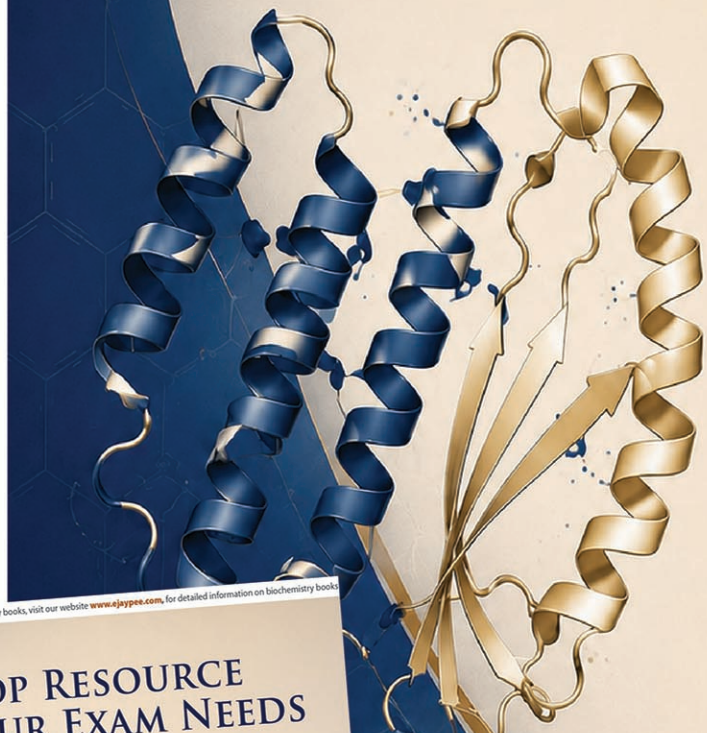
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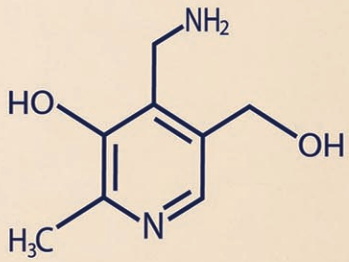
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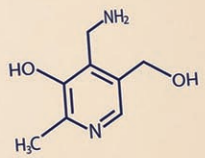
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Metabolic Pathways of Glucose

8

Specific Learning Objectives

The learner will be able to:

- Outline the digestion of carbohydrates
- Describe the absorption of glucose and glucose transporters
- Trace the glycolysis pathway and explain its regulation
- Calculate the energy yield from glycolysis
- Define the Cori cycle and BPG shunt and state their clinical relevance
- Mention the role of pyruvate as a metabolic junction
- Describe gluconeogenesis and malate shuttle
- Explain the significance of gluconeogenesis and glucose alanine cycle
- Enumerate the substrates for gluconeogenesis
- Describe the synthesis and degradation of glycogen
- Explain the regulation of glycogen metabolism and the role of cyclic AMP
- Tabulate major glycogen storage diseases and their salient features
- Trace the hexose monophosphate shunt pathway
- State the metabolic and clinical significance of the shunt pathway
- Outline the glucuronic acid pathway and essential pentosuria
- Enumerate the steps and significance of the polyol pathway
- Outline the metabolism of fructose
- Mention the inborn errors associated with fructose metabolism
- Describe galactose metabolism
- Enumerate the biochemical abnormalities and manifestations in galactosemia
- Outline the metabolism of alcohol
- Explain the harmful effects of alcoholism and toxicity of methanol
- List the amino sugars
- Describe the structure and functions of glycoproteins
- Differentiate the blood group antigens
- Enumerate the structural components of proteoglycans
- List the congenital disorders of glycosylation and mucopolysaccharidoses
- Tabulate the inborn errors associated with metabolism of carbohydrates

Scan me for Chapter's NMC Competencies or, for detailed competencies, please refer Prelims page xxxvii

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DIGESTION OF CARBOHYDRATES

In the diet, carbohydrates are present as complex polysaccharides (starch, glycogen), and to a minor extent, as disaccharides (sucrose and lactose). They are hydrolyzed to monosaccharide units in the gastrointestinal tract. Cooking makes the digestion process easier.

The process of digestion starts in the mouth with the salivary **alpha-amylase**. However, the time available for digestion in the mouth is limited, because the gastric hydrochloric acid will inhibit the action of salivary amylase. In the pancreatic juice, another alpha-amylase is available which will hydrolyze the alpha-1,4 glycosidic linkages randomly, so as to produce smaller subunits like maltose, isomaltose, dextrins and branched or unbranched oligosaccharides.

Starch → Dextrins → Oligosaccharides → Maltose and Isomaltose → Glucose

The cells of the brush border of the intestine contain the enzymes, **sucrase, maltase, isomaltase** and **lactase.** They hydrolyze the corresponding disaccharides into component monosaccharides which are then absorbed **(Table 8.1)**. In the jejunum, the enzyme acting on disaccharides are present as two different complexes, a sucrose-isomaltase complex and a beta-glycosidase complex. The sucrose-isomaltase complex itself has two different catalytic sites. A sucrase-maltase site will hydrolyze the alpha-1,2-bond of sucrose and alpha-1,4-glycosidic bond of maltose. The second site has isomaltase–maltase site, hydrolyzing alpha-1,6 and alpha-1,4-glycosidic bonds. The beta-glycosidase complex also has two catalytic activities, one hydrolyzing the beta-galactosidic bond of lactose (lactase) and the other a beta-glucosidase bond of glucosyl ceramide, a glycolipid. Among the intestinal disaccharidases, lactase activity is most limiting though it is an inducible enzyme.

The clinical applications of lactose intolerance are given in **Box 8.1**.

Prebiotic carbohydrates are slowly digestible carbohydrates which include sugar alcohols, fructose oligosaccharides, hemicellulose, etc. Pulses are rich in prebiotic carbohydrates.

Table 8.1: Dietary carbohydrates and their digestion.

Name of CHO	*Dietary source*	*Digestive enzyme*	*Location*	*Products*
Starch	♦ Cereals – ♦ Rice, wheat	Alpha amylase	♦ Salivary amylase ♦ Pancreatic amylase	♦ Dextrins ♦ Maltose ♦ Isomaltose
Glycogen	Meat	Alpha amylase	Pancreatic amylase	Maltose and isomaltose
Lactose	Milk sugar	Lactase	Intestinal brush border	Glucose and galactose
Sucrose	Cane sugar	Sucrase	Intestinal brush border	Glucose and fructose
Maltose and isomaltose	Hydrolysis of starch	Sucrase-maltase complex and maltase-isomaltase complex	♦ Intestinal brush border of jejunum ♦ Catalytic sites with different glycosidase activity; alpha1-2, alpha -1,4 and alpha-1-6 glycosidase	Glucose
Monosaccharides	Fructose, pentoses Fruits and honey	—	—	Fructose, pentoses
Fiber	♦ Plant polysaccharides ♦ Cellulose and hemicelluloses, pectin, etc.	—	—	♦ Needed for bowel movements ♦ Fermented by intestinal bacteria



BOX 8.1 Clinical Application of Lactose Intolerance.

Lactose Intolerance

Lactase hydrolyses lactose to glucose and galactose. Lactase is present in the brush border of enterocytes of the jejunum and the activity is highest around 1 month after birth. **Deficiency of lactase** leads to lactose intolerance. In this condition, lactose accumulates in the gut. Irritant diarrhea and flatulence are seen. Stool analysis is useful for diagnosis where Benedict's and stool acidity tests are positive.

Congenital lactase deficiency leads to lactose intolerance that is seen at birth, where symptoms start with the first breast feed. The condition should be recognized and treated immediately in newborns by giving lactose free formula diet instead of milk. Chronic diarrhea and malnutrition can also cause lactase deficiency in children.

Another reason for acquired lactose intolerance may be a sudden change into a milk-based diet. Lactase is an **inducible** enzyme. If milk is withdrawn temporarily, diarrhea will be limited. Curd is also an effective treatment, because the lactobacilli present in curd contains the enzyme lactase. Lactase is abundantly seen in yeast, which could also be used in treatment.

In senior citizens, lactase enzyme may be absent. Normally the adult lactase levels are reached by 6–7 years of age. Adult hypolactasia occurs when lactase expression decreases to 10% of that present in infants. **Secondary lactase deficiency** may result from intestinal diseases that injure the absorptive cells of intestinal villi and decrease lactase activity. The undigested disaccharides, oligosaccharides and dextrins may be hydrolyzed by bacteria and used for their energy needs by converting them to short chain fatty acids (C2–C4) and lactate. Along with this process, gases such as hydrogen, methane and CO_2 are also produced which leads to flatulence. If undigested carbohydrates are left in the intestine, osmotic diarrhea, cramps and flatulence occur.

When selectively fermented, these will provide specific changes in the composition of microbial flora conferring benefits on host cell well-being and growth of gut microbiome. Intestinal bacterial activity is described in Chapter 26.



Early Clinical Exposure

Case 8.1 Lactose Intolerance

A 2-month-old infant developed abdominal distension, watery diarrhea, and flatulence after every breastfeeding session. The mother reports no such problems prior to initiating full breastfeeding. On laboratory examination, stool tested positive for reducing sugars and was acidic in pH.

Questions

1. What is the probable diagnosis?
2. Explain the biochemical basis of this disorder.
3. What are the characteristic clinical features of this condition?
4. What biochemical tests are used for diagnosis?
5. What treatment strategies should be advised?

Answers

1. The most probable diagnosis is Congenital Lactase Deficiency, a form of lactose intolerance due to deficient lactase enzyme activity in the jejunal brush border.
2. Lactase (β-galactosidase), located in the brush border of enterocytes in the jejunum, hydrolyses lactose into glucose and galactose. In its absence:
   - Lactose remains unabsorbed in the intestinal lumen.
   - This undigested lactose increases osmotic load, drawing water into the lumen leading to osmotic diarrhea.
   - It also becomes a substrate for bacterial fermentation, producing short-chain fatty acids and gases (H_2, CH_4, CO_2), resulting in flatulence and abdominal discomfort.

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3. Key clinical manifestations include:
   - Diarrhea
   - Abdominal bloating and cramps
   - Flatulence
   - Vomiting (especially in infants), failure to thrive (in congenital cases)

   Symptoms appear after ingestion of milk or dairy products due to lactose content.
4. Various laboratory tests available are:
   - Stool reducing sugar test (Benedict's test): Positive due to unabsorbed lactose.
   - Stool pH test: Shows acidic pH (<5.5) due to fermentation products.
   - Lactose tolerance test or hydrogen breath test: Used in older children/adults.
   - Genetic testing may be done in suspected congenital cases.
5. Immediate cessation of milk in case of congenital intolerance and use lactose-free formula milk in infants. Curd or yogurt may be better tolerated due to presence of bacterial lactase. Lactase enzyme supplements or lactase-rich probiotics (e.g., yeast/lactobacilli). In adults, gradual reintroduction may help due to lactase being an inducible enzyme.

ABSORPTION OF CARBOHYDRATES

Only monosaccharides are absorbed by the intestine. The absorption rate is maximum for galactose; moderate for glucose; and minimum for fructose.

Absorption of Glucose

Glucose has specific transporters, which are transmembrane proteins. **Table 8.2** shows a summary of the glucose transporters.

Table 8.2: Glucose transporters.

Transporter	*Present in*	*Properties*
GluT1	RBC, brain, kidney,	Glucose uptake in colon, retina, most cells placenta
GluT2	Serosal surface of intestinal cells, liver, beta cells of the pancreas	Low affinity; glucose uptake in the liver; glucose sensor in beta cells
GluT3	Neurons, brain	High affinity; glucose into brain cells
GluT4	Skeletal and heart muscle, adipose tissue	Insulin-mediated muscle, adipose tissue glucose uptake
GluT5	Small intestine, testis, sperm, kidney	Fructose transporter; poor ability to transport glucose
GluT 7	Liver endoplasmic reticulum	Glucose from ER to the cytoplasm
SGluT1	Intestine	Cotransport; from the intestinal lumen into the intestinal cell
SGluT2	Kidney	Cotransport; from lumen into cell

Co-transport from Lumen to Intestinal Cell

- This process is mediated by **Sodium Dependent Glucose Transporter-1 (SGluT-1)** **(Fig. 8.1)**. Absorption from the intestinal lumen into the intestinal cell is by co-transport mechanism (secondary active transport) (Chapter 2).
- A membrane bound carrier protein is involved, which carries glucose, along with sodium. This sodium is later expelled by the **sodium pump** with the utilization of energy. So, energy is needed indirectly.
- The transporter in the intestine is named as **SGluT- 1** and the transporter in the kidney is called **SGluT-2.** The first one is faulty in glucose-galactose malabsorption, while the second one is defective in congenital renal glycosuria.

