

GLYCOGEN METABOLISM

Structure

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3.1 INTRODUCTION

In the preceding unit, we learnt that metabolic pathways such as glycolysis and TCA cycle or at times fermentation oxidize glucose in step wise manner so as to extract maximum energy from it under the physiological conditions. These pathways also provide precursors which are used for other important pathways and synthetic activities. We understood how glucose play central role in energy metabolism. The level of blood glucose is stringently controlled. Excess of glucose is stored in form of glycogen in animals and starch in plants, which are mobilised to provide energy and biosynthetic precursors in case of short term starvation.

In this unit, we shall describe the synthesis (glycogenesis) and breakdown (glycogenolysis) of glycogen in animals. We shall also discuss coordinated regulation of glycogen metabolism and the consequences of genetic deficiencies of enzymes involved in synthesis and degradation of glycogen. In addition to the enzyme regulation, carbohydrate metabolism is also under hormonal regulation which will be explained. Synthesis of glucose from non-carbohydrate sources and glucuronic acid pathways and their importance will also be discussed.

Expected Learning Outcomes

After studying this unit, you should be able to:

- ❖ describe the steps of glycogenesis;
- ❖ explain glycogenolysis and conversion of glucose 1-phosphate to glucose 6-phosphate;
- ❖ describe the coordinated metabolism of glycogen metabolism; and
- ❖ indicate the cause and symptoms associated with glycogen storage diseases;
- ❖ discuss about hormones regulating carbohydrate metabolism;
- ❖ explain gluconeogenesis and justify why it is not reciprocal of glycolysis; and
- ❖ draw reactions of glucuronic pathway and explain its importance.

3.2 GLYCOGEN: A STORAGE POLYMER

Although you have read about glycogen already in the course MBC001, we will just revise it for you to recall. Glycogen is an extensively branched (after every 8-10 residues on average) homopolymer of glucose with approximately 6×10^5 glucose residues. The sugars are linked by α 1,4 glycosidic bonds except at branch points where it is α 1,6 linked (Fig. 3.1). The biological effect of branching is to increase the number of non reducing ends and its solubility. If n is the number of branches, there are $(n+1)$ non reducing ends; both synthesis and degradation of glycogen begins from the non reducing ends.

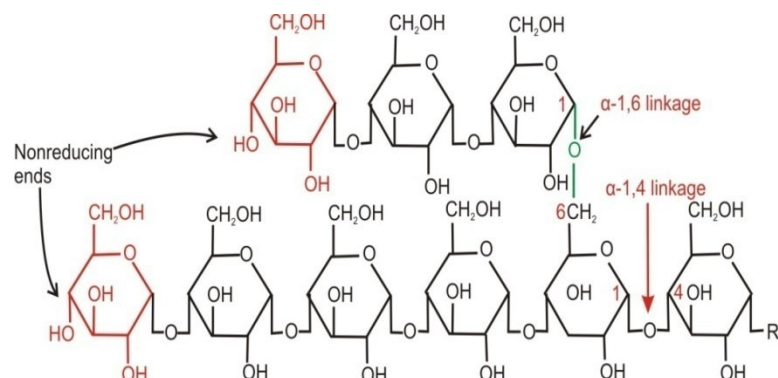


Fig. 3.1: Structure of glycogen.

Glycogen is stored as a heavily hydrated, short term energy reserve in vertebrates and many microorganisms. In animals, it is especially abundant in the liver and muscles. It accounts for as much as 10% weight of the liver and only 1-2% of the mass of muscles in humans. Liver stores are used to provide glucose to other tissues, especially brain and can sustain them only up to 12-24 hours. In muscles, these stores are meant for in-house use such as to provide energy for muscle contraction.

Glycogen is distributed in cytosol as granules. These granules also contain enzymes for its synthesis and degradation. A glycogen granule differs from a multienzyme complex in that the enzymes are not present in defined ratio and it is structurally less organized.

We know that our adipose tissue stores fats as source of energy at times of need, then why nature chose glycogen also when they serve the same function. With reference to animals the possible reasons could be (a) they lack the ability to convert fatty acids to glucose and therefore, fat metabolism alone cannot maintain blood glucose levels or even their complete breakdown, (b) fatty acids cannot be metabolised anaerobically and (c) some tissues cannot use fats as efficiently as glycogen.

SAQ 1

What are the advantages of having glycogen as branched storage polymer?

In the next two sections, we shall discuss synthesis (glycogenesis) and breakdown (glycogenolysis) of glycogen.

3.3 GLYCOGENESIS

The process of synthesis of glycogen from glucose is known as glycogenesis. Glycogen is synthesised in almost all tissues of animals but the most important sites are liver and muscles. As mentioned in section 3.2, the purpose of storing glycogen in both these locations is different. Liver for maintaining blood glucose levels while muscle for their own use.

The first step in glycogenesis is the synthesis of activated donor, UDP-glucose (Fig. 3.2) from glucose 1-phosphate and UTP by **UDP-glucose pyrophosphorylase**. Generally excess glucose in liver and muscles is first converted to glucose 6-phosphate by glucokinase (in liver) or hexokinase (in muscles) and then to glucose 1-phosphate by phosphoglucomutase (PGM). In liver, gluconeogenesis can directly provide glucose 6-phosphate (Fig. 3.3).

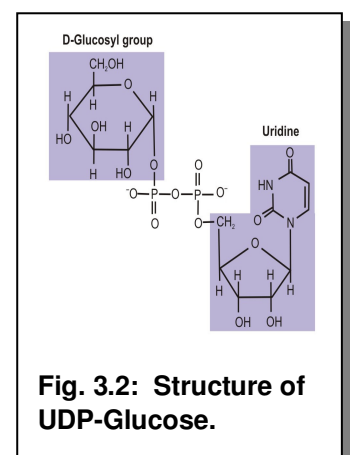


Fig. 3.2: Structure of UDP-Glucose.

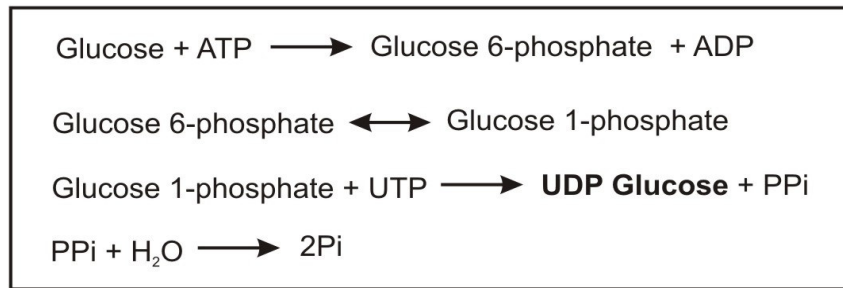


Fig. 3.3: Synthesis of UDP-glucose from glucose.

The reaction catalysed by UDP-glucose pyrophosphorylase proceeds in the direction of synthesis as the product pyrophosphate (PPi) is readily removed by a ubiquitous **inorganic pyrophosphatase**. The biosynthesis of many polymers including DNA and RNA are driven in one direction by hydrolysis of PPi.

The polymerizing enzyme glycogen synthase is incapable of initiating glycogen synthesis. It is a chain elongating enzyme. Therefore, the initial steps of polymerisation are primed by a protein **glycogenin**. It is both an enzyme (glucosyl transferase) and a primer for assembling glycogen chains. The primer is synthesised by step by step addition of eight glucose residues from UDP-glucose by glucosyl transferase; the first one is attached to the tyrosine residue of glycogenin. Further elongation is taken over by glycogen synthase and glycogenin remains bound to the single reducing end.

