 mg/dl. Glucose-6-phosphate has got no effect on action of glucokinase. Glucose-6-phosphate has got inhibitory effect on hexokinase activity.

Q 65. In glycolysis, the first committed step is catalysed by: ***(AIIMS Dec 97)***

a. 2, 3-BPG kinase
b. Glucokinase
c. Hexokinase
d. Phosphofructokinase

Ans. d: Phosphofructokinase

- Committed step is that step of the pathway, the product of which is utilized in the same pathway alone and no other pathway utilizes it.
- In glycolysis, PFK-1 converts fructose-6-phosphate to fructose-1,6-bisphosphate, which is destined only for glycolysis and no other pathway.

- Action of hexokinase and glucokinase converts glucose to glucose-6-phosphate. Glucose-6-phosphate has got many additional fates also, in addition to entering in glycolysis. So, the step catalysed by phosphofructokinase is the committed step of glycolysis.

Q 66. In well-fed state, acetyl CoA obtained from the diet is least used for the synthesis of:

a. Palmityl CoA
b. Citrate
c. Acetoacetate
d. Oxalosuccinate

Ans. c: Acetoacetate

- Acetoacetate is the ketone body which is synthesized during fatty acid oxidation in starvation.
- In well-fed state acetyl CoA is rather used for fatty acid synthesis. (Palmityl CoA is a fatty acid.)
- Acetyl CoA is used in the TCA cycle for energy production, citrate and oxalosuccinate are intermediate during TCA cycle.

Q 67. Pyruvate can be converted directly to all of the following *except*:

a. Phosphoenol pyruvate
b. Alanine
c. Acetyl CoA
d. Lactate

Ans. a: Phosphoenol pyruvate

- For the conversion of pyruvate to phosphoenol pyruvate, pyruvate has to undergo carboxylation and decarboxylation reactions by pyruvate carboxylase and phosphoenol pyruvate carboxykinase respectively (see gluconeogenesis steps).
- Pyruvate may directly get converted to alanine by transamination reaction.
- Pyruvate may get directly converted to acetyl CoA by pyruvate dehydrogenase complex (PDH complex).
- Pyruvate may get converted to lactate by LDH enzyme.

Q 68. The activity of pyruvate carboxylase is dependent upon which positive allosteric effector? *(Delhi 09)*

a. Succinate
b. Acetyl CoA
c. AMP
d. Isocitrate

Ans. b: Acetyl CoA

Acetyl CoA derived from fatty acid oxidation is an important positive allosteric activator of pyruvate carboxylase enzyme. So, in condition of starvation when there is excessive fatty acid oxidation, the acetyl CoA produced by fatty acid oxidation acts as a stimulator of pyruvate carboxylase enzyme, stimulating gluconeogenesis.

Q 69. Insulin causes lipogenesis by all *except*: *(AIIMS May 08)*

a. Increasing acetyl CoA carboxylase activity
b. Increases the transport of glucose into the cell
c. Inhibits PDH activity
d. Decreases intracellular cAMP level

Ans. c: Inhibits PDH activity

- Insulin stimulates activity of PDH complex and thus enhances oxidative decarboxylation of pyruvate converting it to acetyl CoA.
- During lipogenesis insulin stimulates acetyl CoA carboxylase activity and thus stimulates lipogenesis.
- Insulin increases transportation of glucose into the cell by enhancing the recruitment of GLUT to the cell membrane.
- Insulin decreases level of cAMP in the cell by inhibiting the activity of adenylyl cyclase enzyme.

Q 70. The biosynthesis of the enzyme pyruvate carboxylase is repressed by: ***(Delhi 09)***

a. Insulin
b. Cortisol
c. Glucagon
d. Epinephrine

Ans. a: Insulin

Insulin diminishes gluconeogenesis. It does so by repressing the activity of pyruvate carboxylase enzyme.

Q 71. Essential pentosuria is due to defect in:

a. HMP shunt pathway
b. Glycolysis
c. Gluconeogenesis
d. Uronic acid pathway

Ans. d: Uronic acid pathway

- Essential pentosuria is due to deficiency of enzyme converting L-xylulose to xylitol using reducing equivalent from NADPH.
- Also remember: Vitamin C also gets synthesized in the uronic acid pathway.

In humans and other primates, as well as in guinea pigs, bats, some birds and fishes, ascorbic acid cannot be synthesized because of the **absence of L-gulonolactone oxidase.**

Q 72. After an overnight fast, levels of glucose transporter are reduced in: ***(AI 09, AIIMS 2010)***

a. Brain cell
b. Hepatocyte
c. Adipocyte
d. RBCs

Ans. c: Adipocyte

Insulin is needed for GLUT mediated uptake of glucose in skeletal muscle, cardiac muscle and adipose tissue via GLUT-4. So, in these organs the expression of GLUT will be affected after an overnight fast.

Brain cells, liver cells and RBC do not require insulin for glucose transportation.

Q 73. Glucose can be synthesized from all of the following *except*: ***(AIIMS 97)***

a. Acetoacetate
b. Lactic acid
c. Glycerol
d. Amino acid

Ans. a: Acetoacetate

Ketone body cannot synthesize glucose. The reason is that the conversion of acetyl CoA to pyruvate is irreversible.

Lactic acid, glycerol and glucogenic amino acid all can synthesize glucose.

Q 74. Factor common to both glycolysis and gluconeogenesis is:

a. Phosphofructokinase
b. Fructose-2,6-bisphosphate
c. Hexokinase
d. Glucose-6-phosphatase

Ans. b: Fructose-2,6-bisphosphate

Phosphofructokinase and hexokinase are the enzymes important in glycolysis alone, while glucose-6-phosphatase is the enzyme which is utilised in gluconeogenesis. Glucose-6-phosphatase is also used in glycogenolysis in the liver. This enzyme is not used in glycolysis.