The clinical application of the absorption of carbohydrates is mentioned in **Box 8.2**.

Another Uniport System Releases Glucose into Blood

- The same intestinal epithelial cells have a different transport mechanism on the membrane facing capillaries **(Fig. 8.2)**.
- Intestinal cells release glucose into bloodstream by the carrier mechanism called **Glucose Transporter Type 2 (GluT2)**. This transporter is not dependent on sodium. It is a **uniport, facilitated diffusion** system.
- Glucose binds to the transporter on one side of the membrane. When fixed, the configuration of the complex changes. This leads to the closure of the first binding site.
- At the same time, the binding site is now exposed on the inner side of the membrane, releasing glucose. The process is called **ping-pong mechanism** **(Fig. 8.3)**.

The GluT2 **(facilitated transport)** is involved in the absorption of glucose from bloodstream to cells. GluT2 is present in intestinal epithelial cells, liver cells, beta cells of

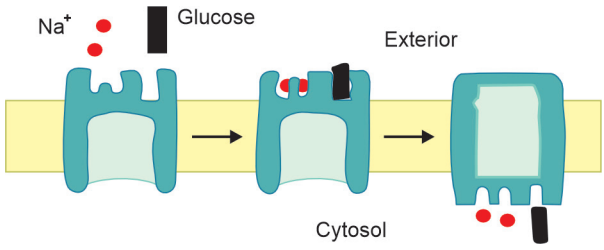


Fig. 8.1: SGluT. Sodium and glucose cotransport system at the luminal side; sodium is then pumped out.

BOX 8.2 **Clinical Application of Absorption of Carbohydrates.**

- Common treatment for diarrhea is the intake of oral **rehydration fluid.** It contains glucose and sodium. The presence of glucose in oral rehydration fluid allows the uptake of sodium to replenish body sodium chloride.
- Inhibiting absorption of glucose from intestinal lumen is a therapeutic measure to reduce hyperglycemia (Chapter 9).

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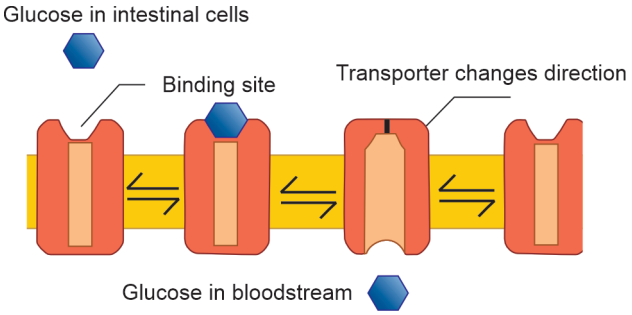


Fig. 8.2: Glucose absorption (Glu2).

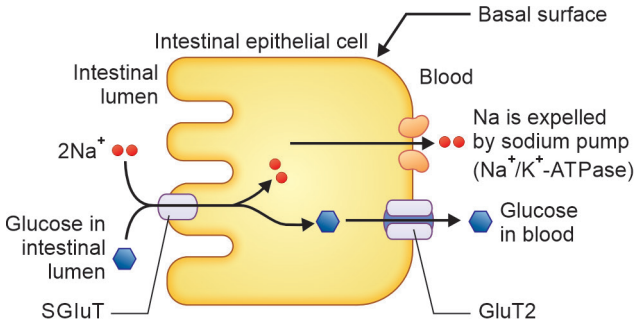


Fig. 8.3: Intestinal absorption of glucose. At the intestinal lumen, absorption is by SGluT and at the blood vessel side, absorption is by GluT2.

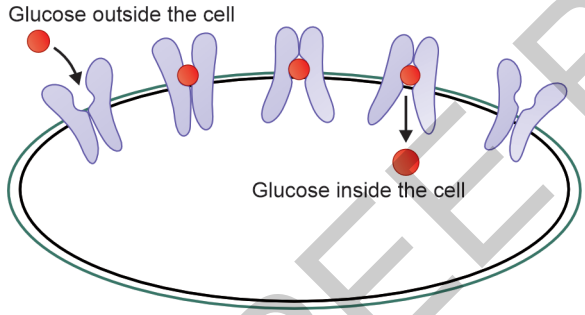


Fig. 8.4: GluT4. Glucose transport in cells.

the pancreas and kidney. So, this mechanism enables the pancreas to **monitor the glucose level** and adjust the rate of insulin secretion. Comparisons between SGluT and GluT2 are shown in **Figure 8.3**.

Glucose Transporter 4 (GluT4)

- The GluT4 is the major glucose transporter in **skeletal muscle and adipose tissue (Fig. 8.4)**.
- GluT4 is under the control of **insulin**. But other glucose transporters are not under the control of insulin.

The clinical importance of glucose transporter 4 is given in **Box 8.3**.

Absorption of Other Monosaccharides

Glucose and galactose are absorbed by the same transporter, SGluT1 **(Fig. 8.5)**. This process is energy dependent, works against a concentration gradient, and therefore absorption is almost complete from the intestine. So, in SgluT1 deficiency, glucose and galactose malabsorption can result. Fructose is absorbed by GluT5 **(Fig. 8.5)**. Other monosaccharides are absorbed by carrier mediated facilitated transport. Therefore, absorption is not complete, and the remaining molecules in the intestine will be fermented by bacteria.

BOX 8.3 Clinical Application of Glucose Transporter 4.

Insulin induces the movement of intracellular GluT4 molecules to the cell surface and thus increases glucose uptake. In Type 2 **diabetes mellitus** (Chapter 9), GluT4 available on cell membrane is reduced, leading to insulin resistance in muscle and fat cells. In diabetes, the entry of glucose into muscle is only half of the normal cells.

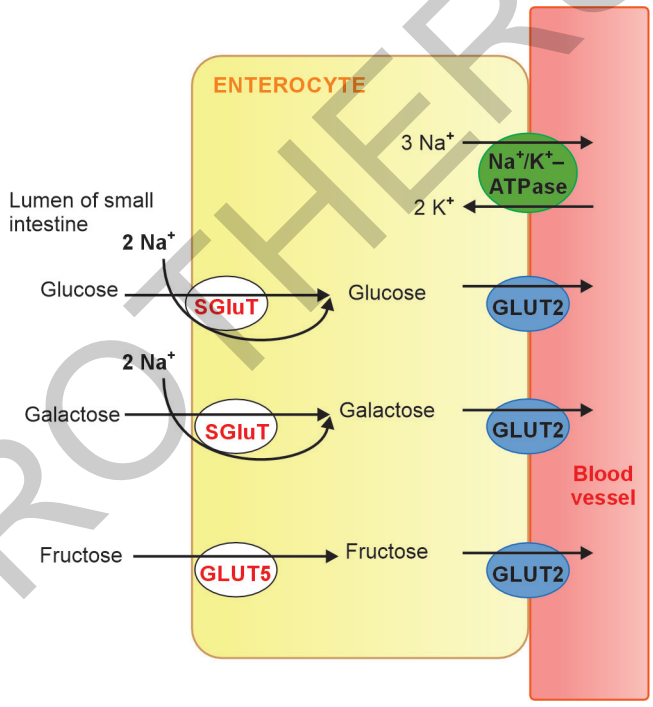


Fig. 8.5: Absorption of monosaccharides.

GLYCOLYSIS (EMBDEN-MEYERHOF PATHWAY)

In 1914, Embden **(Fig. 8.6)** studied the lactic acid formation from pyruvate. In 1919, Meyerhof **(Fig. 8.7)** enunciated most of the steps of the glycolytic pathway (Nobel Prize, 1922). Between 1935 and 1943, all enzymes of the glycolytic pathway were crystallized and characterized by Warburg **(Fig. 8.8)**. He was awarded Nobel Prize in 1931 and the second time



Fig. 8.6: Gustav Georg Embden (1874–1933).

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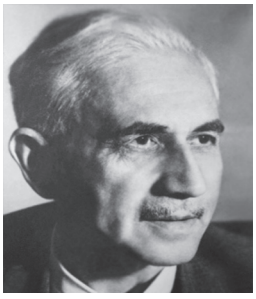


Fig. 8.7: Otto Fritz Meyerhof, Nobel Prize1922 (1884–1951).



Fig. 8.8: Otto Warburg, Nobel Prize 1931 (1883–1970).

BOX 8.4 Clinical Importance of Glucose.

- Glucose is the preferred source of energy for most of the body tissues.
- Brain cells derive energy mainly from glucose.
- When glucose metabolism is deranged, life-threatening conditions may occur.
- A minimum amount of glucose is always required for normal functioning.
- **Normal fasting plasma glucose level is 70–100 mg/dL.** After a heavy carbohydrate meal, it rises but in a normal person, this level is below 150 mg/dL.

in 1944 for his contributions to glycolysis; but Hitler did not permit him to receive it! The clinical importance of glucose is shown in **Box 8.4**.

Overview of Glycolysis

- In the pathway of glycolysis, glucose is split into two 3-carbon **pyruvate** molecules under aerobic conditions, or **lactate** under anaerobic conditions, along with the production of a small quantity of energy.
- Glycolysis is derived from the Greek words, glykys = sweet; and lysis = splitting.
- All the reaction steps take place in the cytoplasm.
- Most of the reactions of the glycolytic pathway are reversible, which are also used for gluconeogenesis.

A summary is shown in **Figure 8.9**.

Significance of the Glycolysis Pathway

- It is the only pathway that is taking place in all the cells of the body.
- Glycolysis is the only source of energy in erythrocytes.
- In strenuous exercise, when muscle tissue lacks enough oxygen, **anaerobic glycolysis forms the major source of energy for muscles.**
- The glycolytic pathway may be considered as the preliminary step before complete oxidation.
- The glycolytic pathway provides carbon skeletons for the synthesis of nonessential amino acids as well as the glycerol part of fat.

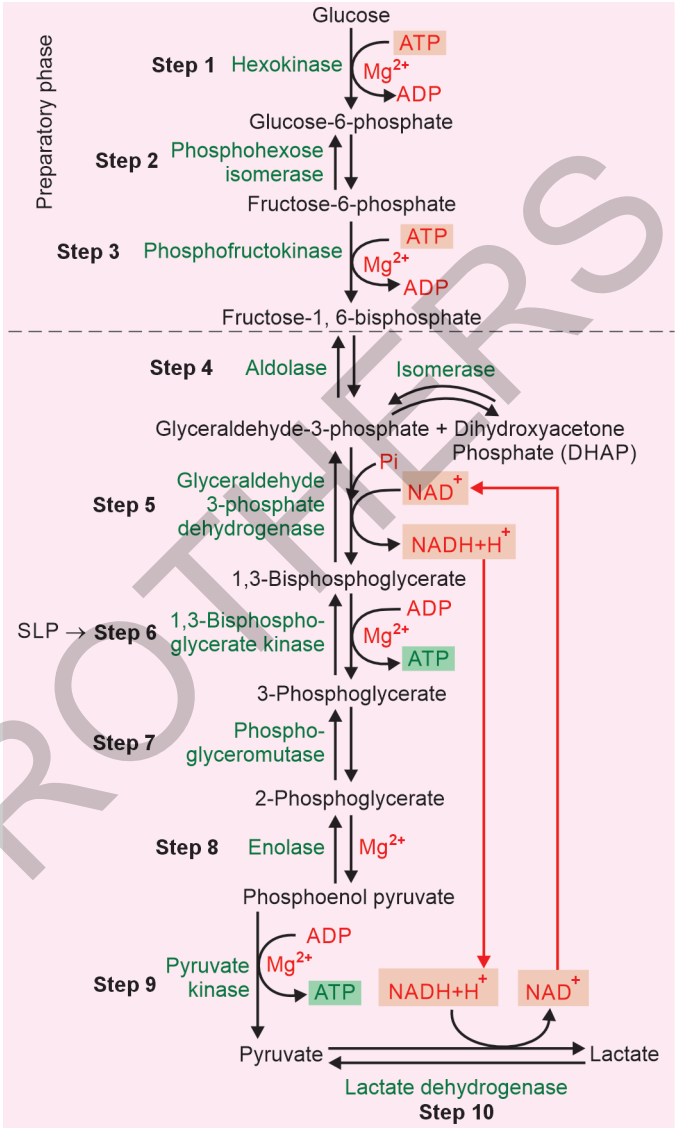


Fig. 8.9: Summary of glycolysis (Embden-Meyerhof pathway). Steps 1, 3 and 9 are key enzymes; these reactions are irreversible. Steps 5, 6 and 9 produce energy. Steps 5 and 10 are coupled for regeneration of NAD^+.