Glycogen synthase catalyses the transfer of glucose residues from UDP-glucose to the non-reducing end of the growing chain. It links glucose units by α -1, 4 glycosidic bonds (Fig. 3.4). The synthase cannot introduce α -1, 6 linkages at branch points.

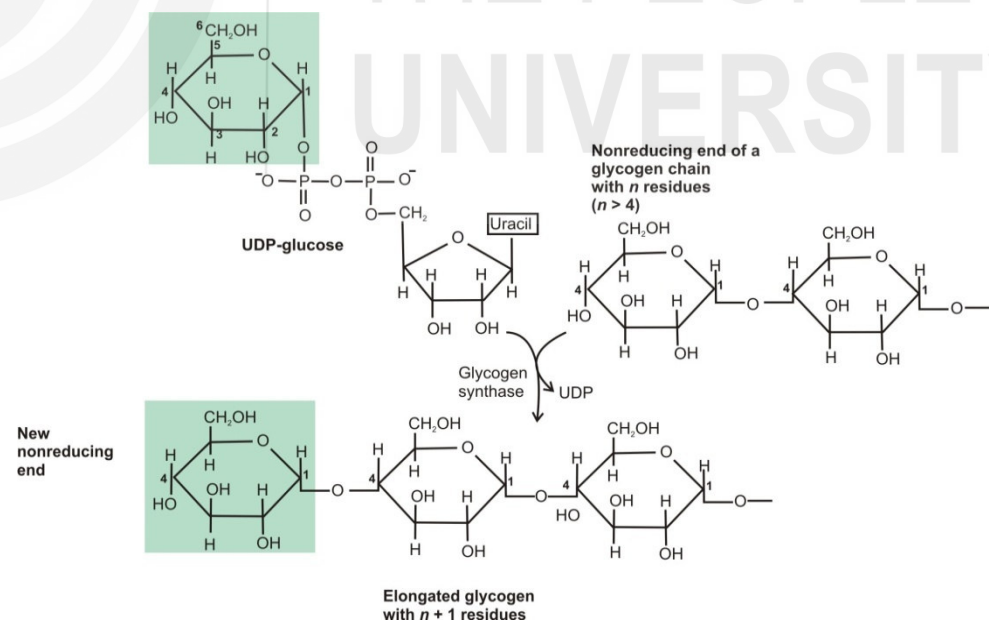


Fig. 3.4: Chain elongation by glycogen synthase.

The final stage is the conversion of a linear chain to a branched polymer by **branching enzyme** (amylo (1 \rightarrow 4) to (1 \rightarrow 6) transglycosylase or glucosyl (4 \rightarrow 6) transferase). This enzyme transfers terminal fragment of five to eight glucose residues from the non reducing end of a glycogen branch that has at

least eleven glucose residues to the C-6 hydroxyl of glucose in the same or another chain. The newly transferred oligosaccharide in the more interior position is linked by α (1 \rightarrow 6) glycosidic bond. Fig. 3.5 gives overview of the complete glycogenesis pathway.

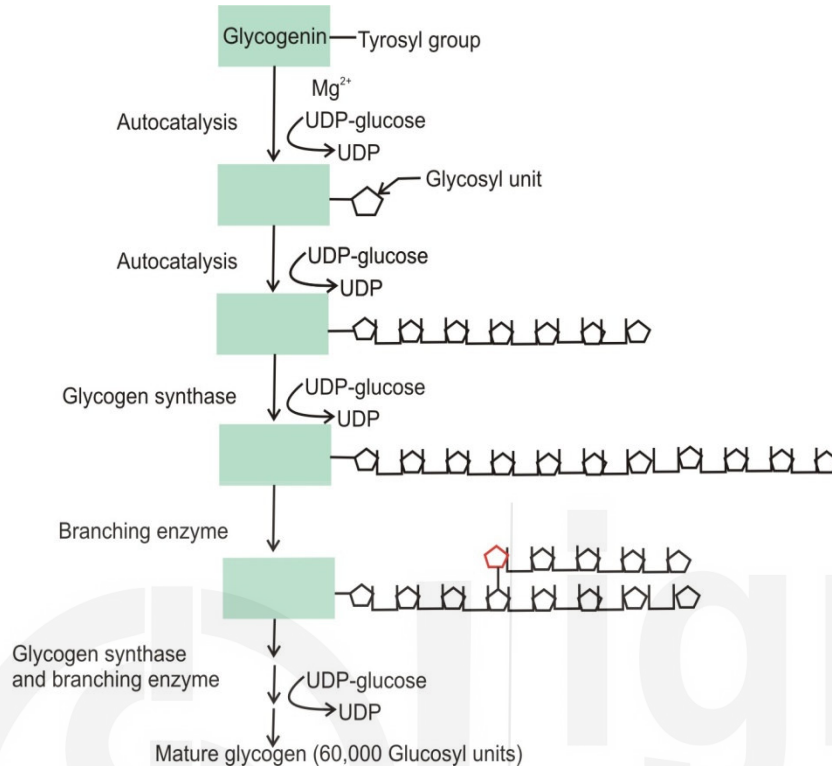


Fig. 3.5: An overview of glycogenesis pathway.

Overall reaction:



For each molecule of glucose incorporated into glycogen, two molecules of ATP are required. One is required for the phosphorylation of glucose and other for the conversion of UDP to UTP.

SAQ 2

- a) Compare glycogenin and glycogen synthase.
- b) Answer the following questions:
 - i) In which organs is glycogen predominantly stored in humans?
 - ii) Which enzyme in liver converts glucose to glucose 6-phosphate?
 - iii) How is glycogen granule different from the multi-enzyme complex?
 - iv) How many ATPs are consumed for each glucose added for glycogen synthesis?

3.4 GLYCOGENOLYSIS

Glycogenolysis is the process of conversion of glycogen to glucose-1 phosphate (90%) and to a lesser extent to glucose (10%). The breakdown of glycogen is catalysed by a separate set of enzymes than those used for synthesis. It is initiated by **glycogen phosphorylase**; but it stops cleaving four residues before a branch point. Further degradation is dependent on other enzymes that remodel the substrate for phosphorylase to resume degradation.

Glycogenolysis is the breakdown of glycogen to glucose-1 phosphate by glycogen phosphorylase. It is the key enzyme in glycogen breakdown and is subject to stringent regulation.

Glucose-1-phosphate and free glucose are produced in a ratio 8:1 in glycogenolysis.

It is interesting to note that hydrolysis of dietary glycogen does not involve phosphorolysis but is degraded by the combined action of amylases, debranching enzymes and maltase to un-phosphorylated sugars, facilitating its absorption.

Glycogen phosphorylase (homodimer) catalyses the sequential removal of glucose residues by phosphorolytic cleavage of α -1,4- glycosidic bonds from the non-reducing end of glycogen. The product released is glucose-1-phosphate (Fig. 3.6).