So, the answer of the above question is fructose-2,6-bisphosphate as it has got effect both on PFK-1 and on frucose-1,6-bisphosphatase enzyme.

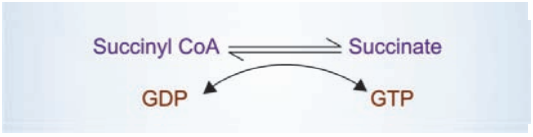
Fructose 2,6-bisphosphate is positive allosteric modifier of PFK-1 and it is an negative allosteric modifier of fructose 1,6-bisphosphatase enzyme.

Q 75. Substrate level phosphorylation in TCA cycle occurs at: ***(AI 2002)***

a. Succinyl CoA to succinate
b. Fumarate to malate
c. Succinate to fumarate
d. Acetoacetate to α-KG

Ans. a: Succinyl CoA to succinate

In TCA cycle substrate level phosphorylation occurs only once at the step catalysed by succinate thiokinase.



Animal cells have two isoenzymes of succinyl CoA synthetase. One specific for ADP and other for GDP. The GTP formed by succinyl CoA synthetase can donate its terminal phosphoryl group to ADP to form ATP in a reversible reaction catalyzed by nucleoside diphosphate kinase.

$$GTP + ADP = GDP + ATP$$

Thus, the net result of activity of either isoenzyme of succinyl CoA synthetase is conservation of energy as ATP *(Lehninger 5th ed, pg. 627).*

Q 76. Regarding proteoglycans, which of the following statements is wrong?

(AI 2007)

a. Chondroitin sulfate is a proteoglycan
b. They hold less water
c. They are made up of sugar and amino acids
d. They carry charge

Ans. b: They hold less water

- Proteoglycans are complex structure making an important component of extracellular matrix.
- Proteoglycans are proteins that contain covalently linked glycosaminoglycans.
- Examples are syndecan, betaglycan, serglycin, perlecan, aggrecan, versican, decorin, biglycan, and fibromodulin.
- It contains a long strand of hyaluronic acid (one type of GAG) to which link proteins are attached noncovalently.
- GAG as such is made up of repeating disaccharide units, one component of which is uronic acid and another is amino sugar (option c). Examples of GAG are hyaluronic acid, chondroitin sulfate, keratan sulfates I and II, heparin, heparan sulfate, and dermatan sulfate.

So, even option (a) is wrong, chondroitin sulfate is a GAG not a proteoglycan. But one has to choose one answer, it will be option (b).

GAGs present in the proteoglycans are **polyanions** (option d) and hence bind polycations and cations such as Na^+ and K^+. This latter ability **attracts water** by osmotic pressure into the extracellular matrix and contributes to its turgor.

Q 77. Products produced by action of aldolase on substrate formed from fructose are:

a. Two molecules of dihydroxyacetone phosphate
b. Two molecules of glyceraldehyde-3-phosphate
c. Dihydroxyacetone phosphate and glyceraldehyde-3-phosphate
d. Glyceraldehyde and dihydroxyacetone phosphate

Ans. d: Glyceraldehyde and dihydroxyacetone phosphate

DHAP is utilized after getting converted into glyceraldehyde-3-phosphate in the presence of enzyme phosphotriose isomerase. Glyceraldehyde is also utilized after getting converted into glyceraldehyde-3-phosphate in the presence of triokinase. *(Refer* Diagram 1.23, *page 21.)*

Q 78. Fructokinase reaction produces which of the following intermediates? ***(PGI 98)***

a. Fructose-1-phosphate
b. Fructose-6-phosphate
c. Fructose-1,6-diphosphate
d. Glyceraldehydes and dihydroxyacetone phosphate

Ans. a: Fructose-1-phosphate

First step of fructose metabolism is catalysed by fructokinase and the product is fructose-1-phosphate.

Q 79. Which of the following enzymes does not catalyse decarboxylation reaction? ***(MAHE 04)***

a. Pyruvate dehydrogenase
b. α-ketoglutarate dehydrogenase
c. Phosphoenol pyruvate carboxykinase
d. Pyruvate carboxylase

Ans. d: Pyruvate carboxylase

Pyruvate carboxylase converts pyruvate to oxaloacetate by incorporation of CO_2. So, it is a carboxylation reaction and not the decarboxylation reaction. PDH, α-ketoglutarate dehydrogenase and phosphoenol pyruvate carboxykinase catalyse decarboxylation reaction.

Q 80. True statement regarding phosphofructokinase:

a. Is activated by high concentration of ATP and citrate
b. Uses fructose-1-phosphate as substrate
c. Is the regulated reaction of glycolysis
d. Is inhibited by fructose-2,6-bisphosphate

Ans. c: Is the regulated reaction of glycolysis

- ATP and citrate allosterically inhibit it
- Fructose-6-phosphate is the substrate
- PFK-1 is allosterically stimulated by fructose-2,6-bisphosphate

Q 81. Which enzyme does not act in fructose metabolism?

a. Fructokinase
b. Aldolase A
c. Aldolase B
d. Pyruvate kinase

Ans. b: Aldolase A

Only aldolase B which is found exclusively in liver acts in fructose metabolism. Aldolase which is universal in localization acts on glycolysis. (In glycolysis, aldolase A or aldolase B may be used for splitting fructose-1,6-bisphosphate to DHAP and glyceraldehyde-3-phosphate.)

Q 82. Which of the following is a debranching enzyme? ***(AIIMS 90)***

a. Glycogen synthetase
b. Glucose-6-phosphatase
c. Amylo-1,6-glucosidase
d. Amylo-1,4-1,6-transglycosylase

Ans. c: Amylo-1,6-glucosidase

Debranching enzyme acts during glycogenolysis once phosphorylase and glucan 1,4 → 1,4 transferase has been acted upon glycogen. The last residue of glucose attached to glycogen in 1,6-linkage is removed via action of debranching enzyme (1,6-glucosidase).