Glucose Entry into Cells

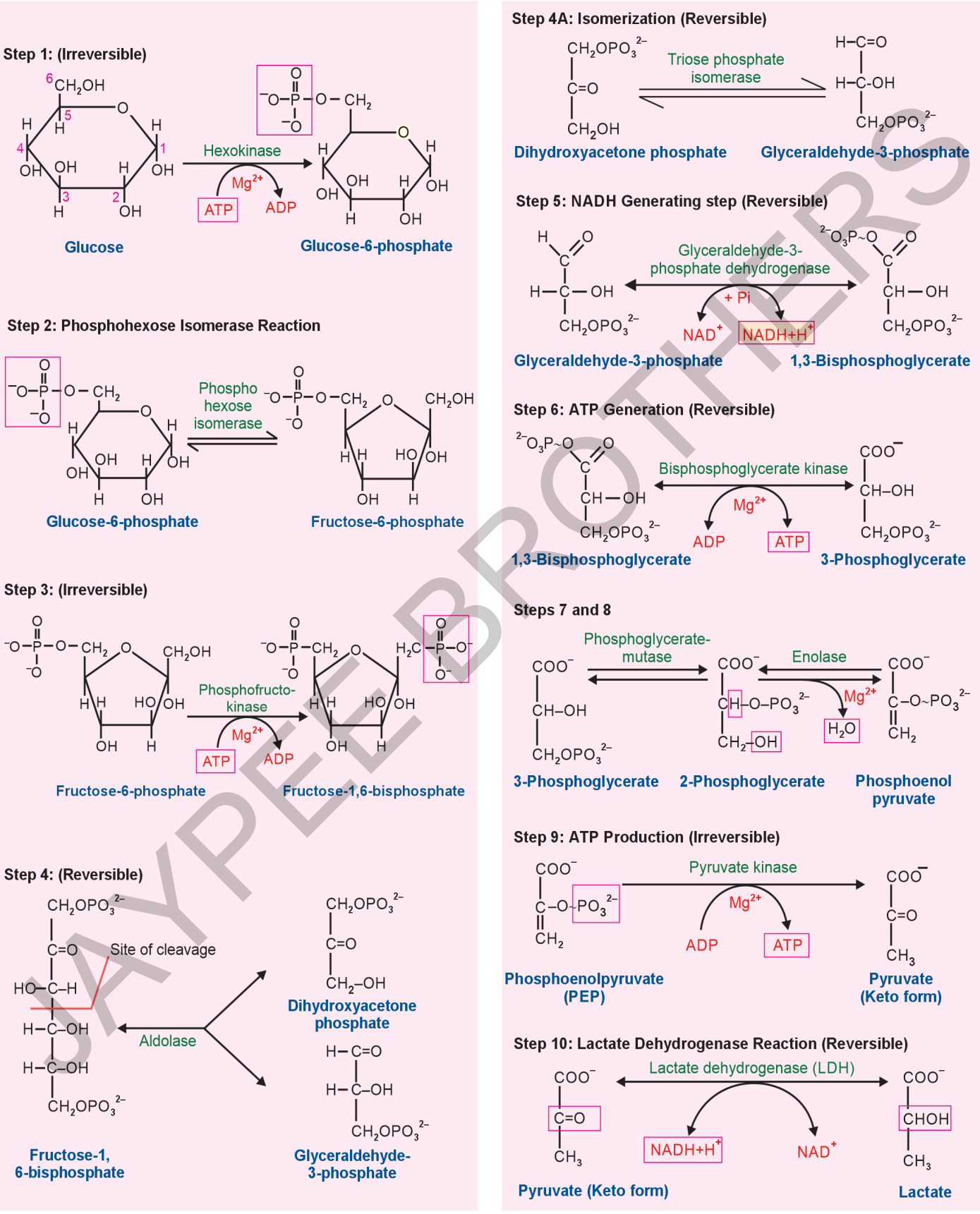
Glucose transporter-4 **(GluT4)** transports glucose from the extracellular fluid to muscle cells and adipocytes **(Table 8.2)**. This translocase is under the influence of **insulin**. Hence, insulin favors the uptake and utilization of glucose by peripheral tissues. In diabetes mellitus, insulin deficiency hinders the entry of glucose into the peripheral cells. But **GluT2** is the transporter in liver cells; it is not under the control of insulin. Hence, insulin favors the uptake and utilization of glucose by peripheral tissues.

Steps of Glycolytic Pathway

Step 1: Glucose to Glucose-6-phosphate

Glucose is phosphorylated to glucose-6-phosphate **(Fig. 8.10)**. The enzyme is **hexokinase** (HK), which splits the ATP into

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Fig. 8.10: Steps of glycolysis.

Table 8.3: Comparison of hexokinase and glucokinase.

	Hexokinase	*Glucokinase*
Occurrence	In all tissues	Only in liver
Km value	10^{-2} mmol/L	20 mmol/L
Affinity to substrate	High	Low
Specificity	Acts on glucose, fructose and mannose	Acts only on glucose
Induction	Not induced	Induced by insulin and glucose
Function	Even when the blood glucose level is low, glucose is utilized by body cells	Acts only when the blood glucose level is more than 100 mg/dL; then glucose is taken up by liver cells for glycogen synthesis

ADP, and the Pi is added to the glucose. The energy released by the hydrolysis of ATP is utilized for the forward reaction.

Hexokinase is a **key glycolytic enzyme.** Hexokinase catalyzes a regulatory step in glycolysis that is **irreversible**. But this irreversibility is circumvented by another enzyme glucose-6-phosphatase (see gluconeogenesis). Hexokinase and glucokinase may be considered as isoenzymes; their properties are compared in **Table 8.3**. Glucokinase is under the influence of insulin; but hexokinase is not.

The metabolic fates of glucose-6-phosphate are shown in **Figure 8.11**. The phosphorylation of glucose traps it within the cells. Once phosphorylated, glucose-6-phosphate is trapped within the cell and has to be metabolized.

Step 2: Glucose-6-phosphate to Fructose-6-phosphate

- Glucose-6-phosphate is isomerized to fructose-6-phosphate by phosphohexose **isomerase (Fig. 8.10)**. This is readily reversible.
- This isomerization of aldose to ketose involves the opening of the glucopyranose ring of glucose-6-phosphate to a linear structure which then changes to the furanose ring structure of fructose-6-phosphate.

Step 3: Fructose-6-phosphate to Fructose-1,6-bisphosphate

- Fructose-6-phosphate is further phosphorylated to fructose-1,6-bisphosphate (**Fig. 8.10** and **Box 8.5**).
- The enzyme is **phosphofructokinase (PFK)**, which is an allosteric, inducible, regulatory enzyme. It is an important **key enzyme** of this pathway. This is again an activation process; the energy being derived by hydrolysis of yet another molecule of ATP.
- This **irreversible** step is the rate limiting reaction in glycolysis. However, during gluconeogenesis, this step is circumvennted by fructose-1,6-bisphosphatase.

Steps 1,2 and 3 together are called the **preparatory phase** of glycolysis.

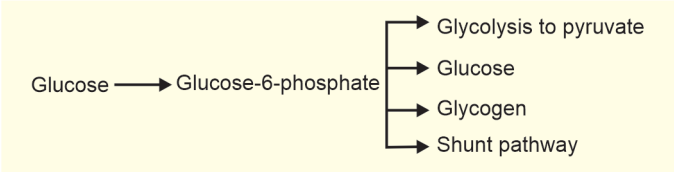


Fig. 8.11: Fate of glucose-6-phosphate.

BOX 8.5 Diphosphate and Bisphosphate are Different.

When two phosphate groups are linked together and then attached to a parent compound, it is called diphosphate, e.g., adenosine-diphosphate **(Fig. 3.3)**.

But when phosphoric acid groups are present at two different sites of the compound, it is named as bisphosphate, e.g., fructose-1,6-bisphosphate (step 3, **Fig. 8.10**). This is a rule in organic chemistry.

Step 4: Fructose-1,6-bisphosphate to Glyceraldehyde-3-phosphate

- The 6-carbon fructose-1,6-bisphosphate is cleaved into two 3-carbon units; one molecule of glyceraldehyde-3-phosphate and another molecule of dihydroxyacetone phosphate (DHAP) **(Fig. 8.14)**.
- Since the backward reaction is an aldol condensation, the enzyme is called **aldolase**. This reaction is reversible. (This enzyme is sometimes called aldolase A to differentiate it from aldolase B which is described in **Figure 8.44** and is involved in fructose intolerance).

Step 4A of Glycolysis

- Dihydroxyacetone phosphate is isomerized to glyceraldehyde-3-phosphate by the enzyme phosphotriose **isomerase**. Thus, the net result is that glucose is now cleaved into two molecules of glyceraldehyde-3-phosphate **(Fig. 8.14)**.
- The steps 4 and 4A are together called the **splitting phase**. The glycerol portion of the neutral fat can enter into glycolytic or gluconeogenic pathways at this point.
- Similarly for neutral fat synthesis, glycerol is required which can be derived from glucose through DHAP.

Step 5: Glyceraldehyde-3-phosphate to 1,3-BPG

- Glyceraldehyde-3-phosphate is dehydrogenated and simultaneously phosphorylated to 1,3-bisphosphoglycerate (1,3-BPG) with the help of NAD^+ **(Fig. 8.16)**.
- The enzyme is **glyceraldehyde-3-phosphate dehydrogenase.** The product contains a **high energy bond**. This is a reversible reaction.
- The oxidation of the aldehyde is an exergonic reaction that drives the synthesis of the high energy compound, 1,3-bisphosphoglycerate with high phosphoryl group transfer potential.

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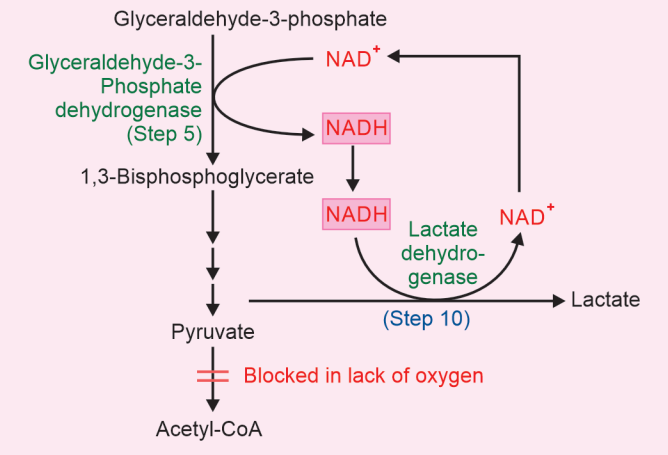


Fig. 8.12: Lactate formation is necessary for the reconversion of NADH to NAD^+ during anaerobiosis.

- During this reaction, NAD^+ is reduced to NADH. The enzyme has a cysteinyl SH group at the active center and is inhibited by **iodoacetate**.
- **Arsenate** inhibits the enzyme, glyceraldehyde 3-phosphate dehydrogenase The arseno-3-phosphoglycerate is unstable and hydrolyzes spontaneously. Thus, ATP formation in glycolysis is inhibited by arsenate.