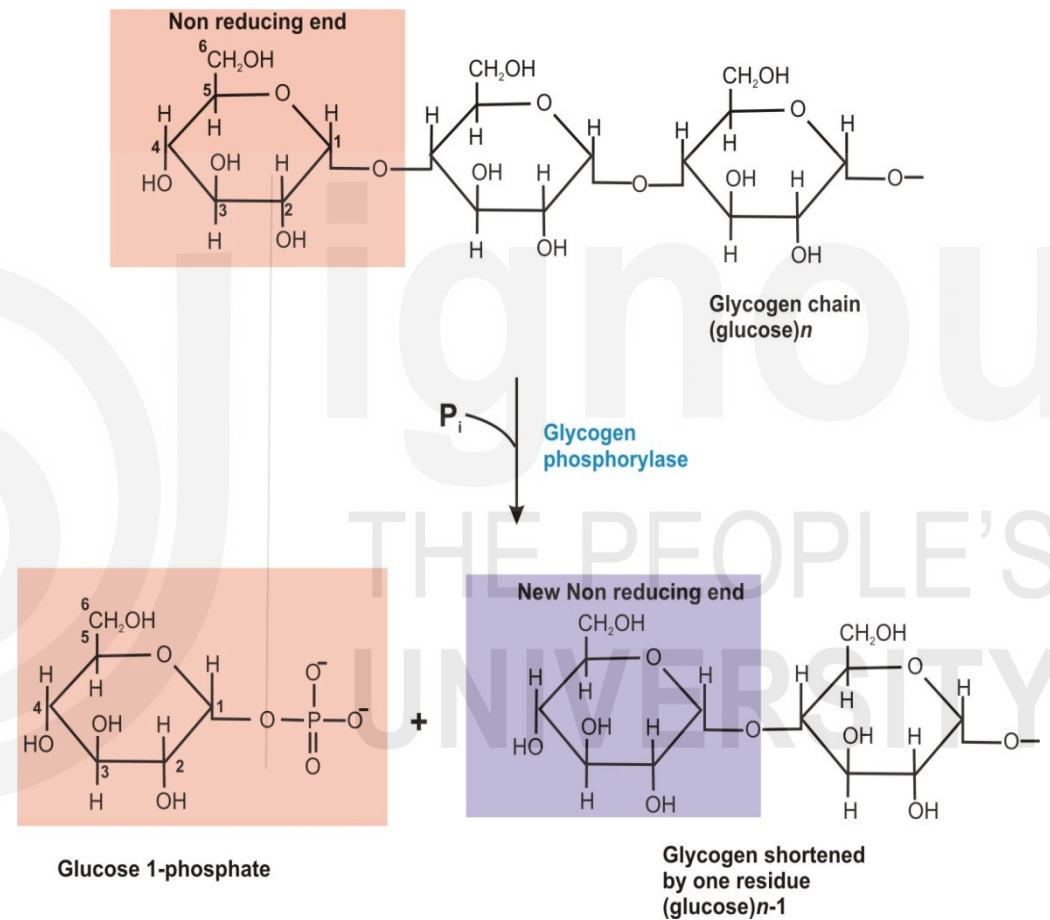


Fig. 3.6: Phosphorolytic cleavage of glycogen by glycogen phosphorylase.

The reaction proceeds in the direction of breakdown *in vivo* as the intracellular ratio of [P_i] / [glucose 1-phosphate] is high (30-100). The enzyme requires pyridoxal phosphate (PLP) which plays an unusual role along with orthophosphate as a general acid-base catalyst. You will study the role of PLP as a versatile cofactor in amino acid metabolism. The release of phosphorylated sugar is energetically advantageous as compared to simple hydrolysis to glucose as it can then enter catabolic pathways like glycolysis or pentose phosphate pathway following isomerization to glucose 6-phosphate. You may have noticed that by this mechanism the activation of glucose by hexokinase is bypassed. In addition, the negatively charged sugar phosphate would not leave the cell.

The process continues until four glucose residues remain on either side of the branch point. The branched structure so formed is called **limit dextrin** and cannot be further metabolized by glycogen phosphorylase. The processing of the branched intermediate to an unbranched substrate suitable for phosphorylase action is catalysed in eukaryotes by a bifunctional **debranching enzyme**. The two enzymes that catalyse two successive reactions are glycosyl transferase and amylo α -1,6-glucosidase.

The glycosyl transferase transfers a trisaccharide from an outer branch to the non reducing end of another branch leaving a single glucose residue at the branch point. Now glucose at the branch point, linked via α -1,6 linkage is hydrolytically released by amylo α -1,6-glucosidase (Fig. 3.7). This reaction accounts for the minor product (10%) of glycogen breakdown. It may either be released (in case of liver) or phosphorylated before feeding to other pathways.

At this stage glycogen phosphorylase can resume degradation of the unbranched product to glucose-1-phosphate.

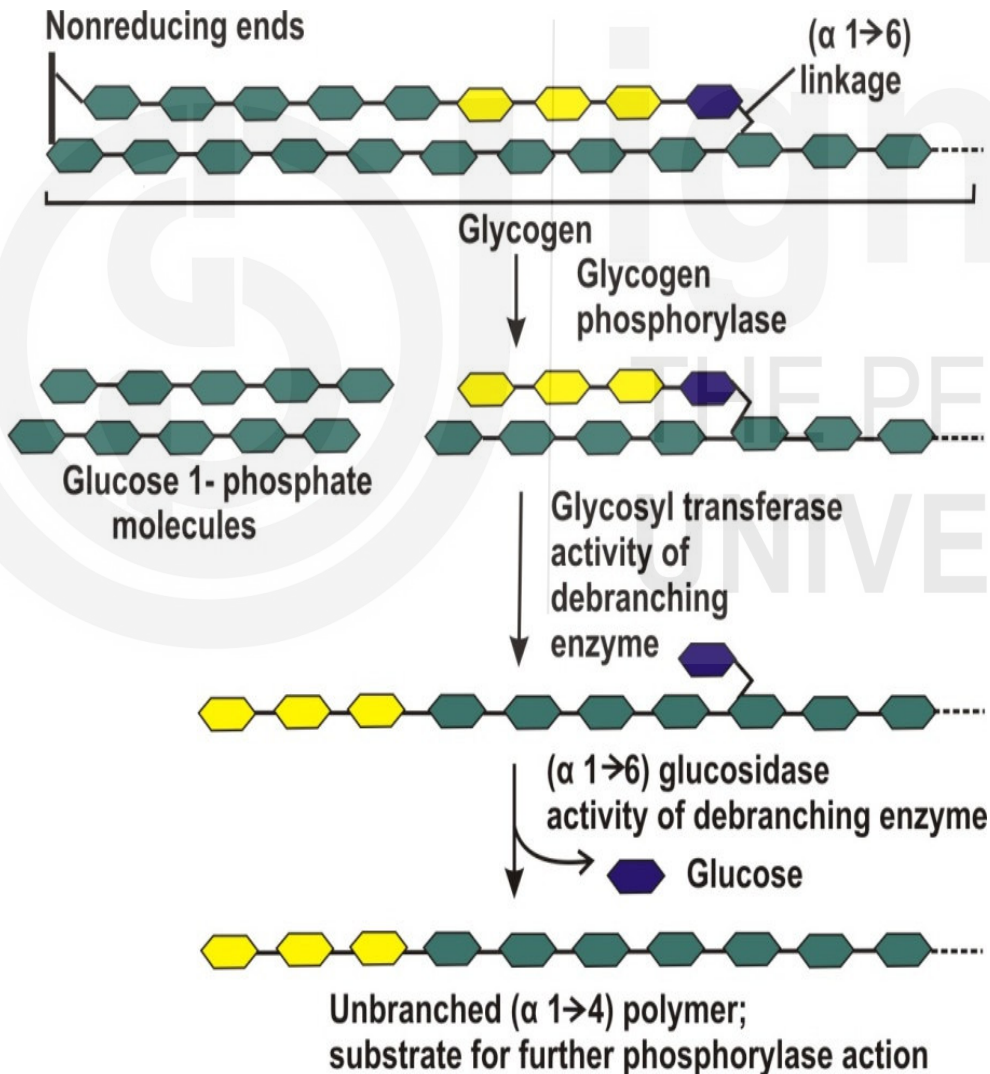


Fig. 3.7: Action of debranching enzyme on limit dextrin.