Q 83. A 54-year-old male presents with weakness, fatigue, shortness of breath and dizziness. Hb was found to be 6.4 g/dl. RBC shows low lactate production. Which enzyme deficiency is most likely in this patient?

a. Phosphoglucoisomerase
b. Phosphofructokinase
c. Pyruvate kinase
d. Lactate dehydrogenase

Ans. c: Pyruvate kinase

- Out of all the cases showing deficiency of glycolytic enzymes, about 95% of the

patients show the deficiency of pyruvate kinase and 4% exhibit deficiency of phosphoglucoisomerase.

- Most common enzyme to be deficient in hemolytic anemia is the glucose-6-phosphate dehydrogenase, the second most common enzyme to be deficient in a case of hemolytic anemia is the pyruvate kinase.

Q 84. Reaction unique to gluconeogenesis:

a. Lactate → pyruvate
b. Oxaloacetate → phosphoenolpyruvate
c. Phosphoenolpyruvate → pyruvate
d. Glucose-6-phosphate → fructose-6-phosphate

Ans. b: Oxaloacetate → phosphoenolpyruvate

Option a: Seen both in glycolysis and gluconeogenesis.

Option b: Unique to gluconeogenesis.

Option c: Only in glycolysis.

Option d: Seen both in glycolysis and gluconeogenesis.

Q 85. Sudden elevation of cytosolic Ca^{++} during muscle contraction will result in which of the following?

a. Activation of phosphorylase kinase
b. Activation of cAMP-dependent protein kinase
c. Conversion of cAMP to AMP by phosphodiesterase
d. Dissociation of cAMP-dependent protein kinase to its regulatory and catalytic units.

Ans. a: Activation of phosphorylase kinase

Calcium released from sarcoplasmic reticulum binds calmodulin subunit of phosphorylase kinase, thereby activating this enzyme.

Q 86. In starvation, activities of all of the following enzymes are increased *except:*

a. Pyruvate carboxylase
b. Pyruvate kinase
c. PEP carboxykinase
d. Glucose-6-phosphatase

Ans. b: Pyruvate kinase

- In starvation, activities of all enzymes responsible for gluconeogenesis are increased.
- Pyruvate kinase is the enzyme of glycolysis. Activities of enzymes of glycolysis are suppressed in starvation. So, pyruvate kinase activity is suppressed in starvation.
- All other enzymes given in this question are gluconeogenic enzymes whose activity is enhanced in starvation.

Q 87. Which of the following glycolytic enzymes is used in gluconeogenesis?

a. Glucokinase b. Pyruvate kinase
c. Aldolase d. Phosphofructokinase

Ans. c: Aldolase

A reversible enzyme of the glycolysis is used in gluconeogenesis.

- Aldolase is the enzyme which catalyses reversible reaction of glycolysis. So, this enzyme is utilised in gluconeogenesis.
- Glucokinase, pyruvate kinase and phosphofructokinase are enzymes which catalyse irreversible reaction of glycolysis and which are bypassed by different sets of enzymes during gluconeogenesis.

Q 88. At which of the following enzymes catalysed step of the TCA cycle, there occurs incorporation of the water in the intermediate of the TCA cycle?

a. Aconitase b. Citrate synthase
c. Malate dehydrogenase
d. Succinyl CoA synthase

Ans. b: Citrate synthase

- Water is required at citrate synthase step to hydrolyse the thioester bond of the acetyl CoA.
- Aconitase removes water and then adds it back in TCA cycle.
- Malate dehydrogenase removes 2 protons and 2 electrons.

Succinyl CoA synthase catalyses phosphorylation, not the hydrolysis.

Q 89. All the following TCA cycles intermediate may be added or removed by other metabolic pathways *except*:

(PGI)

a. Citrate
b. Fumarate
c. Isocitrate
d. Alpha-ketoglutarate
e. Oxaloacetate

Ans. c: Isocitrate

- Citrate is transported out of the mitochondria to be used as a source of cytoplasmic acetyl CoA.
- Fumarate is produced during degradation of tyrosine and phenylalanine.
- Alpha-ketoglutarate can be formed from glutamate.
- Oxaloacetate may be produced from pyruvate during gluconeogenesis.

Q 90. Inner mitochondrial membrane contains a transporter of:

a. NADH
b. Acetyl CoA
c. ATP
d. NADPH

Ans. c: ATP

Inner mitochondrial membrane contains following transporters:

1. Monocarboxylate transporter
2. Dicarboxylate transporter
3. Tricarboxylate transporter
4. Phosphate transporter
5. Adenine nucleotide translocase (ADP–ATP transporter)
6. Aspartate glutamate transporter
7. Malate alpha-ketoglutarate transporter

Q 91. The first step in liver's metabolism of fructose is:

a. Isomerization of glucose
b. Phosphorylation to fructose-1,6-bisphosphate by ATP
c. Phosphorylation to fructose-6-phosphate by ATP
d. Phosphorylation to fructose-1-phosphate by ATP

Ans. d: Phosphorylation to fructose-1-phosphate by ATP.

This reaction is catalysed by fructokinase. Deficiency of fructokinase leads to essential fructosuria.

Q 92. When blood glucagon rises, which of the following hepatic enzymes activity falls?

a. Adenylate cyclase
b. Protein kinase
c. 6-Phosphofructo-2-kinase (PFK-2)
d. Fructose-1,6-bisphosphatase

Ans. c: 6-Phosphofructo-2-kinase (PFK-2)

When glucagon level rises, adenylate cyclase is activated producing cAMP which activates protein kinase, which inactivates 6-phosphofructo-2-kinase (PFK-2).