Step 6: 1,3-BPG to 3-Phosphoglycerate

- The energy of 1,3-BPG is trapped to synthesize one ATP molecule with the help of **bisphosphoglycerate** kinase. **(Fig. 8.12)**.
- This is an example of **substrate level phosphorylation**, where energy is trapped directly from the substrate, without the help of the complicated electron transport chain reactions.
- When energy is trapped by oxidation of reducing equivalents such as NADH, it is called **oxidative phosphorylation.** Step 6 is reversible.

Step 7: 3-Phosphoglycerate to 2-Phosphoglycerate

3-phosphoglycerate is isomerized to 2-phosphoglycerate by shifting the phosphate group from the 3rd to the 2nd carbon atom **(Fig. 8.10)**. The enzyme is **phosphoglucomutase**. This is a readily reversible reaction.

Step 8: 2-Phosphoglycerate to Phosphoenolpyruvate

- 2-phosphoglycerate is converted to phosphoenolpyruvate by the enzyme **enolase.** One water molecule is removed **(Fig. 8.16)**.
- A **high energy phosphate bond** is produced. The reaction is reversible.
- Enolase requires Mg^{++}, and by removing magnesium ions, **fluoride** will irreversibly inhibit this enzyme. Thus, fluoride will stop the whole glycolysis.
- So, when taking blood for glucose estimation, fluoride is added to the blood in grey vacutainer. If not, glucose is metabolized by the blood cells, so that lower blood glucose values are obtained.

Step 9: Phosphoenolpyruvate to Pyruvate

- Phosphoenolpyruvate (PEP) is dephosphorylated to pyruvate, by **pyruvate kinase**.
- First PEP is made into a transient intermediate of enol pyruvate; which is spontaneously isomerized into keto pyruvate, the stable form of pyruvate.
- One mole of ATP is generated during this reaction. This is again an example of **substrate level phosphorylation (Fig. 8.10)**.
- The pyruvate kinase is a **key glycolytic enzyme.** This step is **irreversible**.
- The reversal, however, can be brought about in the body with the help of two enzymes (pyruvate kinase and phosphoenolpyruvate carboxykinase) and hydrolysis of 2 ATP molecules (see gluconeogenesis).

Step 10: Pyruvate to Lactate

- In anaerobic conditions, pyruvate is reduced to lactate-by-lactate dehydrogenase (LDH) **(Fig. 8.12)**. (Greek; an = not; aer = air; bios = life). LDH has five isoenzymes **(Table 3.10)**. The cardiac isoenzyme of LDH will be increased in myocardial infarction.
- In aerobic conditions, the pyruvate enters the citric acid cycle for complete oxidation. The end product of anaerobic glycolysis is lactate which enters the Cori cycle.

Significance of Lactate Production

The steps 5 and 10 are coupled. In the 5th step, for each molecule of glucose entering the pathway, two molecules of NAD^+ are reduced to NADH. The availability of coenzymes inside a cell is limited. Therefore, this step becomes a bottleneck in the whole reaction sequence.

For the smooth operation of the pathway, the NADH is to be reconverted to NAD^+. This can be done by oxidative phosphorylation. However, during exercise, there is a lack of oxygen. So, this reconversion is not possible. Therefore, the cell has to couple some other reaction in which NAD^+ is regenerated in the cytoplasm itself. Hence, pyruvate is reduced to lactate; the NAD^+ thus generated is reutilized for uninterrupted operation of the pathway **(Fig. 8.12)**.

In RBCs, there are no mitochondria. Hence RBCs derive energy only through glycolysis, where the end product is lactic acid.

Energy Yield from Glycolysis

During **anaerobic** (oxygen deficient) conditions, when one molecule of glucose is converted to two molecules of lactate, there is a net yield of two molecules of ATP. Four molecules of ATP are synthesized by the two substrate level phosphorylation steps (steps 6 and 9). But two molecules of ATP are used in

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Table 8.4: Energy yield (number of ATP generated) per molecule of glucose in the glycolytic pathway, under *anaerobic conditions* (oxygen deficiency).

Step	*Enzyme*	*Source*	*Number of ATPs gained per glucose mol*
1	Hexokinase	—	Minus 1
3	Phosphofructokinase	—	Minus 1
6	1,3-bisphospho-glycerate kinase	ATP	1 × 2 = 2
9	Pyruvate kinase	ATP	1 × 2 = 2
			Total = 4 minus 2 = 2

Table 8.5: Energy yield (number of ATP generated) per molecule of glucose in the glycolytic pathway, under aerobic conditions (oxygen is available).

Step	*Enzyme*	*Source*	*No. of ATP gained per glucose mol*
1	Hexokinase	–	Minus 1
3	Phosphofructokinase	–	Minus 1
5	Glyceraldehyde-3-phosphate dehydrogenase	NADH	2.5 × 2 = 5
6	1,3-bisphosphoglycerate kinase	ATP	1 × 2 = 2
9	Pyruvate kinase	ATP	1 × 2 = 2
			Total = 9 minus 2 = 7

steps 1 and 3, hence the **net yield is only 2 ATP (Table 8.4)**. The whole reaction is summarized as:

Glucose + 2 Pi + 2 ADP → 2 Lactate + 2 ATP.

But when **oxygen is in plenty**, the two NADH molecules, generated in the glyceraldehyde-3-phosphate dehydrogenase reaction (step 5), can enter the mitochondrial electron transport chain for complete oxidation (Chapter 7). As each NADH provides 2.5 ATPs, this reaction generates 2.5 × 2 = 5 ATPs. Thus, when oxygen is available, the net gain of energy from the glycolysis pathway is **7 ATPs (Table 8.5)**. Hence the ATP yield from glycolysis is different in anaerobic and aerobic conditions (compare **Tables 8.4 and 8.5**).

Pyruvate is later oxidatively decarboxylated to acetyl CoA (see below), which enters into the citric acid cycle (Chapter 7). Complete oxidation of glucose through glycolysis plus citric acid cycle will yield a **net 32 ATPs (Table 8.6)**.

Regulation of Glycolysis

The regulation is summarized in **Fig. 8.13** and **Table 8.7**. The regulatory enzymes or key enzymes of glycolysis are:

- Glucokinase/hexokinase, step 1
- Phosphofructokinase, step 3
- Pyruvate kinase, step 9

Enzymes Regulating Glycolysis

- **Glucokinase/hexokinase:** Phosphorylation of glucose by these enzymes is a reaction that is regulated by feedback inhibition (hexokinase by glucose-6-phosphate) and activated by insulin (glucokinase is induced by insulin). Glucokinase which is active in the liver has a high Km for glucose and low affinity. Hence, glucokinase can act only when there is an adequate glucose supply so that excess can be stored. Hexokinase with low km and high affinity can phosphorylate glucose even at lower concentrations so that glucose is made available to the brain, cardiac and skeletal muscle. Glucokinase can act only when there is plenty of glucose. Thus, when the supply of glucose is limited, glucose is made available to the brain, cardiac and skeletal muscles.
- **Phosphofructokinase (PFK1)** (step 3) is the most important **rate limiting** enzyme for the glycolysis pathway. **ATP** and **citrate** are the most important allosteric inhibitors. AMP acts as an allosteric activator **(Figs. 8.13 and 8.14)**.
- **Fructose-2,6-bisphosphate (F-2,6-BP)** increases the activity of PFK1. The F-2,6-BP is formed from fructose-6-phosphate by the action of an enzyme called PFK-2. (It is different from the PFK1). Fructose-2,6-bisphosphate is hydrolyzed to fructose-6-phosphate by fructose-2,6-bisphosphatase. The activities of both the enzymes (PFK2 and fructose-2,6-bisphosphatase) are **reciprocally regulated** and are present on the same polypeptide chain as **tandem enzymes**. When glucose supply is in plenty, PFK-2 is dephosphorylated and activated; so, F-2,6-BP concentration increases; this in turn, activates PFK. Thus, glycolysis is favored **(Fig. 8.14)**. When glucose level is low, the PFK2 and Fructose-2,6-bisphosphatase become phosphorylated, PFK2 is inactive and F-2,6-bisphosphatase is activated, and fructose-2,6-bisphosphate level falls. Thus, glycolysis slows down. These two enzyme activities are present as a tandem enzyme, hence regulation by phosphorylation of a single serine residue is achieved very easily.
- **Pyruvate kinase** catalyzes an irreversible step and is a regulatory enzyme of glycolysis. When energy is plenty in the cell, glycolysis is inhibited. Insulin increases its activity whereas glucagon inhibits it **(Fig. 8.15)**.

Insulin favors glycolysis by activating the above three key glycolytic enzymes. **Glucagon and glucocorticoids** inhibit glycolysis and favor gluconeogenesis **(Tables 8.7 and 8.8)**. Insulin induces glucokinase, and activates PFK1 and PK.

Cori Cycle or Lactic Acid Cycle

It is a process in which glucose is converted to lactate in the muscle and in the liver this lactate is re-converted into glucose **(Fig. 8.16)**. Carl Cori and Gerty Cori described this process, for which they were awarded Nobel Prize in 1947. In an actively contracting muscle, pyruvate is reduced to lactic acid which may tend to accumulate in the muscle. The muscle cramps, often associated with strenuous muscular exercise, are thought to be due to lactate accumulation. To prevent

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Table 8.6: Energy yield (number of ATP generated) per molecule of glucose when it is completely oxidized through glycolysis plus citric acid cycle, under *aerobic conditions.*

Pathway	*Step*	*Enzyme*	*Source*	*Method of ATP formation*	*No. of ATPs gained per glucose (new calculation)*	
Glycolysis	1	Hexokinase	–		Minus	1
Do	3	Phosphofructokinase	–		Minus	1
Do	5	Glyceraldehyde-3-P DH	NADH	Respiratory chain	2.5 × 2 =	5
Do	6	1,3-BPG kinase	ATP	Substrate level	1 × 2 =	2
Do	9	Pyruvate kinase	ATP	Substrate level	1 × 2 =	2
Pyruvate to Acetyl CoA	—	Pyruvate dehydrogenase	NADH	Respiratory chain	2.5 × 2 =	5
TCA cycle	3	Isocitrate DH	NADH	Respiratory chain	2.5 × 2 =	5
Do	4	Alpha-keto glutarate DH	NADH	Respiratory chain	2.5 × 2 =	5
Do	5	Succinate Thiokinase	GTP	Substrate level	l × 2 =	2
Do	6	Succinate DH	$FADH_2$	Respiratory chain	1.5 × 2 =	3
Do	8	Malate DH	NADH	Respiratory chain	2.5 × 2 =	5
Net generation in glycolytic pathway						9 minus 2 = 7
Generation in pyruvate dehydrogenase reaction						= 5
Generation in citric acid cycle						= 20
Net generation of ATP from one glucose mol						= 32

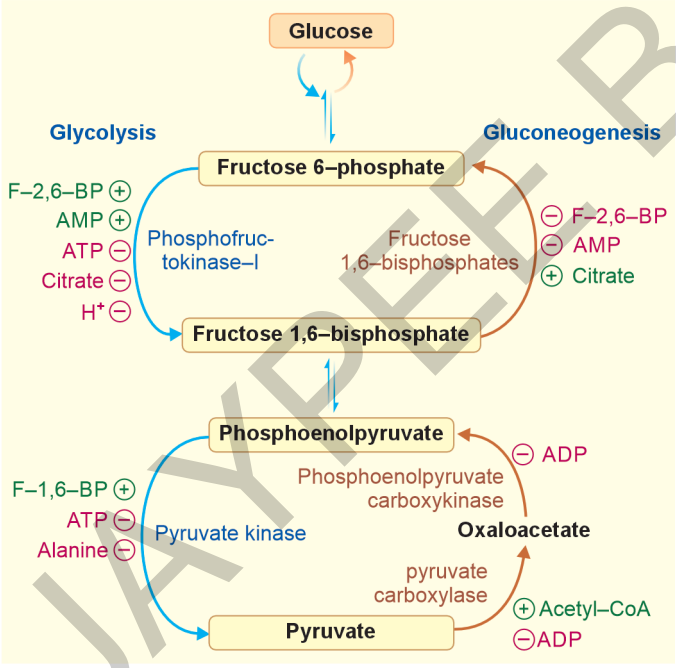


Fig. 8.13: Summary of regulation of glycolysis and gluconeogenesis. (Gluconeogenesis is described below).

lactate accumulation, the body utilizes the Cori cycle. This lactic acid from muscle diffuses into the blood. Lactate then reaches the liver, where it is oxidized to pyruvate. Thus, it is channeled to gluconeogenesis. Regenerated glucose can enter into the blood and then into the muscle. This cycle is called the Cori cycle **(Fig. 8.16)**.