The fate of glucose-1-phosphate varies, depending on the tissue following its conversion to glucose-6-phosphate by **phosphoglucomutase** (Fig. 3.8). The reaction proceeds via an enzyme bound intermediate, glucose 1,6 biphosphate.

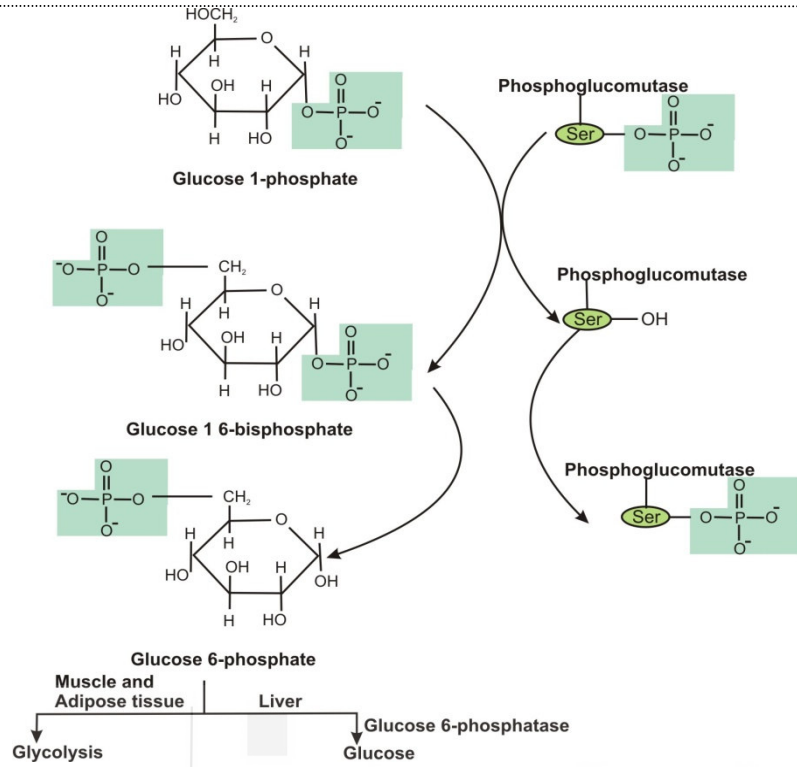


Fig. 3.8: Conversion of glucose-1-phosphate to glucose-6-phosphate by phosphoglucomutase (PGM).

The liver expresses a hydrolytic enzyme **glucose-6-phosphatase** that converts glucose-6-phosphate to glucose. Glucose is not a major fuel for the liver. On the contrary, it is released into circulation to be made available to other tissues especially between meals and muscular activity. You have already studied this enzyme in gluconeogenesis. Since glucose-6-phosphatase is absent in muscle and adipose tissue, therefore free glucose cannot be produced/released from these tissues. Instead, glucose-6-phosphate produced by the combined action of glycogen phosphorylase and PGM enters glycolysis to generate energy for muscle contraction. The fate of glucose-6-phosphate in different tissues is summarised in Fig. 3.9 as discussed in last unit also.

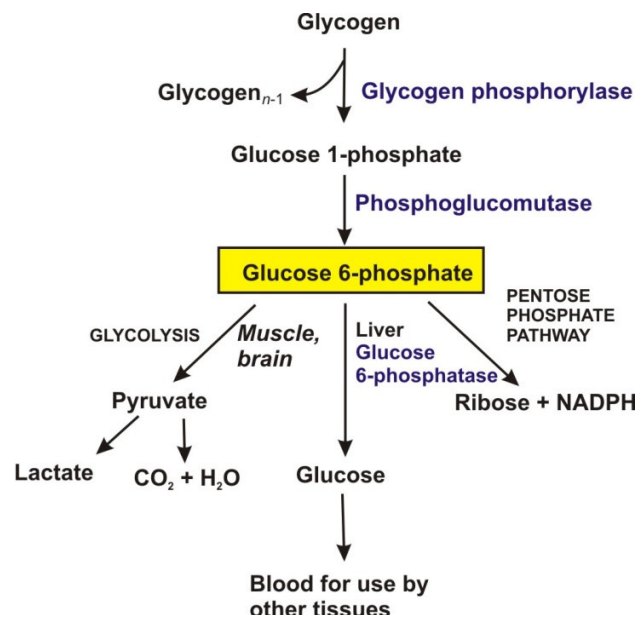


Fig. 3.9: Fates of glucose-6-phosphate in different tissues.

SAQ 3

Name the enzymatic activities of debranching enzyme.

3.5 REGULATION OF GLYCOGEN METABOLISM

Glycogenesis occurs when blood glucose levels are high such as after a meal and glycogenolysis is favored when blood glucose levels are low, for instance during fasting or vigorous exercise.

The coordinated regulation of glycogenesis and glycogenolysis occurs by both; allosteric modulators and hormones. The hormones act by inducing reciprocal covalent modifications. The major hormones involved are glucagon, epinephrine and insulin. While glucagon and epinephrine (adrenaline) trigger the breakdown of glycogen; insulin favors glycogen synthesis. Glucagon action is more pronounced on liver than muscle whereas epinephrine mainly acts on muscle.

The key enzymes of synthesis and degradation (glycogen synthase and phosphorylase) are the primary targets of regulation. The isozymes of glycogen phosphorylase present in liver and muscle respond differently to regulators, which in turn is accordance with their role.

Carl and Gerty Cori showed the existence of two interconvertible forms of glycogen phosphorylase in skeletal muscles: *phosphorylase a* and *phosphorylase b*; the former was active while the latter was less active. The active form of phosphorylase is phosphorylated while less active/inactive form is dephosphorylated (Fig. 3.10). Their inter conversion is triggered by hormones and allosteric modulators. The hormones activate an enzyme cascade leading to enormous amplification of the initial signal.

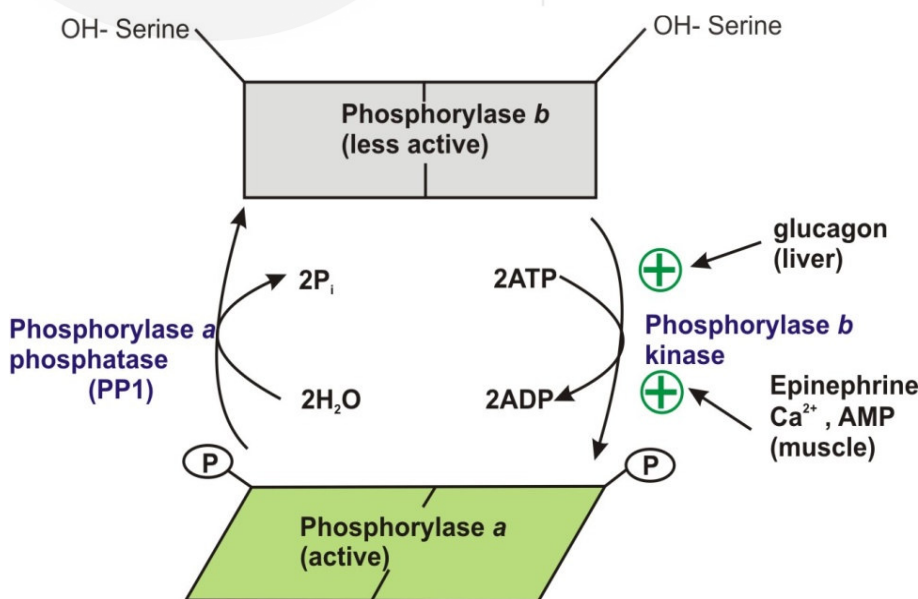


Fig. 3.10: The two interconvertible forms of glycogen phosphorylase.