Q 93. All are true about glucuronic acid *except*:

a. It is a charged molecule at the physiological pH
b. As a UDP derivative, it can be decarboxylated to a component used in proteoglycan synthesis
c. It is a precursor of ascorbic acid in humans
d. It can ultimately be converted to xylulose-5-phosphate and thus enters in pentose phosphate pathway.

Ans. c: It is a precursor of ascorbic acid in humans.

- Man does not make ascorbic acid.
- The **charged acid group** enhances water solubility, which is a major physiological role for glucuronic acid, for example, bilirubin metabolism.
- Decarboxylation of UDP glucuronic acid gives rise to UDP xylose which is involved in proteoglycan synthesis.
- Reduction of d-glucuronic acid to l-gluconic acid leads to ascorbate as well as xylulose-5-phosphate for pentose phosphate pathway.

Q 94. Glycosaminoglycans:

a. Are the carbohydrate portion of the glycoprotein
b. Contain large segment of a repeating unit typically consisting of a hexosamine and a uronic acid
c. Always contain sulfate
d. Exist only in two forms

Ans. b: Contain large segment of a repeating unit typically consisting of a hexosamine and a uronic acid.

- This is a major distinction from the glycoprotein, which by definition do not have repeating units of hexosamine and uronic acid.
- They are carbohydrate portion of the proteoglycan, not the glycoprotein.
- Hyaluronate does not contain sulfate.
- Exist in 6 different classes, e.g. heparin, heparan sulfate, keratan sulfates I and II, dermatan sulfate, chondroitin sulfate.

Q 95. You are working in a PHC and have to send a sample for blood glucose estimation, which of the following anti-coagulants will you use?

(AIIMS Nov 2006, 2011)

a. EDTA
b. Heparin
c. Potassium oxalate + NaF
d. Trisodium citrate

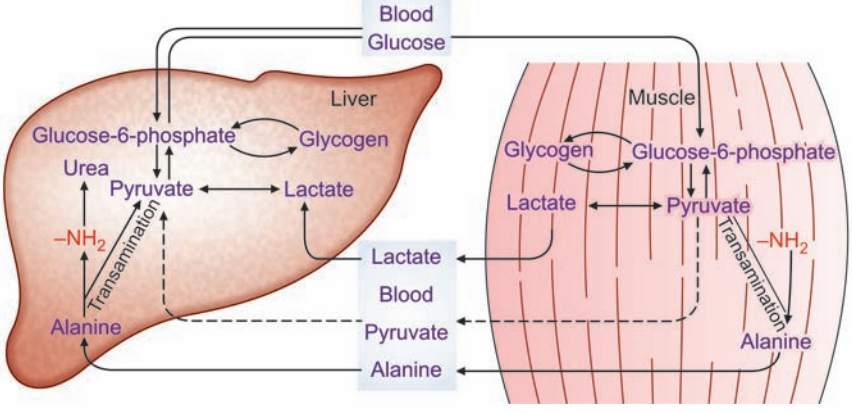
Ans. c: Potassium oxalate + NaF

They are anticoagulant and antiglycolytic agents and used for blood collection for blood glucose estimation. Potassium oxalate is anticoagulant and NaF is antiglycolytic.

Q 96. During prolonged starvation, the rate of gluconeogenesis depends on:

(AIIMS Nov 2011)

a. Increased alanine levels in liver
b. Decreased cGMP in liver
c. ADP in liver
d. Decreased essential fatty acids in liver



Ans. a: Increased alanine levels in liver

- In the fasting state, there is a considerable output of alanine from skeletal muscle, far in excess of its concentration in the muscle proteins that are being catabolized. It is formed by transamination of pyruvate produced by glycolysis of muscle glycogen, and is exported to the liver. In the liver after transamination, alanine is converted back to pyruvate, which is a substrate for gluconeogenesis.
- This glucose-alanine cycle thus provides an indirect way of utilizing muscle glycogen to maintain blood glucose in the fasting state. The ATP required for the hepatic synthesis of glucose from pyruvate is derived from the oxidation of fatty acids.

Q 97. Acetyl CoA is necessary for:

a. Amino acid
b. Fatty acid synthesis
c. Glucose storage
d. All of the above

Ans. b: Fatty acid synthesis

Acetyl CoA is needed for:
a. TCA cycle
b. Fatty acid synthesis
c. Cholesterol synthesis
d. Ketone body synthesis

Q 98. *In vivo* control of citric acid cycle is effected by: *(PGI 01)*

a. Acetyl CoA
b. Coenzyme A
c. ATP
d. Citrate
e. NADH

Ans. a, b, c, d, e

TCA cycle is tightly regulated at 2 levels:
a. PDH complex reaction
b. Citrate synthase reaction

Other places of control:
c. ICD
d. Alpha-ketoglutarate dehydrogenase

Level of control of TCA cycle		
Enzyme	*Activator*	*Inhibitor*
PDH complex	AMP CoA NAD^+ Ca^{++}	ATP Acetyl CoA NADH Fatty acid
Citrate synthase	ADP	NADH Succinyl CoA Citrate ATP
ICD	ADP Ca^{++}	ATP
α-Ketoglutarate dehydrogenase	Ca^{++}	Succinyl CoA NADH

Q 99. Total number of dehydrogenase in Krebs cycle is:

a. 3
b. 2
c. 4
d. 5

Ans. c: 4

There are 4 dehydrogenases in Krebs cycle
1. ICD
2. αKD
3. SCD
4. MDH

Q 100. McArdle's disease is due to the deficiency of:

a. Glucose-1-phosphatase
b. Glucose-1, 6-diphosphatase
c. Myophosphorylase
d. Glucose-6-phosphatase

Ans. c: Myophosphorylase

This disease is characterized by poor exercise tolerance, abnormal high glycogen (2.5–4%), low level of blood lactate even after exercise.