Table 8.7: Regulatory enzymes of glycolysis.

Enzyme	*Activation*	*Inhibition*
Hexokinase	—	Glucose-6-phosphate
Glucokinase	Insulin	Glucagon
Phospho-fructokinase (PFK)	Insulin, AMP F-6-P, PFK-2 F-2,6-BP	Glucagon, ATP Citrate, Low pH Cyclic AMP
Pyruvate kinase	Insulin, F-1,6-BP	Glucagon, ATP Cyclic AMP
Pyruvate dehydrogenase (PDH)*	CoA, NAD^+	Acetyl-CoA, NADH

*PDH is not an enzyme of glycolysis, but has a regulatory role in glycolysis, because the product of glycolysis (pyruvate) is the substrate for PDH. Hence the rate of utilization of pyruvate will affect the rate of glycolytic pathway.

Significance of the Cori Cycle

The lactate produced in the muscle is efficiently reutilized by the body. But this is an energy-consuming process. During exercise, lactate production is high, which is utilized by the liver to produce glucose. This process needs ATP in significant quantities, which is provided by increased metabolism, leading to increased oxygen consumption. This is the explanation for the **oxygen debt** after vigorous exercise.

Pasteur Effect

Under aerobic conditions, glycolysis is inhibited. This inhibitory effect of oxygen on glycolysis is known as the

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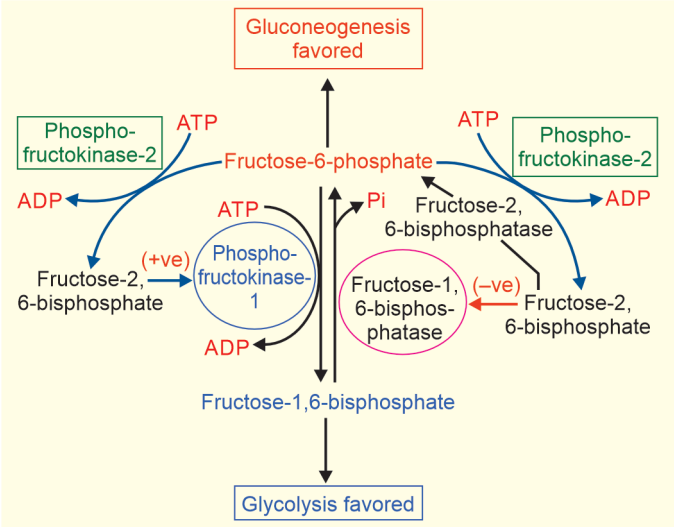


Fig. 8.14: Reciprocal regulation of PFK-2 and fructose-2,6-bisphosphatase by phosphorylation.

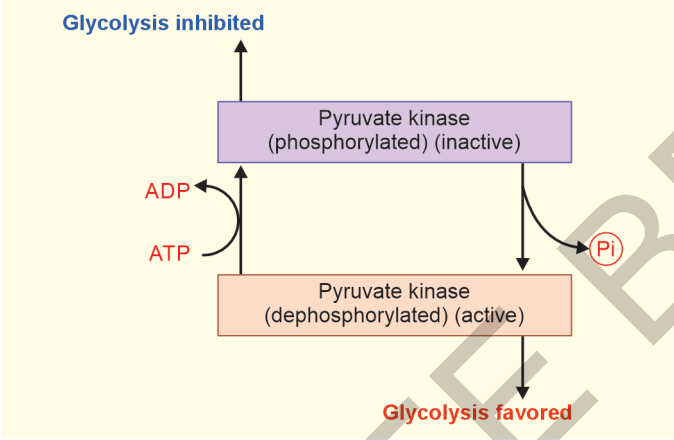


Fig. 8.15: Covalent modification of pyruvate kinase reaction; this is similar to PFK-2.

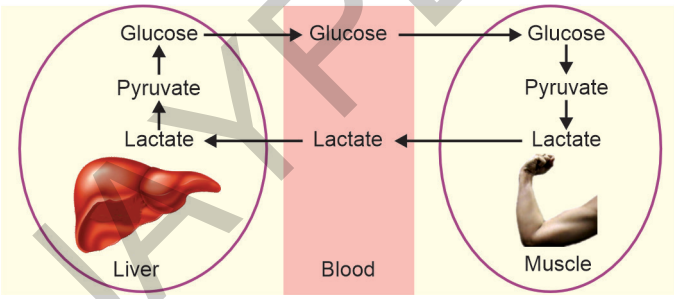


Fig. 8.16: Cori cycle. Contracting muscles lack oxygen. So, pyruvate is reduced to lactate. This can be reconverted to glucose in the liver by gluconeogenesis.

Pasteur effect. This was discovered in yeasts by Louis Pasteur in 1857. This phenomenon is explained as follows: In anaerobic condition, ATP generation is only 2 mole per mole of glucose, while when oxygen is available, ATP generation will be 32 **(Tables 8.4 and 8.6)**. Thus 16 times more ATP is generated when oxygen is available. In other words, about 16 times more glucose must be consumed anaerobically to produce the same amount of ATP aerobically. Or, under anaerobic conditions, the rate of glucose metabolism is faster. So, when oxygen is given to the cells, the glucose metabolism suddenly decreases. Pasteur effect is due to the inhibition of PFK-1 by citrate and ATP.

Warburg hypothesis (cancer cells utilize energy from glycolysis) is explained in Chapter 36.

Rapaport Leubering Cycle (BPG Shunt)

In the erythrocytes, step 6 of glycolysis is bypassed. Bisphosphoglycerate mutase converts 1,3-bisphosphoglycerate (BPG) to 2,3-BPG. Then BPG-phosphatase removes the phosphate group to form 3-phosphoglycerate **(Fig. 8.17)**. However, ATP formation is not taking place in this bypass pathway.

Significance of BPG

- The 2,3-BPG combines with hemoglobin, and **reduces the affinity towards oxygen**. So, in the presence of 2,3-BPG, oxyhemoglobin will unload oxygen more easily in tissues.
- Under **hypoxic conditions** the 2,3-BPG concentration in the RBC increases, thus favoring the release of oxygen to the tissues even when PO_2 is low.
- The compensatory increase in 2,3-BPG in high altitudes favors oxygen dissociation. BPG is increased in fetal circulation.
- In this shunt pathway, **no ATP is generated**. Please compare **Figure 8.17** with step 6 in **Figure 8.10**.

METABOLIC FATE OF PYRUVATE

Under aerobic conditions, pyruvate is converted to acetyl-CoA which enters the TCA cycle to be oxidized to CO_2. As glycolysis is taking place in the cytoplasm, pyruvate is generated in the cytoplasm which is transported into mitochondria by a **pyruvate transporter**.

Pyruvate Dehydrogenase Complex

Inside the mitochondria, pyruvate is **oxidatively decarboxylated** to acetyl-CoA by pyruvate dehydrogenase (PDH). It is a multi-enzyme complex with five coenzymes and three apoenzyme. The coenzymes needed are:

1. Thiamine pyrophosphate (TPP)
2. Coenzyme A (CoA)
3. FAD
4. NAD^+
5. Lipoamide.

The lipoic acid, otherwise called thioctic acid has two sulfur atoms and eight carbon atoms. It can accept or donate hydrogen atoms **(Fig. 8.18)**. The enzyme part of the PDH complex is made up of three component enzymes **(Fig. 8.19)**:

- **Pyruvate dehydrogenase** (Enzyme 1): It catalyzes oxidative decarboxylation. TPP is required in this step. So, **Thiamine,** a B-complex group vitamin is essential for

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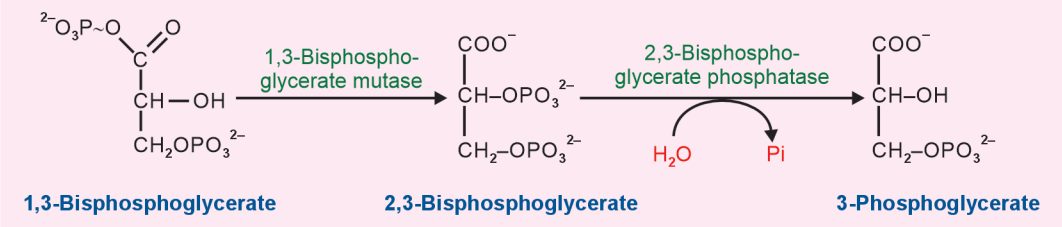


Fig. 8.17: BPG shunt; step 6 of glycolysis is bypassed in erythrocytes. Compare with step 6 in **Figure 8.10**.

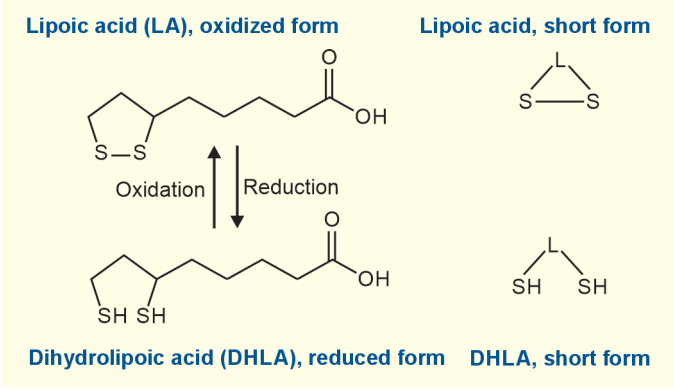


Fig. 8.18: Structure of lipoic acid.

the utilization of pyruvate. The two-carbon unit remains attached to the enzyme, as hydroxyethyl thiamine pyrophosphate.

- **Dihydrolipoyl transacetylase** (Enzyme 2): Then, the hydroxyethyl group is oxidized to form an acetyl group and then transferred from TPP to lipoamide to form acetyl-lipoamide.
- **Dihydrolipoyl dehydrogenase** (Enzyme 3): The last step is the oxidation of lipoamide. At the end of the reaction the cofactors, namely TPP, lipoamide and FAD are regenerated **(Fig. 8.19)**. A similar enzyme complex brings about the oxidative decarboxylation of alpha-ketoglutarate to succinyl-CoA in the TCA cycle (Chapter 7).

Regulation

PDH is subject to regulation by allosteric mechanisms and covalent modification.

- Allosteric inhibitors are the products acetyl-CoA and NADH. PDH or E1 is covalently modified by phosphorylation by PDH kinase and dephosphorylated by PDH phosphatase.
- The dephosphorylated form of the enzyme is active. Hence activators of PDH kinase like ATP, NADH and acetyl-CoA inhibit PDH reaction.
- PDH phosphatase is activated by Ca^{++}, Mg^{++} and AMP; this will increase the rate of PDH reaction whereas PDH kinase is inhibited by Ca^{++}. When there is adequate ATP and acetyl-CoA, the enzyme is inhibited.