Let us consider the regulation in both skeletal muscle and liver. During vigorous muscular activity or a fall in blood glucose, the hormone released (epinephrine or glucagon) act through cell surface receptors on muscle or liver cells by inducing the synthesis of an intracellular second messenger, cAMP (cyclic AMP). The second messenger transduces the signal by activating protein kinase A (PKA) which sets into action a cascade of phosphorylations.

Glycogen phosphorylase acts as sensor of glucose while glycogen synthase senses glucose -6-phosphate.

The activated PKA phosphorylates *phosphorylase b* kinase, activating it to phosphorylate glycogen *phosphorylase b* converting it into *phosphorylase a*. Glycogen *phosphorylase a* (active) degrades glycogen to glucose 1-phosphate that may be oxidized to provide energy for muscle contraction or released as glucose from the liver through the action of glucose 6-phosphatase to maintain blood glucose levels (Fig. 3.11).

The allosteric control mechanisms differ in muscle and liver. In the muscle, calcium which is a signal for muscle contraction activates *phosphorylase b* kinase and AMP activates phosphorylase; both increase the rate of glycogen breakdown. ATP has an opposite effect to AMP. The liver isozyme of glycogen phosphorylase is allosterically inhibited by glucose; at this point blood glucose levels return to normal.

The conditions that favor glycogenolysis inhibit glycogenesis. The active form of glycogen synthase (a-form) is converted into inactive form (b-form) by phosphorylation. The enzyme remains phosphorylated unless glucose 6-phosphate (allosteric activator) is present. The reciprocal regulation in response to hormonal signals is depicted in Fig. 5.11.

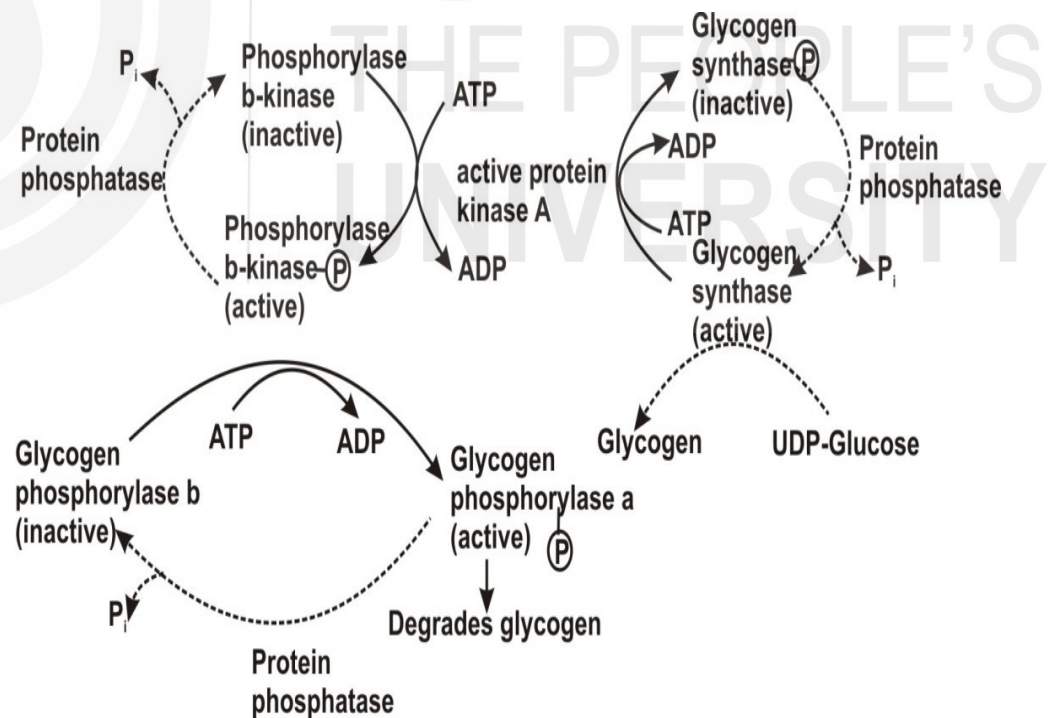


Fig. 3.11: Hormonal regulation of glycogen metabolism by reversible covalent modification.

It is important to note here that glycogen synthase can be phosphorylated by a variety of protein kinases; among these glycogen synthase kinase 3 (GSK3) plays important role in its regulation.

Insulin is antagonistic to epinephrine. It is released when blood glucose levels are elevated. When insulin binds to target cell surface, it inhibits the activity of adenylate cyclase. Thus protein kinase A is not activated. Glycogen synthase remains active and the net result is glycogen synthesis occurs when blood glucose levels are high. It is interesting that insulin activates another kinase, protein kinase B (PKB) which phosphorylates and inactivates GSK3. Inactivation of GSK3 means glycogen synthase remains dephosphorylated (active form), again favoring glycogen synthesis.

While phosphorylation of these enzymes is mediated by different types of kinases, dephosphorylation of all three enzymes; glycogen synthase, glycogen *phosphorylase* and phosphorylase kinase b is by protein phosphatase I (PPI) (Fig 3.11). It is inactivated by phosphorylation by PKA and activated by the positive modulator, glucose 6-phosphate.

SAQ 4

Indicate whether the phosphorylated form of the following enzymes is active or inactive?

- i) Glycogen phosphorylase
- ii) Protein phosphatase I
- iii) Glycogen synthase

3.6 SIGNALLING AND HORMONAL REGULATION OF CARBOHYDRATE METABOLISM

The essence of carbohydrate metabolism lies at maintenance of blood glucose levels. Rise in blood glucose levels such as following meals is brought down by promoting (i) its uptake by cells and utilization for energy through glycolytic, TCA and oxidative phosphorylation pathways (ii) storage as glycogen in liver and muscle as short term energy reserve and (iii) conversion to triacylglycerols in adipose tissue. At the same time, pathways which generate glucose such as gluconeogenesis and glycogenolysis are inhibited.

Liver primarily has processing and distribution function by providing all other organs and tissues with an optimum level of nutrients via the bloodstream. The role of liver is so important that the whole organ system is divided into hepatic and extra hepatic. Liver and kidney are responsible for the synthesis of the glucose, whereas brain, muscle, blood cells and other extra hepatic tissues utilize glucose for energy.

The inter organ coordination of carbohydrate metabolism is mediated by hormones which fall broadly into two groups based upon their role:

(a) Those which exert a fundamental regulatory influence; their normal function being essential for optimal carbohydrate metabolism, for example, hormones of pancreatic islet cells especially insulin and glucagon and hormones of adrenal cortex and anterior pituitary.