Q 101. NADPH is generated by the action of:

a. Glucose-1-phosphatase
b. Glucose-1,6-diphosphatase
c. Glucose-6-phosphate dehydrogenase
d. Myophosphorylase

Ans. c: Glucose-6-phosphate dehydrogenase

Q 102. Cyclic AMP accelerates glycogenolysis by:

a. Converting inactive protein kinase to active protein kinase
b. Acting on glucose-1-phosphatase
c. Acting on glucose-6-phosphatase
d. All of the above

Ans. a: Converting inactive protein kinase to active protein kinase

cAMP dependent protein kinase in turn phosphorylate phosphorylase kinase which in turn phosphorylates, phosphorylase enzyme favouring glycogenolysis.

Q 103. Galactosaemia commonly is due to deficiency of: ***(PGI 95)***

a. Galactose-1-phosphate uridyl transferase
b. Galactose-1-phosphatase
c. Glucose-1-phosphatase
d. Glucose-6-phosphatase

Ans. a: Galactose-1-phosphate uridyl transferase

Most common galactosemia is classical galactosemia. This is due to deficiency of enzyme galactose-1-phosphate uridyl transferase.

Q 104. Adrenaline acts on which enzyme in glycogenolysis? ***(AI 99)***

a. Glucokinase
b. Hexokinase
c. Phosphorylase
d. Glucose diphosphatase

Ans. c: Phosphorylase

Q 105. What is the major fate of glucose-6-phosphate in the tissue in the fed state? ***(AI 97)***

a. Isomerisation to fructose-6-phosphate
b. Hydrolysis to glucose
c. Conversion to glycogen
d. Conversion to ribulose-6-phosphate

Ans. c: Conversion to glycogen

In well-fed state the major fate of glucose-6-phosphate is storage in the form of glycogen

Q 106. Gluconeogenesis does not occur significantly from …. in humans. ***(AI 96)***

a. Lactate
b. Fatty acids
c. Pyruvate
d. Amino acid

Ans. b: Fatty acids

In human major fatty acid which is oxidized is even chain fatty acid, resulting in formation of acetyl CoA. Acetyl CoA does not produce glucose.

Q 107. Activity of which of the following is not decreased in diabetic mellitus?

a. Glucokinase
b. Acetyl CoA carboxylase
c. Pyruvate carboxylase
d. All of the above

Ans. c: Pyruvate carboxylase

Diabetes is characterized by low level of insulin.

List of enzymes, gene expression of which is regulated by insulin.

Enzymes where gene expression is increased by insulin

- HK II
- HK IV
- PFK-1
- Pyruvate kinase
- PFK-2/F2, 6-Bisphosphatase
- G6PD
- 6-phosphogluconate dehydrogenase
- PDH

- Acetyl CoA carboxylase
- Malic enzyme
- ATP citrate lyase
- FA synthase complex
- Acyl CoA glycerol transferase
- Stearoyl CoA dehydrogenase

Enzymes where gene expression is decreased by insulin

- Phosphoenol pyruvate carboxykinase
- Glucose-6-phosphatase

(Lehninger 5th ed, page 591)

Q 108. All are common in diabetes and starvation *except*:

a. Increased gluconeogenesis
b. Increased glycogen degradation
c. Increased fatty acid mobilization from adipose tissue
d. Cholesterol synthesis

Ans. d: Cholesterol synthesis

Q 109. Muscle glycogen is mainly utilized for supplying energy to:

a. Liver b. Heart
c. Brain d. Muscle

Ans. d: Muscle

Muscle lack glucose-6-phosphatase enzyme. This results in accumulation of glucose-6-phosphate within the muscle cell, as glucose-6-phosphate does not cross the cell wall.

This glucose-6-phosphate is utilized in glycolysis within the muscle itself.

Q 110. Which of the following is not a product of HMP shunt? *(PGI 2004)*

a. NADPH
b. Fructose-6-phosphate
c. Sedoheptulose-7-phosphate
d. Glyceraldehyde-3-phosphate

Ans. c: Sedoheptulose-7-phosphate

As it is the intermediate

Q 111. In which of the following tissues, glycogen is incapable of contributing directly to blood glucose? *(AI 2008)*

a. Liver b. Muscle
c. Both d. None

Ans. b: Muscle

See the explanation of previous question.

Q 112. An enzyme not involved in glycolysis is:

a. Enolase
b. Phosphoglyceromutase
c. Aldolase
d. Glucose-6-phosphate dehydrogenase

Ans. d: Glucose-6-phosphate dehydrogenase

Glucose-6-phosphate dehyrogenase (G6PD) is the rate limiting enzyme of HMP shunt pathway.

Q 113. Which of the following has no free aldehyde or ketone group?

a. Fructose
b. Maltose
c. Sucrose
d. Galactose

Ans. c: Sucrose

Sucrose is a disaccharide.

Q 114. Chitin is a:

a. Polypeptide b. Polysaccharide
c. Fatty ester d. None of the above

Ans. b: Polysaccharide

Chitin is a homopolymer made up of repeating units of N-acetyl D-glucosamine.

Q 115. Phosphorylase b is maintained in an inactivated state by: *(AI 08, AIIMS 08)*

a. ATP b. cAMP
c. Calcium d. Insulin

Ans. d: Insulin

Q 116. Specific poison for succinate dehydrogenase is: *(Delhi 03, Rohtak 04, Raj 04)*

a. Arsenic
b. Cyanide
c. Malonate
d. Fluoride

Ans. c: Malonate

Malonate is a competitive inhibitor of succinate dehydrogenase enzyme.