Significance of Pyruvate Dehydrogenase

- **Completely irreversible Process.** There is no pathway available in the body to circumvent this step. Glucose through this step is converted to acetyl-CoA from which fatty acids can be synthesized.
- But the backward reaction is not possible, so **there is no net synthesis of glucose from fat.**

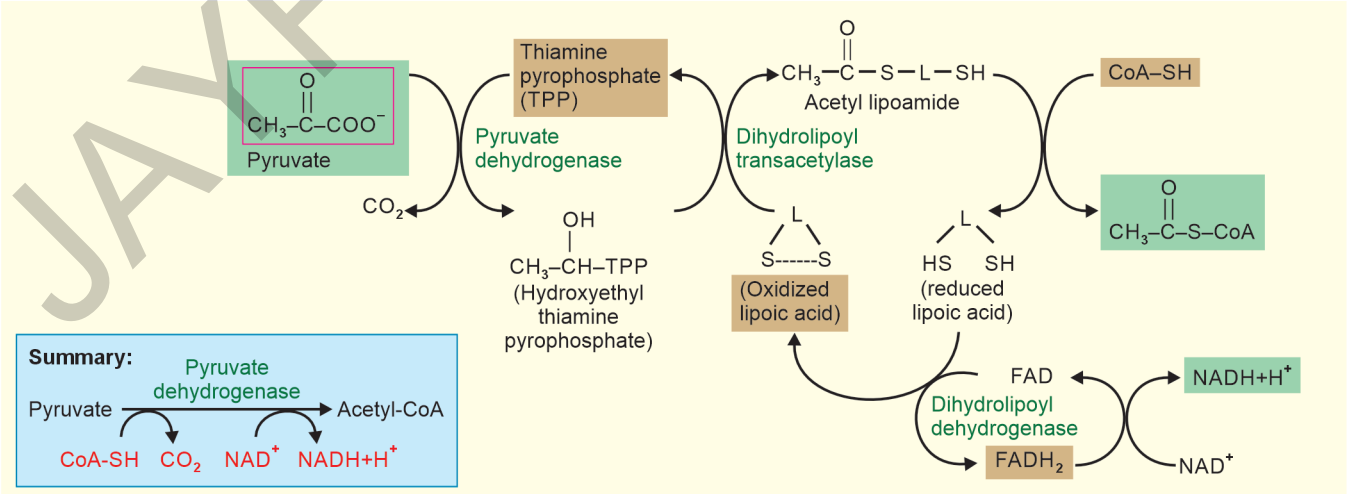


Fig. 8.19: Details of pyruvate dehydrogenase reaction. See the summary in the inset.

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BOX 8.6 Clinical Applications of Glycolytic Enzymes.

- **Lactic acidosis** may be seen in hypoxia, shock, pulmonary failure, alcohol abuse, diabetes mellitus (Chapter 9) and mitochondrial myopathies (Chapter 30).
- **Deficiency of glycolytic enzymes.** These conditions are rare, out of which **pyruvate kinase** deficiency and **hexokinase** deficiency are comparatively common. Though rare, these deficiency states can lead to hemolytic anemia, because energy depleted RBCs are destroyed. Hexokinase deficient RBCs have a low level of 2,3-BPG and a high affinity for oxygen. On the other hand, a deficiency of pyruvate kinase leads to a decreased affinity for oxygen since 2,3-BPG levels are high. Inherited aldolase deficiency also causes hemolysis. In PFK deficiency, muscle weakness is seen.
- **Pyruvate dehydrogenase (PDH).** PDH requires thiamine pyrophosphate (TPP); this explains the serious afflictions in **beriberi** due to thiamine deficiency (Chapter 24). TPP deficiency in alcoholism causes pyruvate accumulation in tissues and resultant lactic acidosis. Inherited PDH deficiency may also lead to lactic acidosis.

- Pyruvate may be channeled back to glucose through gluconeogenesis. But when pyruvate becomes acetyl-CoA, it cannot go back. Thus, the pyruvate dehydrogenase step is the **committed step** towards the oxidation of glucose.
- Pyruvate dehydrogenase is regulated by **end product inhibition** as well as by **covalent modification**. Phosphorylation of the enzyme by a kinase decreases the activity of the enzyme. Dephosphorylation activates the enzyme.

Diseases associated with the glycolytic pathway are described in **Box 8.6**.

Energetics

The NADH generated in this reaction enters the electron transport chain to produce 2.5 ATP molecules.

Pyruvate is a Junction Point

Pyruvate occupies an important junction between various metabolic pathways. It may be decarboxylated to **acetyl-CoA** which enters the TCA cycle or may be utilized for fatty acid synthesis. Pyruvate may be carboxylated to **oxaloacetate** which is used for gluconeogenesis. These pathways are summarized in **Figure 8.20**.

GLUCONEOGENESIS

Definition

Gluconeogenesis is the process by which glucose molecules are produced from noncarbohydrate precursors, such as lactate, glucogenic amino acids, glycerol part of fat and propionyl-CoA derived from odd chain fatty acids **(Fig. 8.21)**.

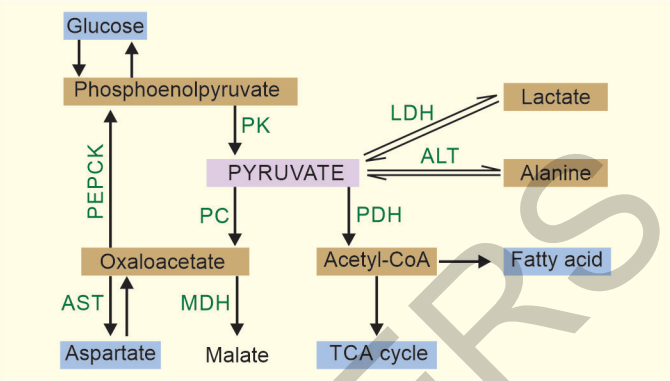


Fig. 8.20: Pyruvate as a metabolic junction point. PK = pyruvate kinase; LDH = lactate dehydrogenase; ALT = alanine aminotransferase; PDH = pyruvate dehydrogenase; PC = pyruvate carboxylase; MDH = malate dehydrogenase; AST = aspartate aminotransferase; PEPCK = phosphoenolpyruvate carboxykinase.

Site

Gluconeogenesis occurs mainly in the liver, and to a lesser extent in the renal cortex. The pathway is partly mitochondrial and partly cytoplasmic.

Key Gluconeogenic Enzymes

- Pyruvate carboxylase
- Phosphoenolpyruvate carboxykinase
- Fructose-1-6-bisphosphatase
- Glucose-6-phosphatase

Steps of Gluconeogenesis

Gluconeogenesis involves several enzymes of glycolysis, but **it is not a reversal** of glycolysis. The irreversible steps in glycolysis are circumvented by four enzymes which are designated as the key enzymes of gluconeogenesis **(Tables 8.8 and 8.9)**.

Step 1: Pyruvate Carboxylase Reaction

Pyruvate in the cytoplasm enters the mitochondria. Then, the carboxylation of pyruvate to oxaloacetate is catalyzed by a mitochondrial enzyme, pyruvate carboxylase **(Fig. 8.22)**. It needs the co-enzymes biotin and ATP.

Step 2: Malate Aspartate Shuttle

The carboxylation of pyruvate (previous reaction) takes place in mitochondria. So, oxaloacetate is generated inside the mitochondria. This **oxaloacetate has to be transported from mitochondria to cytosol**, because further reactions of gluconeogenesis are taking place in the cytosol. This is achieved by the **malate aspartate shuttle.**

Oxaloacetate is first converted to malate, which traverses the membrane and reaches the cytoplasm. Malate is then re-converted to oxaloacetate. Malate dehydrogenase is present in both mitochondria and cytoplasm **(Fig. 8.23)**.

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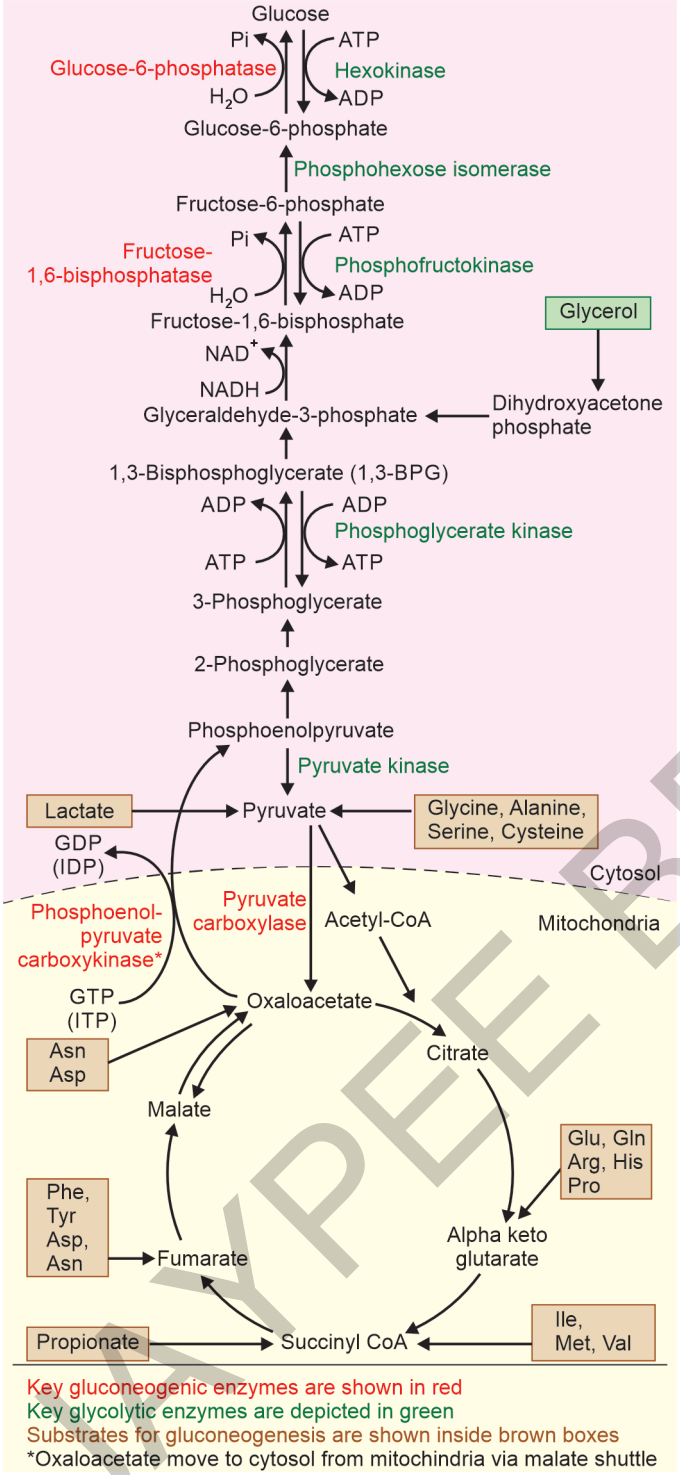


Fig. 8.21: Gluconeogenesis pathway.

Table 8.8: Key enzymes.

Irreversible steps in glycolysis	*Corresponding key gluconeogenic enzymes*
Pyruvate kinase (step 9)	Pyruvate carboxylase; Phospho-enolpyruvate carboxykinase
Phosphofructokinase (step 3)	Fructose-1,6-bisphosphatase
Hexokinase (step 1)	Glucose-6-phosphatase

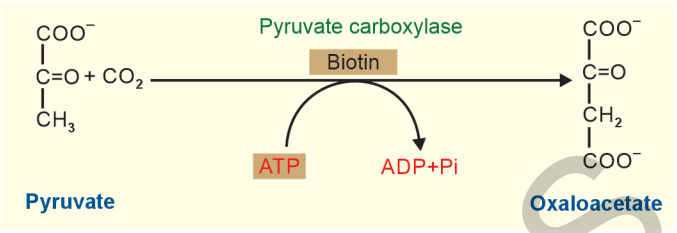


Fig. 8.22: The first step in gluconeogenesis.

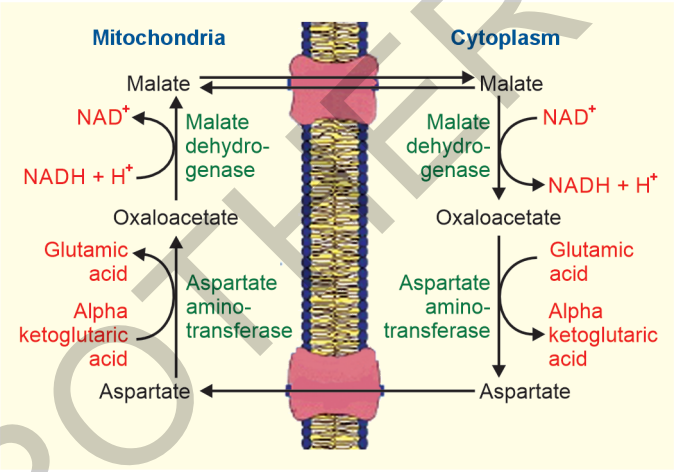


Fig. 8.23: Malate-Aspartate Shuttle. MDH = malate dehydrogenase. Please refer **Figure 7.18** also.