(b) Those which influence carbohydrate metabolism, but are not essential for its regulation under normal physiological conditions, e.g. thyroid hormones.

When blood glucose concentration is high, insulin secreted by pancreatic β cells promotes glucose uptake by cells and its oxidation through glycolysis to lower glucose levels. It also inhibits enzymes of glycogenolysis and promotes glycogenesis. On the other hand, when glucose concentration drops, such as several hours after a meal or during exercise, glucagon released by pancreatic α - cells promotes gluconeogenesis and glycogenolysis and release of glucose by the liver to raise the blood glucose levels. Glucagon promotes uptake of amino acids from the blood by liver hepatocyte, and convert them to glucose. A rise in blood glucose levels inhibits glucagon via a negative feedback mechanism. Thus, insulin and glucagon help to maintain glucose homeostasis.

In addition to these two hormones, cortisol secreted by adrenal cortex increases blood glucose level by promoting gluconeogenesis from amino acid pool and diminishing peripheral uptake and utilization of glucose. It also increases liver glycogen with the increased activity of glycogen synthase.

Growth hormone and ACTH (adrenocorticotropin) secreted by the anterior pituitary hormones raise the blood glucose level and antagonize the effect of insulin as their secretion is stimulated by hypoglycemia. Thyroxine, a thyroid hormone accelerates hepatic glycogenolysis, with consequent rise in blood glucose. Thyroid hormones may also increase the rate of absorption of hexoses from the intestine and hepatic glucose-6-phosphatase activity. Excessive thyroid hormones increase the rate of protein catabolism, thereby promoting gluconeogenesis from amino acids.

The partial degradation of most amino acids except lysine and leucine generate one or more gluconeogenic precursors. These amino acids are classified as glucogenic amino acids.

Surprisingly, xylulose which is an intermediate of pentose phosphate pathway is a strong regulator of carbohydrate levels. Following intake of a carbohydrate meal, when glucose levels are high, glycolysis and pentose phosphate pathways are activated in liver. Xylulose phosphate produced by PPP activates protein phosphatase 2A (PP2A) that in turn triggers dephosphorylation of bifunctional PFK2/F2,6BPase increasing F2,6BP levels. It promotes glycolysis and inhibits gluconeogenesis. Simultaneously, PP2A dephosphorylates carbohydrate -responsive element- binding protein (ChREBP). It is a transcription factor that activates expression of liver genes to synthesize lipids. Activation of both, glycolysis and ChREBP result in increased acetyl CoA, the principal substrate of lipid biosynthesis (Fig. 3.12).

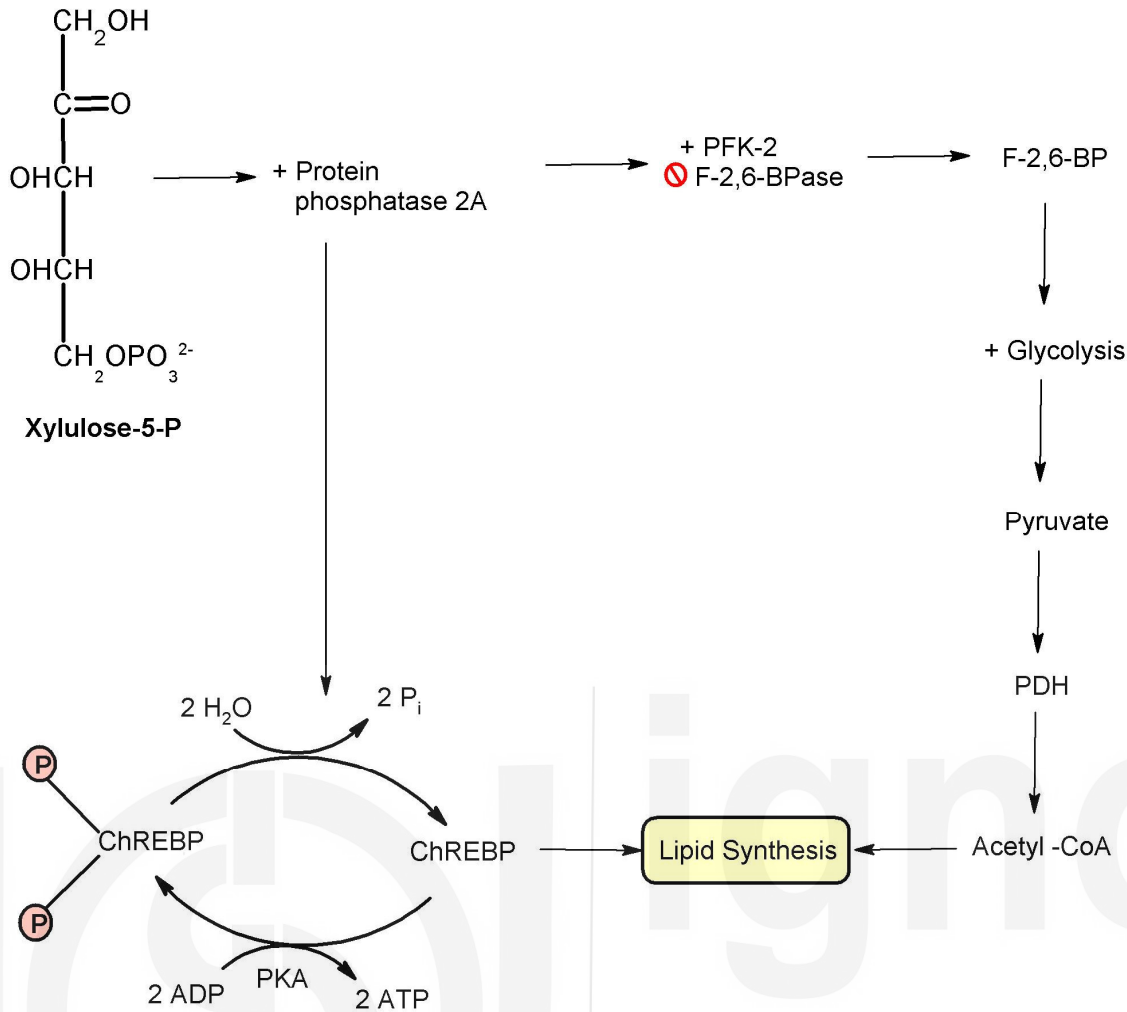


Fig. 3.12: Role of xylulose 5-phosphate as metabolic regulator of carbohydrates.

3.7 SYNTHESIS OF GLUCOSE FROM NON-CARBOHYDRATE SOURCES

Gluconeogenesis refers to synthesis of glucose from non-carbohydrate precursors such as lactate, pyruvate, glycerol, and products derived from glucogenic amino acids. These precursors are either converted to pyruvate or they may enter as intermediates at other points in the pathway such as DHAP and OAA. You may recall that lactate is formed in skeletal muscles during vigorous exercise which is readily oxidised to pyruvate in the liver. The gluconeogenic precursors derived from partial breakdown of amino acids come from proteins in our diet or skeletal muscles during starvation. Similarly, hydrolysis of triacylglycerols yields glycerol and fatty acids.

You know that glycogen stored in liver can at best provide postprandial glucose only for about a day. In case of longer fasting, these stores are depleted and gluconeogenesis becomes increasingly important to maintain blood glucose levels. In addition, animals lack the ability to convert fatty acids to glucose.