Q 117. The first product of glycogenolysis is:

a. Glucose-6-phosphate
b. Glucose-1,3-diphosphate
c. Glucose-1-phosphate
d. Fructose-1-phosphate

Ans. c: Glucose-1-phosphate

Q 118. Which of the following is not a polymer of glucose?

a. Glycogen
b. Cellulose
c. Amylose
d. Inulin

Ans. d: Inulin

Inulin is a polymer of insulin

Q 119. Inhibition of glycolysis by O_2 is known as:

a. Crabtree effect
b. Pasteur effect
c. Hill reaction
d. Gluconeogenesis

Ans. b: Pasteur effect

(Refer to page 9)

Q 120. The reducing ability of a carbohydrate is due to the presence of:

a. A hemiacetal
b. Cupric ions
c. A free carboxyl
d. A free hydroxyl

Ans. a: A hemiacetal

Q 121. Pyruvate dehydrogenase contains all *except*: *(AI 96, TN 98)*

a. Biotin
b. NAD
c. FAD
d. CoA

Ans. a: Biotin

Biotin is a prosthetic group of carboxylase enzyme.

Q 122. In starvation, nitrogen is carried from muscle to liver and kidney by:

a. Alanine
b. Aspartic acid and sulfate
c. Glycine
d. Asparagine

Ans. a: Alanine

During starvation, in the muscle major keto acid which accepts the amino group is the pyruvate. This results in the formation of alanine.

Q 123. Pompe's disease is due to deficiency of which enzyme?

a. Branching enzyme
b. Glucose-6-phosphatase
c. Acid maltase deficiency (type II GSDs)
d. Muscle phosphorylase

Ans. c: Acid maltase deficiency (type II GSD)

Pompe's disease is type II GSD.

Liver is spared in this disease. Other GSDs where liver is spared are: V, VII

Q 124. Muscles are not involved in which glycogen storage disease?

a. I
b. II
c. III
d. IV

Ans. a: I

Other GSDs where muscle is spared are: types 0, Ia, Ib, IIIb, VI, VIII, IX.

Q 125. All of the following enzymes are involved in neoglucogenesis *except*:

a. Phosphoglycerate kinase
b. Fructose-1,6-bisphosphatase
c. Phosphoglucomutase
d. Pyruvate carboxylase
e. Isomerase

Ans. c: Phosphoglucomutase

Phosphoglucomutase is the enzyme which is needed in glycogenesis and glycogenolysis.

Q 126. Cyclic AMP increases the rate of glycogenolysis by:

a. Promoting the formation of phosphorylated form of glycogen phosphorylase
b. Acting as a cofactor for glycogen phosphorylase
c. Furnishing phosphate for the phosphorylysis of glycogen
d. Acting as a precursor of 5′AMP which is a cofactor for a glycogen phosphorylase

Ans. a: Promoting the formation of phosphorylated form of glycogen phosphorylase

Q 127. Which of the following is an aldose?

a. Ribulose
b. Ribose
c. Erythrulose
d. Dihydroxyacetone

Ans. b: Ribose

Rest all others are ketose.

Q 128. Composition of hyaluronic acid is:

a. N-acetyl glucosamine + D-glucosamine acid
b. N-acetyl glucosamine + D-glucuronic acid
c. N-acetyl glucosamine + sulfated glucosamine acid
d. N-acetyl glucosamine + iduronic acid

Ans. b: N-acetyl glucosamine + D-glucuronic acid

Hyaluronic acid does not contain sulphate, and the uronic acid which is present in hyaluronic acid is glucuronic acid.

Q 129. Fructose-2,6-bisphosphate is:

a. Intermediate of glycolysis
b. Positive allosteric regulation of phosphoglucomutase
c. Negative allosteric regulation of PFK-1
d. Positive allosteric regulation of PFK-1

Ans. d: Positive allosteric regulation of PFK-1

Fructose 2,6-bisphosphate is positive allosteric modifier of PFK-1.

Fructose-2,6-bisphosphate is negtive allosteric modifier of fructose 1,6-bisphosphatase enzyme.

Q 130. Positive signals for glycogen breakdown include all the following *except:*

a. Cyclic AMP
b. Blood glucose
c. Epinephrine
d. Ca^{++}

Ans. b: Blood glucose

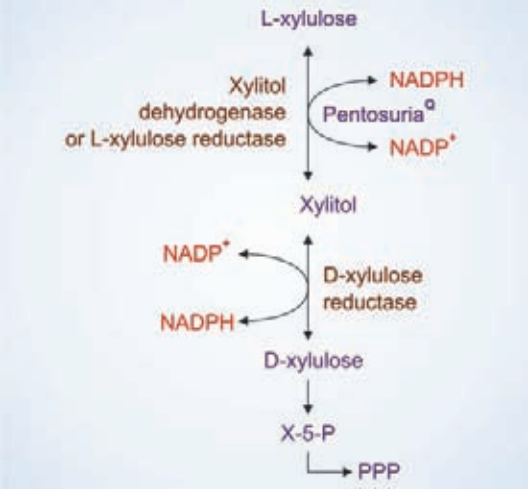
Blood glucose is negative signal.

Q 131. Essential pentosuria is due to defect in:

a. HMP pathway
b. Glycolysis
c. Gluconeogenesis
d. Uronic acid pathway

Ans. d: Uronic acid pathway

Essential pentosuria is due to xylitol dehydrogenase deficiency.