Oxaloacetate may also be transported as aspartate formed by transamination of oxaloacetate.

When alanine is the substrate for gluconeogenesis, the malate shuttle predominantly operates, because NADH is also required in the cytoplasm for the gluconeogenesis to continue. When lactate is the substrate for gluconeogenesis, the aspartate shuttle operates, because sufficient NADH is available in the cytoplasm by the LDH reaction.

Please also see the malate aspartate shuttle described under electron transport chain, where the shuttle is used to transport NADH from the cytoplasm to mitochondria for oxidation **(Fig. 7.18)**. Although the reactions are essentially the same in both situations, these two figures are slightly different from each other, so as to emphasize the dissimilar purposes served by the same shuttle.

Step 3: Phosphoenolpyruvate Carboxykinase

In the cytoplasm, phosphoenolpyruvate carboxykinase (PEPCK) enzyme then converts oxaloacetate to phosphoenolpyruvate by removing a molecule of CO_2. GTP or ITP donates the phosphate **(Fig. 8.24)**. The net effect of these two reactions is the conversion of pyruvate to phosphoenolpyruvate. This circumvents the irreversible step in glycolysis catalyzed by pyruvate kinase (step 9 of glycolysis). In humans, there are two isoforms of PEPCK; a cytosolic form (PEPCK-C) and a mitochondrial isoform (PEPCK-M). These two are encoded by separate genes, PCK1 and PCK2. The cytosolic form is more important in gluconeogenesis. The

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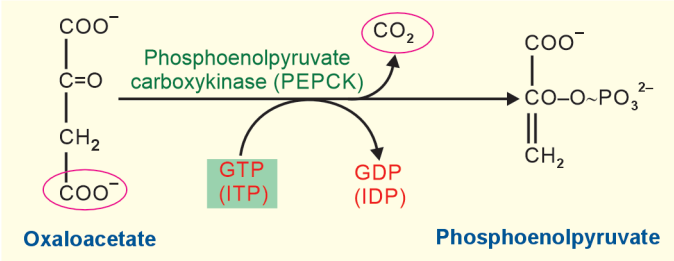


Fig. 8.24: Phosphoenolpyruvate carboxykinase.

PEP formed in the mitochondria is transported by a carrier to the cytoplasm for further metabolism.

Steps 4, 5, 6, 7, 8: Partial Reversal of Glycolysis

The phosphoenolpyruvate undergoes further reactions catalyzed by the glycolytic enzymes to form fructose-1,6-bisphosphate (see glycolysis steps 8, 7, 6, 5 and 4). All these reactions are freely reversible.

Step 9: Fructose-1, 6-bisphosphatase

- Fructose-1,6-bisphosphate is then acted upon by fructose-1,6-bisphosphatase to form fructose-6-phosphate. This will bypass the step of the PFK reaction (see step 3 of glycolysis).

  Fructose-1-6-bisphosphate $\xrightarrow{\text{Fructose-1,6-bisphosphatase}}$ Fructose-6-phosphate + Pi
- Then fructose-6-phosphate is isomerized to glucose-6-phosphate by the freely reversible reaction catalyzed by hexose phosphate isomerase (step 2 in glycolysis).

Step 10: Glucose-6-phosphatase

- The glucose-6-phosphate is hydrolyzed to free glucose by glucose-6-phosphatase.

  Glucose-6-phosphate + H_2O ⟶ Glucose + Pi
- Glucose-6-phosphatase is **active in the liver**. It is present in kidney and intestinal mucosa to a lesser extent but is **absent in muscle**.

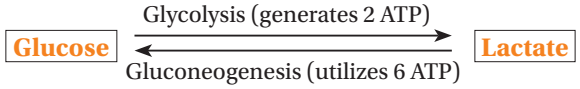
The detailed steps of gluconeogenesis are shown in **Figure 8.21**.

Significance of Gluconeogenesis

Energy Requirement

The reactions catalyzed by pyruvate carboxylase, phosphoenolpyruvate carboxykinase and phosphoglycerate kinase require one ATP each; so 3 ATPs are used by 1 pyruvate residue to produce one-half molecule of glucose; or 6 ATPs are required to generate one glucose molecule.

2 pyruvate → 2 oxaloacetate	= 2 ATP
2 oxaloacetate → 2 phosphoenolpyruvate (2GTP)	= 2 ATP
2 × 3-phosphoglycerate→2 × 1,3-bisphosphoglycerate	= 2 ATP
Total	= 6 ATP



Substrates for Gluconeogenesis

- Lactate
- Glucogenic amino acids
- Glycerol part of fat and
- Propionyl-CoA derived from odd chain fatty acids

Out of these, lactate and glucogenic amino acids are the most important substrates for gluconeogenesis.

Lactate

- The lactate formed in the muscle is transported to the liver. In the liver cell lactate dehydrogenase converts lactate to pyruvate **(Fig. 8.25)**.
- The pyruvate enters the gluconeogenic pathway to form glucose. See also the Cori cycle **(Fig. 8.16)**.

Glucogenic Amino Acids

- Glucogenic amino acids are alanine, glutamic acid, aspartic acid, etc **(Fig. 8.21)**.
- When glucose is not readily available (starvation or diabetes mellitus), the glucogenic amino acids are transaminated to corresponding keto acids. These then enter the TCA cycle and form oxaloacetate.
- **Alanine** released from the muscle is the major substrate for gluconeogenesis **(Fig. 8.26)**. Muscle wasting seen in uncontrolled diabetes mellitus could be explained by this factor.

Glucose Alanine Cycle (Cahill Cycle)

Alanine is transported to the liver, transaminated to pyruvate and converted to glucose. This glucose may again enter the glycolytic pathway to form pyruvate, which in turn, can be transaminated to alanine.

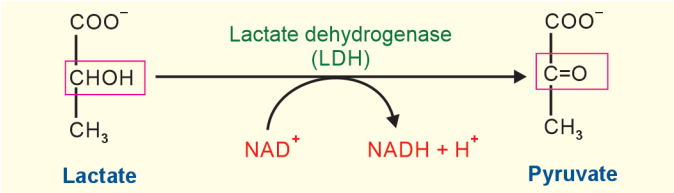


Fig. 8.25: Reversal of step 10 of glycolysis.

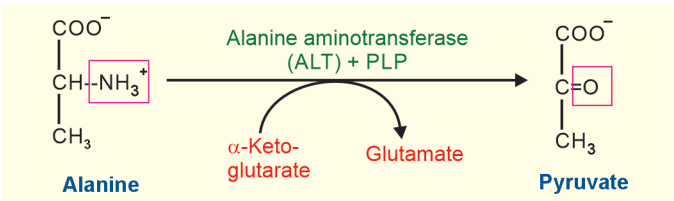


Fig. 8.26: Transamination of alanine.

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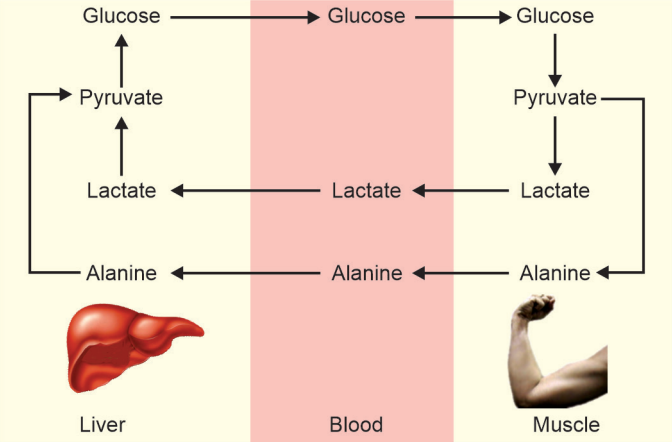


Fig. 8.27: Glucose alanine cycle.

- The glucose-alanine cycle is important in **conditions of starvation (Fig. 8.27)**. Thus, the net transfer of amino acid (nitrogen) from muscle to the liver and the corresponding transfer of glucose (energy) from the liver to the muscle is affected.
- The alanine cycle is intimately related to the Cori cycle (compare **Figs. 8.16 and 8.27**).

Glycerol

The glycerol part of fat is phosphorylated in the liver cytosol by ATP to glycerol-3-phosphate. It is then oxidized to dihydroxyacetone phosphate by an NAD^+ dependent dehydrogenase **(Fig. 8.28)**.

Propionyl-CoA

- Propionyl-CoA is formed from odd chain fatty acids and the carbon skeleton of some amino acids. It is converted to succinyl-CoA **(Fig. 10.11)**. It is a minor source of glucose.
- **Important:** Even-chain fatty acids **cannot** be converted to glucose; **they are not** substrates for gluconeogenesis.

Regulation of Gluconeogenesis

Gluconeogenesis and glycolysis are **reciprocally regulated** so that one pathway is relatively inactive when the other is active. The regulatory steps are:

- **Pyruvate carboxylase:** It is an allosteric enzyme. Acetyl-CoA is an activator of pyruvate carboxylase so that the generation of oxaloacetate is favored when the acetyl-CoA level is sufficiently high **(Fig. 8.22)**.
- **Fructose-1,6-bisphosphatase: Citrate** is an activator while fructose-2,6-bisphosphate and AMP are inhibitors. All these three effectors have an exactly opposite effect on the phosphofructokinase (PFK) **(Fig. 8.29)**.
- **Adenosine triphosphate:** Gluconeogenesis is enhanced by ATP.
- **Hormonal regulation of gluconeogenesis:** The hormones **glucagon** and **glucocorticoids** increase gluconeogenesis **(Fig. 8.30)**. Glucocorticoids induce the synthesis of hepatic aminotransferases thereby providing the substrate for gluconeogenesis. The high glucagon-insulin ratio also favors the induction of synthesis of gluconeogenic enzymes (PEPCK, fructose-1,6-bisphosphatase and glucose-6-phosphatase).
- Phosphoenolpyruvate carboxykinase (PEPCK) activity is induced by both cortisol and glucagon. Glucagon elevates the expression of PEPCK by increasing the levels of cAMP (via activation of adenylyl cyclase) in the liver. Cortisol activates the PEPCK gene and induces PEPCK transcription and synthesis of the enzyme.
- At the same time, the synthesis of glycolytic enzymes (HK, PFK and PK) is depressed. **Insulin** inhibits the process **(Fig. 8.30)**.

A summary of regulatory enzymes of gluconeogenesis is shown in **Table 8.9**, which may be compared with **Table 8.7**. The metabolic significance of gluconeogenesis is given in **Box 8.7**. The clinical significance of gluconeogenesis is shown in **Box 8.8**.

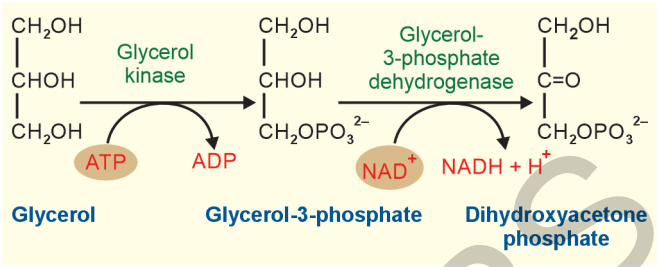


Fig. 8.28: Gluconeogenesis from glycerol.

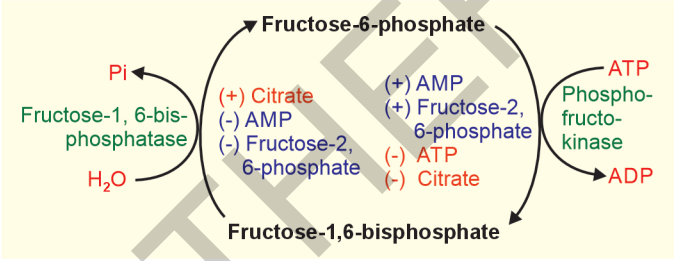


Fig. 8.29: Reciprocal regulation of PFK (glycolytic enzyme) and fructose-1,6-bisphosphatase (gluconeogenic enzyme).