You may appreciate the importance of this pathway from the fact that gluconeogenesis contributes as much as 64% of glucose during first 22 hrs of

fasting and accounts for almost all the glucose production by 46 hrs. In nutshell, gluconeogenesis:

- is essential in maintaining blood glucose levels especially during prolonged fasting thereby ensuring continuous supply of glucose to the brain and other organs that prefer glucose over other carbon sources;
- removes certain metabolites from circulation which may be harmful if their concentration reach toxic levels such as lactate.

Most reactions of gluconeogenesis occur in the cytosol while few of these are catalysed by mitochondrial enzymes. In mammals, liver is the major site of gluconeogenesis and to some extent kidneys and epithelial cells lining the small intestine also help to maintain blood glucose levels. Even brain, skeletal and heart muscles also do limited glucose synthesis from non carbohydrate precursors.

3.7.1 Gluconeogenesis from Pyruvate/Lactate

The conversion of pyruvate or other non carbohydrate precursors to glucose is not a simple reversal of glycolysis. The two pathways differ in three essentially irreversible steps of glycolysis that account for most of the negative free energy change. We will study in detail how these three steps are bypassed in gluconeogenesis by separate enzymes. These three reactions are also irreversible under cellular conditions. As expected the two pathways are subject to reciprocal regulation at these three steps. Let us learn about the unique reactions of gluconeogenesis.

a) Conversion of pyruvate to phosphoenolpyruvate (PEP)

The first reaction in gluconeogenesis is an energy dependent conversion of pyruvate to PEP. It is a two step reaction catalysed by **pyruvate carboxylase** and **PEP carboxykinase** (Fig. 3.13a). These enzymes are compartmentalised in mitochondria and cytoplasm, respectively.

The substrate, pyruvate for the first reaction comes from either transamination of alanine in the mitochondria itself or glycolysis in the cytosol followed by transport to mitochondria. It is converted to oxaloacetate by biotin dependent **pyruvate carboxylase**. This reaction requires ATP and CO₂. The carboxylation proceeds via activation of bicarbonate by ATP to form carboxyphosphate which is then transferred to the N-1 of biotin, covalently bound to the enzyme. The vitamin biotin functions as a carrier of activated CO₂ that is finally transferred to pyruvate forming OAA. This reaction occurs only when the positive activator, acetyl CoA is bound to the enzyme. We have come across this reaction earlier as an important way to replenish TCA intermediates.

Oxaloacetate cannot cross mitochondrial membrane; therefore, it is reduced to malate by mitochondrial **malate dehydrogenase**. You have come across this reaction in TCA cycle although it performs different role in gluconeogenesis and TCA cycle. Malate is transported by a specific transporter present in the inner mitochondrial membrane to cytosol where it is reoxidised back to OAA

by cytosolic **malate dehydrogenase**. The reduction of NAD^+ to NADH in the cytosol provides NADH for gluconeogenesis. By using this complicated way to synthesise PEP, the organism has successfully shuttled reducing equivalents in the form of malate to the cytosol.

The second step catalysed by PEP carboxykinase requires GTP to bring about the decarboxylation and stabilisation of the unstable enol by phosphorylation to form PEP. The CO_2 released is the same carbon that was added in the preceding step in the mitochondria (Fig. 3.13a).

The two step conversion of pyruvate to PEP is energetically more favourable at cellular concentrations of intermediates than a single step although two high energy phosphate bonds have been consumed. This is a common theme in biochemistry where decarboxylations drive an unfavourable reaction such as in fatty acid biosynthesis.

The net outcome of these reactions is:



In situations, when lactate is the gluconeogenic precursor such as skeletal muscles during vigorous exercise or erythrocytes; pyruvate is formed from lactate oxidation by lactate dehydrogenase in the cytosol.

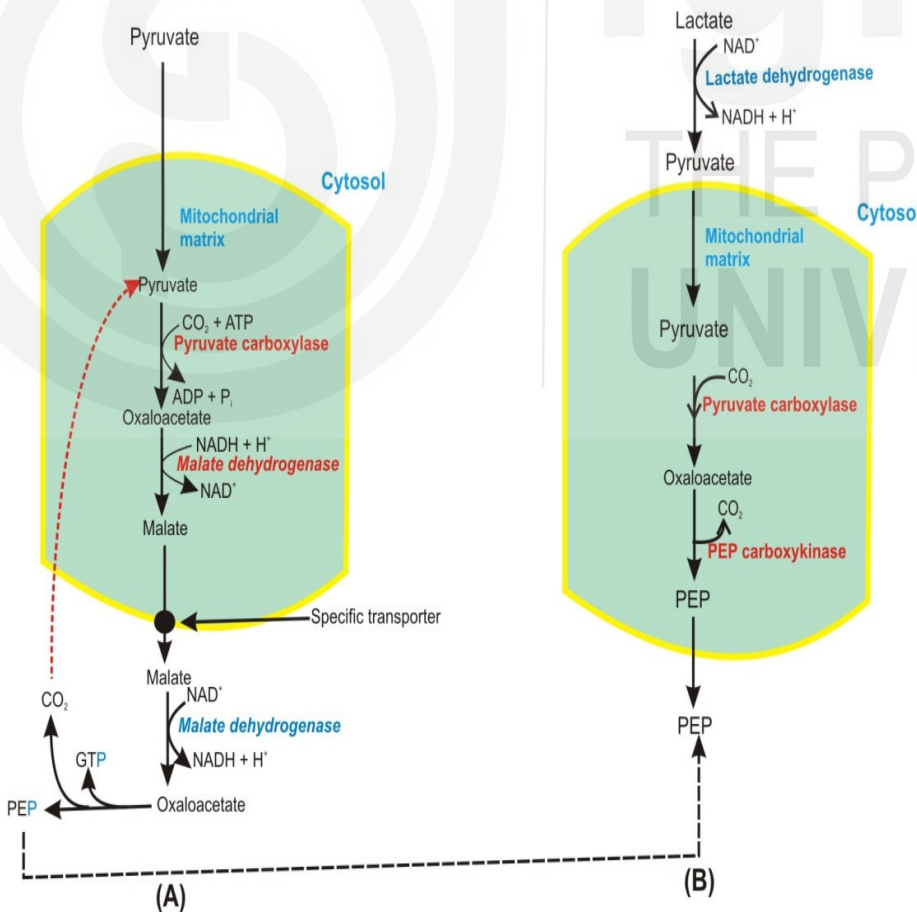


Fig. 3.13: The conversion of pyruvate to phosphoenol pyruvate. Gluconeogenesis from (a) pyruvate (b) lactate.

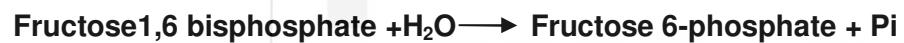
The conversion of pyruvate to PEP takes place in the mitochondria by the same two steps; the difference being the mitochondrial isozyme of PEP carboxykinase catalyses the second step (Fig. 3.13b).

In this route we do not need to reduce OAA in one compartment and reoxidise in the other because NADH to support gluconeogenesis has already been produced by lactate dehydrogenase catalysed reaction. Recall Cori cycle from unit 2, that operates between the liver and skeletal muscles under oxygen stress.

PEP can proceed in the direction of glucose synthesis up to fructose 1,6 bisphosphate by the enzymes of the glycolytic cycle working in the reverse direction. As you know that the reaction catalysed by PFK-1 is the second irreversible step of glycolysis.