Q 132. Hemolytic anemia is seen most commonly due to:

a. Pyruvate kinase
b. Phosphofructokinase I
c. Phosphoenolpyruvate carboxykinase
d. Glucose-6-phosphate dehydrogenase

Ans. d: Glucose-6-phosphate dehydrogenase

Hemolytic anemia due to enzyme deficiency
a. G6PD
b. Pyruvate kinase deficiency
c. Phosphoglucomutase deficiency

Q 133. Insulin causes lipogenesis by all *except*:

a. Increasing acetyl-CoA carboxylase activity
b. Increases the transport glucose into the cell
c. Inhibits pyruvate dehydrogenase
d. Decreases intracellular cAMP level

Ans. c: Inhibits pyruvate dehydrogenase

Q 134. The activity of pyruvate carboxylase is dependent upon which of the following positive allosteric effectors?

a. Succinate b. AMP
c. Isocitrate d. Acetyl CoA

Ans. d: Acetyl CoA

Q 135. Which of the following enzymes catalyze the irreversible steps of glycolysis? *(AIIMS May 2013)*

a. Hexokinase pyruvate kinase, fructose-1,6-bisphosphatase
b. Glucokinase, pyruvate kinase, phosphofructokinase
c. Phosphofructokinase, enolase, fructose-1,6-bisphosphatase
d. None of the above

Ans. b: Glucokinase, pyruvate kinase, phosphofructokinase

- Hexokinase/glucokinase, pyruvate kinase, phosphofructokinase catalyze irreversible reaction of the glycolysis.
- Fructose-1,6-bisphosphatase is the enzyme which also catalyses irreversible reaction, but this is the enzyme of gluconeogenesis.
- Enolase is a glycolytic enzyme but it catalyzes reversible reaction.

Q 136. A patient presents with von Gierke's disease and ketosis was detected on investigation. All of the following would be associated findings *except*: *(AIIMS May 2013)*

a. There is hypoglycemia
b. They have low blood sugar levels
c. Oxaloacetate is needed for gluconeogenesis
d. Low fat mobilization

Ans. d: Low fat mobilization

- von Gierke's disease is a GSD type 1 where there is deficiency of glucose-6-phosphatase enzyme which affects liver glycogenolysis.
- This deficiency will lead to low blood sugar and **hypoglycemic** attack.
- Hypoglycemia will enhance gluconeogenesis which will use oxaloacetate.
- Fatty acid will be mobilized from white adipose tissue leading to ketosis.

(Ref: Lippincott 5th ed, page 130)

Q 137. Not an intermediate product of citric acid cycle is: ***(AIIMS May 2014)***

a. Acyl CoA
b. Succinyl CoA
c. Citrate
d. α-ketoglutarate

Ans. a: Acyl CoA

Acyl CoA is activated form of fatty acid. Acyl CoA directly never is a part of citric acid cycle. Once oxidized it producing acetyl CoA, which certainly is utilized in TCA cycle.

Q 138. The enzyme common to both glycogenolysis and glycogenesis: ***(AIIMS May 2014)***

a. Glycogen phosphorylase
b. Glycogen synthase
c. Glucotransferase
d. Carboxykinase

Ans. c: Glucotransferase

During glycogen synthesis α1, 4-α 1, 6-glucotransferase (branching enzyme) and during glycogenolysis α1, 4-α1, 4-glucotransferase (trisaccharide transferase) is needed.

Sometimes on recall basis it is said that the above question was having phosphoglucomutase as a option instead of glucotransferase, in that case the answer of the question will be phosphoglucomutase. Phosphoglucomutase is the enzyme which catalyses following reactions in a reversible fashion.

Glucose-6-phosphate ↔ Glucose-1-phosphate

During glycogen synthesis the equilibrium of reaction is towards the formation of glucose-1-phosphate, and during glycogenolysis, equilibrium of reaction is towards the formation of glucose-6-phosphate.

Q 139. Which of the following enzymes is activated on low insulin/glucagon ratio? ***(Nov 2013)***

a. Pyruvate kinase
b. Glucokinase
c. Hexokinase
d. Glucose-6-phosphatase

Ans. d: Glucose-6-phosphatase

Q 140. All of the following are true about NADPH *except*: ***(Nov 2013)***

a. Produces ATP in RBC
b. Helps in reductive biosynthesis
c. Formed by glucose-6-phosphatase
d. Helps in maintaining membrane structure of RBC

Ans. a: Produces ATP in RBC

NADPH is not responsible for synthesis of ATP in the electron transport chain. Rather it is NADH which forms ATP.

Role of NADPH

a. Reductive biosynthesis
b. Tackle oxidative stress

Main source of NADPH is the HMP shunt pathway, where glucose-6-phosphate dehydrogenase enzyme and 6-phosphogluconate dehydrogenase enzyme synthesize NADPH.

Q 141. A 7-month-old child develops vomiting after fruit juice feeds. She is diagnosed as hereditary fructose intolerance. The enzyme deficient in this disorder is: ***(Nov 2014)***

a. Phosphofructokinase
b. Fructose-1,6-bisphosphatase
c. Hexokinase
d. Aldolase B

Ans. d: Aldolase B

Ref: Kleigman: Nelson Textbook of Paediatrics; 18/e, Chapter 87.3

Hereditary Fructose Intolerance

Deficiency of aldolase B is a severe condition of infants that appears with the ingestion of fructose-containing food and is caused by a deficiency of aldolase B activity in the liver, kidney, and intestine.

The enzyme catalyzes the hydrolysis of fructose-1,6-bisphosphate into triose phosphate and glyceraldehyde phosphate.

The same enzyme also hydrolyzes fructose-1-phosphate.

Deficiency of this enzyme activity causes a rapid accumulation of fructose-1-phosphate and initiates severe toxic symptoms when exposed to fructose.

Q 142. Peroxidase enzyme is used in the estimation of:

a. Hemoglobin
b. Ammonia
c. Creatinine
d. Glucose

Ans. d: Glucose

GOD-POD (glucose oxidase-peroxidase) method is the commonly used method for estimation of glucose in biological fluid. Principle of this test is as follows:

$$\text{D-Glucose} + H_2O + O_2 \xrightarrow{\text{GOD}} \text{D-Gluconic acid} + H_2O_2$$

$$H_2O_2 + 4 - \text{aminoantipyrine} + \text{phenol} \xrightarrow{\text{POD}} \text{Quinoneimine dye} + H_2O$$

Q 143. Assertion (A): Muscle glycogenolysis is not regulated by blood glucose level. Stored glycogen of the muscle is utilised only within the muscle after glycogenolysis.