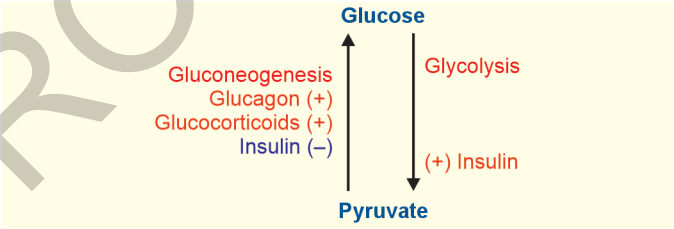


Fig. 8.30: Hormonal regulation of gluconeogenesis.

GN ratio or DN ratio

During gluconeogenesis, proteins are degraded and end-product urea is excreted through urine. The ratio of glucose (dextrose) to urea nitrogen in urine is termed as GN ratio or

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Table 8.9: Regulatory enzymes of gluconeogenesis (compare with Table 8.7).

Enzyme	*Activation*	*Inhibition*
PC	Cortisol, glucagon adrenalin, acetyl-CoA	Insulin, ADP
PEPCK	Do	Insulin
F-1,6-bisphosphatase	Do	F-1,6-bisphosphate, AMP, F-2,6-bisphosphate
G-6-phosphatase	Do	Insulin

BOX 8.7 Metabolic Significance of Gluconeogenesis.

- **Only the liver can replenish blood glucose** through gluconeogenesis, because glucose-6-phosphatase is present mainly in the liver. So, the liver plays a major role in maintaining the blood glucose level.
- **During starvation,** gluconeogenesis maintains the blood glucose level. The stored glycogen is depleted within the first 12–18 hours of fasting. On prolonged starvation, gluconeogenesis is speeded up and protein catabolism provides the substrates, namely glucogenic amino acids.

BOX 8.8 Clinical Significance of Gluconeogenesis.

- **Pyruvate carboxylase deficiency:** It is seen as an inborn error of metabolism, where mental retardation is manifested. Its incidence is 1 in 25,000 births. Lactic acidosis is noticed along with hypoglycemia and hyperammonemia.
- **PEPCK deficiency**, though rare, can present with hypoglycemia, lactic acidosis, hypotonia and hepatomegaly.
- **Fructose,1-6 bisphosphate deficiency**: also causes a severe impairment of the pathway, manifested as hypoglycemia, ketosis and lactic acidosis. These enzyme defects are inherited as autosomal recessive traits.
- **PDH deficiency:** can result from arsenic poisoning. Arsenic (As) binds to the SH group of the lipoamide component of PDH.
- **Inherited PDH deficiency:** is an autosomal recessive trait. It is also characterized by hyperlactatemia. Administration of large doses of thiamine has been found to decrease the symptoms and reduce the level of lactate in some cases.
- **Malignant hyperthermia:** This may occur when halothane is given as an anesthetic to certain persons. There is inappropriate release of calcium from the sarcoplasmic reticulum. This results in uncontrolled heat generation, damage of muscle cells, ATP depletion, lactic acidosis and rhabdomyolysis. CPK is markedly elevated. This defect is seen in 1 per 50,000 population.
- **Ethanol (ethyl alcohol)** inhibits gluconeogenesis. During the metabolism of ethanol, the level of cytoplasmic NADH is raised. So, excessive ingestion of alcohol results in hypoglycemia. Lactate also accumulates as the NADH level is high (see under alcohol metabolism).

DN ratio. In such animals, the ratio is 3.65. That means **1 g of nitrogen (from protein) will form 3.65 g of glucose.** Since proteins contain 16% nitrogen; **58% of protein is glucogenic.** GN ratio is enhanced when catabolism is increased, e.g., insulin deficiency, starvation, pyrexia, hyperthyroidism and cancer.

Hyperlactatemia and Lactic Acidosis

Normally the lactate produced by different tissues will be transported to the liver for gluconeogenesis. The normal blood lactate level is 0.5–1mM/L, with an upper limit of 2 mM/L. The lactate : pyruvate ratio is normally around 25. If it is below 25, a deficiency of gluconeogenic enzymes may be suspected.

- Increased production and decreased utilization of lactic acid can lead to **hyperlactatemia**.
- The term **lactic acidosis** is used when the blood lactate level is above 5 mM/L. When lactate levels are between 2 and 5 mmol/L, the plasma pH may be normal. When lactate level is above 5 mM/L, and pH is below 7.35, the condition of high anion gap metabolic acidosis prevails. Lactate to pyruvate ratio may be as low as 10-15:1.

A common cause of hyperlactatemia is hypoxia due to shock or cardiopulmonary failure. Oxygen deprivation leads to a redox state shifts in favor of NADH producing more lactate from pyruvate.

A similar situation arises in excessive alcohol consumption. Ethyl alcohol is metabolized by alcohol dehydrogenase to form acetaldehyde, which is further oxidized to acetate. Both these reactions utilize NAD^+ which gets reduced to NADH.

GLYCOGEN METABOLISM

Carl Cori and Gerty Cori (Nobel Prize 1947) discovered the pathway of glycogen degradation. Glycogen is a homopolysaccharide with glucose units linked in alpha-1,4 linkages (straight line) and alpha-1,6 linkages (branch points). Branching makes the molecule more globular and less space-consuming. For details of the structure, see **Figure 4.23**.

Functions of Glycogen

Glycogen is the storage form of carbohydrates in the human body. The major sites of storage are the liver and muscle. The major function of **liver glycogen** is to provide glucose during fasting. The glycogen content of the liver (10 g/100 g tissue) is more than in the skeletal muscle (1–2 g/100 g). But the total quantity of muscle glycogen is more than liver glycogen because of the larger muscle mass. Glycogen is also found in the brain and kidneys.

When blood glucose level falls, liver glycogen is broken down and helps to maintain blood glucose level. After taking food, blood glucose tends to rise, which causes glycogen deposition in the liver. About 5 hours after taking food, the blood glucose tends to fall. But, glycogen is broken down to glucose so that the energy needs are met. After about

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18 hours of fasting, most of the liver glycogen is depleted, when depot fats are hydrolyzed and energy requirement is met by fatty acid oxidation.

On the other hand, the function of muscle glycogen is to act as a reserve fuel for muscle contraction during the first thirty minutes of contraction. All the enzymes related to glycogen metabolism are cytoplasmic.

Degradation of Glycogen (Glycogenolysis)

Step 1: Glycogen Phosphorylase

- Glycogen phosphorylase removes glucose as glucose-1-phosphate from glycogen (phosphorolysis) **(Fig. 8.31)**. It contains **pyridoxal phosphate** (PLP) as a prosthetic group. The alpha-1,4 linkages in the glycogen are cleaved.
- The enzyme sequentially hydrolyses alpha-1,4 glycosidic linkages, till it reaches a glucose residue, 3-4 glucose units away from a branch point **(Fig. 8.32)**.
- It cannot attack the 1,6 linkage at the branch point. If glycogen phosphorylase alone acts on a glycogen molecule, the final product is a highly branched molecule; it is called **limit dextrin**.

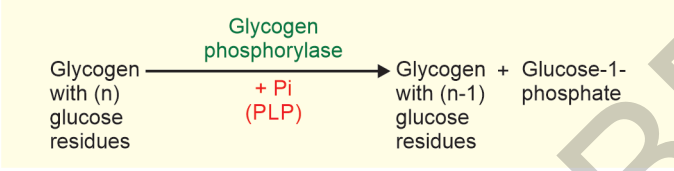


Fig. 8.31: Reaction of glycogen phosphorylase.

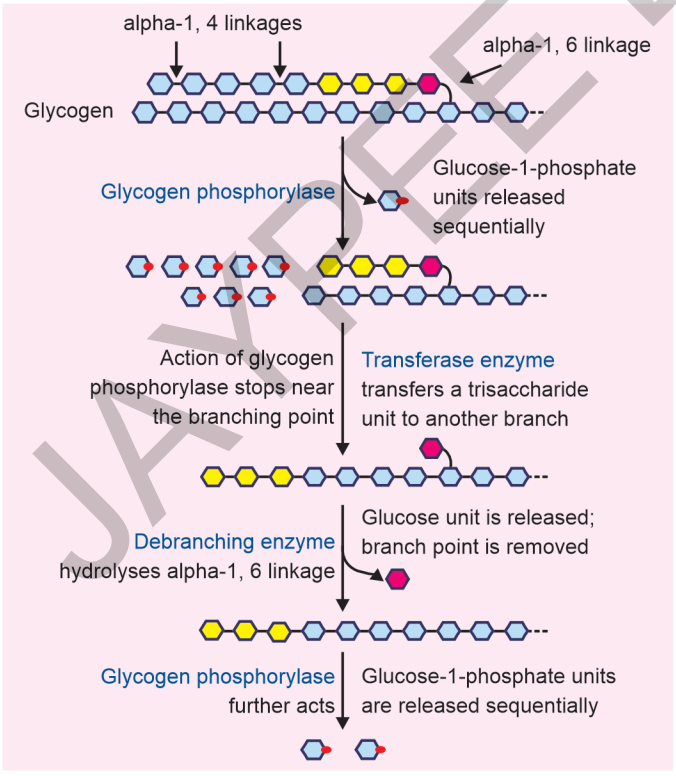


Fig. 8.32: Glycogen breakdown (glycogenolysis) pathway.

Step 2: Debranching by Bifunctional (two) Enzymes

- Then a block of 3 glucose residues (trisaccharide unit) is transferred from the branching point to another branch. This enzyme is called alpha-1,4 → alpha-1,4 glucan **transferase**.
- Now the branch point is free. Then alpha-1,6-glucosidase **(debranching enzyme)** can hydrolyze the remaining glucosyl unit held in alpha-1,6 linkage at the branch point **(Fig. 8.32)**.
- Both these activities are present on the same enzyme molecule. The transferase and debranching enzymes will together convert the branch point to a linear one. With the removal of the branch point, the phosphorylase enzyme can proceed with its action. The glucose residue is released as free glucose.

Step 3: Phosphoglucomutase

Phosphorylase reaction produces glucose-1-phosphate while the debranching enzyme releases glucose. The glucose-1-phosphate is converted to glucose-6-phosphate by phosphoglucomutase **(Fig. 8.33)**.

Step 4: Glucose-6-phosphatase in Liver

- Next, hepatic glucose-6-phosphatase hydrolyses glucose-6-phosphate to glucose. The free glucose is released into the bloodstream.
- It is **important** to remember that muscles will not release glucose to the bloodstream, because muscle tissue does not contain glucose-6-phosphatase.
- Instead, in muscle, glucose-6-phosphate undergoes glycolysis to produce ATP for muscle contraction.

Energetics

In muscle, the energy yield from one glucose residue derived from glycogen is 3 ATP molecules, because no ATP is required for the initial phosphorylation of glucose (step 1 of glycolysis). If glycolysis starts from free glucose only 2 ATPs are produced.

Glycogen Synthesis (Glycogenesis)

The glycogen synthesis occurs by a pathway distinctly different from the reversal of glycogen breakdown, which would prevent the operation of futile cycles. The steps are:

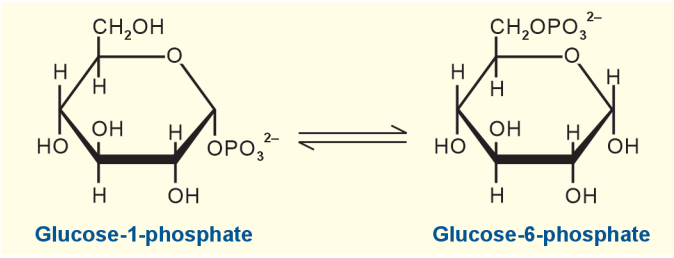


Fig. 8.33: Phosphoglucomutase reaction.

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