Reasoning (R): Lack of glucose transport in the muscle sarcolemma is responsible for such phenomenon.

a. A and R both are right but R is not the correct explanation of A
b. A as well as R are right and R is a correct explanation of A
c. A is right but R is not the correct explanation of A
d. A and R both are wrong

Ans. c: A is right but R is not the correct explanation of A

- As the deficiency of enzyme glucose-6-phosphatase in the muscle is responsible for nonconversion of glucose-6-phosphate to glucose, glucose-6-phosphate is not permeable to muscle wall.
- Skeletal muscle has got GLUT-4.

Q 144. Assertion (A): Human cannot synthesize vitamin C.

Reasoning (R): Enzyme L-gulonolactone oxidase is deficient in human and other species.

a. A and R both are right but R is not the correct explanation of A
b. A as well as R are right and R is a correct explanation of A
c. A is wrong but R is a right statement
d. A and R both are wrong

Ans. b: A as well as R are right and R is a correct explanation of A

Human, other primates, guinea pigs, bats, fishes and some birds cannot synthesize vitamin C due to absence of L-gulonolactone oxidase enzyme.

Q 145. Assertion (A): von Gierke's disease is due to the deficiency of glucose-6-phosphatase and is manifested as hyperuricemia, gout and lactic acidosis:

Reasoning (R): Hyperuricemia in von Gierke's disease is 'solely' due to accumulation of uric acid due to underexcretion of uric acid in low pH due to lactic acidosis.

a. A and R both are right but R is not the correct explanation of A

b. A as well as R are right and R is a correct explanation of A
c. A is right but R is a wrong statement
d. A and R both are wrong

Ans. c: A is right but R is a wrong statement

Hyperuricemia occurs in von Gierke's disease. Reasons for hyperuricemia are multiple.

1. Shunting of excess glucose-6-phosphate in the HMP shunt pathway, leading to excess ribose production, which synthesizes excess purine nucleotide which after degradation leads to excess uric acid production.
2. Low pH in this disorder impairs excretion of uric acid in the urine leading to its accumulation and gout.

Q 146. Assertion (A): Most common enzyme to be deficient in hemolytic anemia is pyruvate kinase.

Reasoning (R): Pyruvate kinase is the most common enzyme to be deficient in glycolysis.

a. A and R both are right but R is not the correct explanation of A
b. A as well as R are right and R is a correct explanation of A
c. A is right but R is a wrong statement
d. A is wrong but R is a right statement

Ans. d: A is wrong but R is a right statement

Most common enzyme to be deficient in hemolytic anemia is glucose-6-phosphate dehydrogenase (G6PD).

Most common enzyme to be deficient in glycolysis is the pyruvate kinase.

Q 147. Assertion (A): Excess shunting of glucose in the sorbitol pathway is one of the reasons for diabetic cataract.

Reasoning (R): Sorbitol path converts glucose into galactitol, which is hygroscopic and swells after absorbing water and causes diabetic cataract.

a. A and R both are right but R is not the correct explanation of A
b. A as well as R are right and R is a correct explanation of A
c. A is right but R is a wrong statement
d. A and R both are wrong

Ans. c: A is right but R is a wrong statement

Non-utilization of glucose in the glycolysis due to absence of insulin leads to shunting of glucose in the sorbitol path where it is acted upon by enzyme aldol reductase to form sorbitol. This sorbitol is hygroscopic, absorbs water, swell and burst the cell leading to cataract formation.

Galactitol is synthesized from galactose by aldose reductase reaction.

Q 148. Assertion (A): Hereditary fructose intolerance (HFI) leads to accumulation of fructose-6-phosphate, which is the reason behind organomegaly seen in this condition.

Reasoning (R): Above condition is due to aldolase A deficiency.

a. A is right but R is a wrong statement
b. A as well as R are right and R is a correct explanation of A
c. A is wrong but R is a right statement
d. A and R both are wrong

Ans. d: A and R both are wrong

During metabolism of fructose, fructose is first converted to fructose-1-phosphate by the enzyme fructokinase. After this **aldolase B** enzyme is needed to break fructose-1-phosphate into glyceraldehyde and dihydroxyacetone phosphate. Deficiency of this aldolase B leads to accumulation of fructose-1-phosphate, which accumulates in various organs leading to organomegaly.

Q 149. Assertion (A): Riboflavin is important for conversion of pyruvate to acetyl CoA by pyruvate dehydrogenase complex.

Reasoning (R): Riboflavin is important for synthesis of FAD and FAD is important as a cofactor for the PDH complex enzyme: 'Dihydrolipoyl transacetylase'.

a. A and R both are right but R is not the correct explanation of A
b. A is right but R is a wrong statement
c. A is wrong but R is a right statement
d. A and R both are wrong

Ans. b: A is right but R is a wrong statement

FAD is required in the PDH complex enzyme, but it is needed for the 'dihydrolipoyl dehydrogenase' enzyme, not for 'dihydrolipoyl transacetylase'.

For dihydrolipoyl transacetylase enzyme lipoic acid, coenzyme A is required.

Q 150. Assertion (A): Glucagon is required for glycogenesis.

Reasoning (R): The enzyme glycogen phosphorylase which is the rate limiting enzyme for glycogenesis is active in phosphorylated form for which glucagon is needed.

a. A and R both are right but R is not the correct explanation of A
b. A as well as R are right and R is a correct explanation of A
c. A is wrong but R is a right statement
d. A and R both are wrong

Ans. d: A and R both are wrong

For glycogenesis, presence of insulin is a must. Insulin is required for dephosphorylation of glycogen synthase enzyme, which is the rate limiting enzyme for glycogenesis.

Glycogen synthase is active in dephosphorylated state.