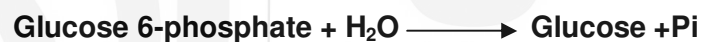
b) Conversion of fructose 1,6-bisphosphate to fructose 6-phosphate

Fructose-1,6-bisphosphate is hydrolysed to fructose-6-phosphate and Pi by **fructose-1,6-bisphosphatase**. The enzyme requires Mg^{2+} for its activity and is absent in smooth muscles.



c) Conversion of glucose-6-phosphate to glucose

The last bottleneck in the generation of glucose is overcome by another hydrolytic enzyme, **glucose-6-phosphatase**. It converts glucose-6-phosphate to glucose.



In most tissues free glucose is not produced and gluconeogenesis ends at glucose-6-phosphate that is used by cells for their own metabolism or stored as glycogen. The organs / tissues which are responsible for maintaining blood glucose express glucose-6-phosphatase. These include the liver, renal cortex and epithelial cells of small intestine. This reaction takes place in the (endoplasmic reticulum). Glucose is transported from the cytosol to the ER lumen via transporter shown as T1 where it is hydrolysed by membrane bound glucose-6-phosphatase. Both glucose and Pi are returned to the cytosol by separate transporters (T3 and T2). The enzyme is stabilised by a Ca^{2+} binding protein (SP; Fig. 3.14).

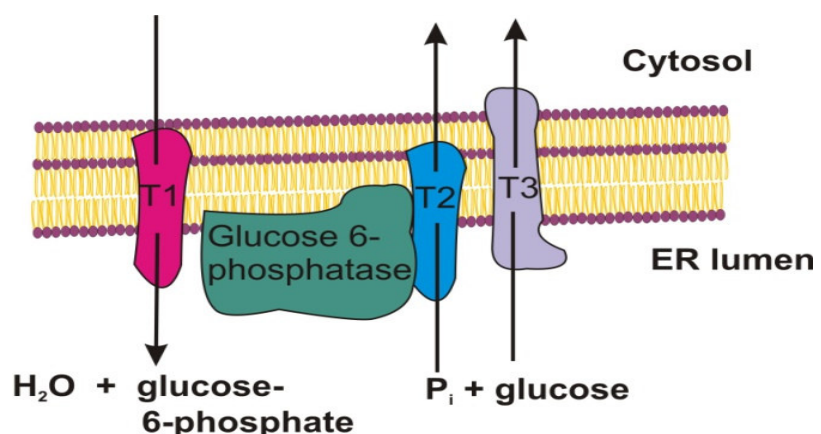


Fig. 3.14: Formation of glucose from glucose-6-phosphate in ER.

Free uncharged glucose can be released into blood by a glucose transporter to be taken up by other tissues. Fig. 3.15 summarizes the reactions of glycolysis and gluconeogenesis. The enzymes catalysing the unique steps are highlighted with different colours and common reactions with black arrows.

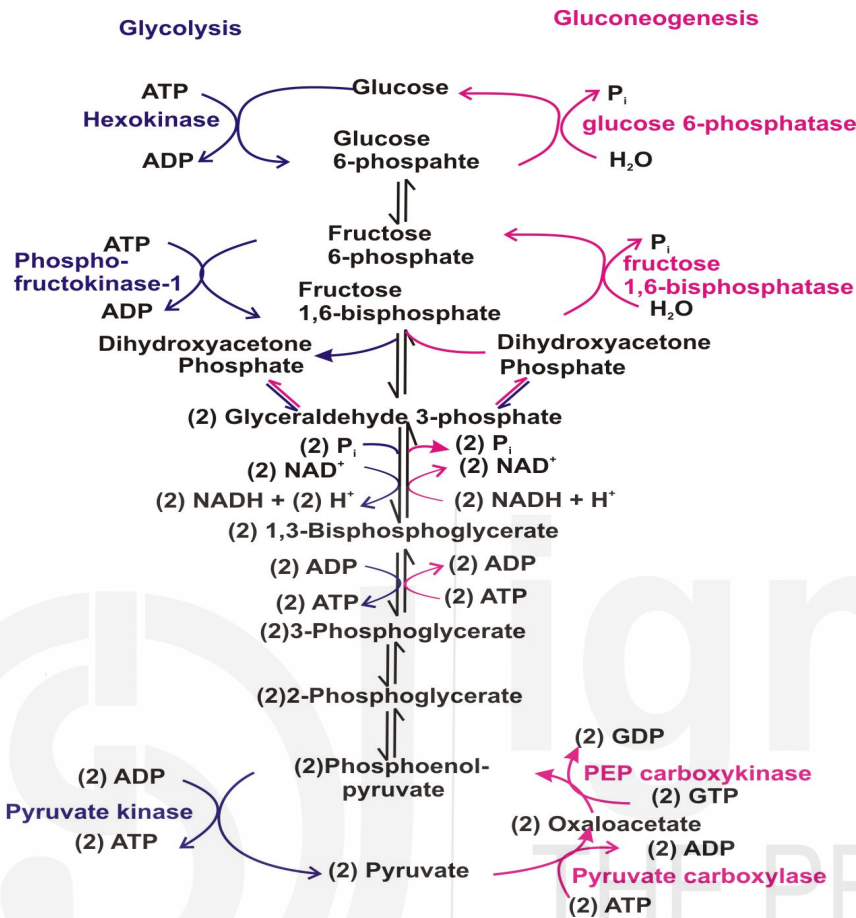
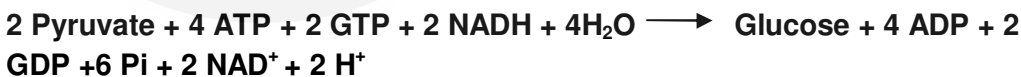


Fig. 3.15: Reactions of glycolysis and gluconeogenesis.

The synthesis of glucose starting from pyruvate is an energetically expensive process. The net reaction is:



It is clear from the net reaction that for glucose formed from pyruvate (two), six high energy phosphate bonds (4ATP and 2GTP) and 2 NADH are consumed. It is much higher than the energy requirement if gluconeogenesis was a simple reversal of glycolysis. The increased energy cost is to make gluconeogenesis irreversible under cellular conditions and exercise independent control.

3.7.2 Gluconeogenesis from Precursors other than Pyruvate

Gluconeogenesis occurs in almost all organisms ranging from animals, plants, fungi and microorganisms. In all groups, the pathway has been conserved throughout evolution. In addition to pyruvate many other compounds can serve as gluconeogenic precursors. These compounds can either be converted to pyruvate or OAA or other intermediates of the TCA and glycolytic cycle. In this section let us study few examples of such gluconeogenic compounds.

(a) Propionate

Propionyl CoA is produced from β -oxidation of odd chain fatty acids; break down of amino acids such as methionine and isoleucine and in some microbes grown on propionate. It is converted to succinyl CoA (TCA cycle intermediate) in three steps. The details of these reactions will be discussed in fatty acid catabolism. Succinyl CoA enters the TCA cycle for a not conversion to OAA; substrate from the first step of gluconeogenesis.

(b) Glycerol

Glycerol is produced from the hydrolysis of triglycerides. It is converted to a gluconeogenic intermediate in two steps. Glycerol is phosphorylated at C-3 by phosphoryl group transfer from ATP by **glycerol kinase** to glycerol-3-phosphate that is then oxidised to dihydroxyacetone phosphate (DHAP) by NAD^+ dependent **glycerol-3-phosphate dehydrogenase** as shown in the Fig. 3.16.

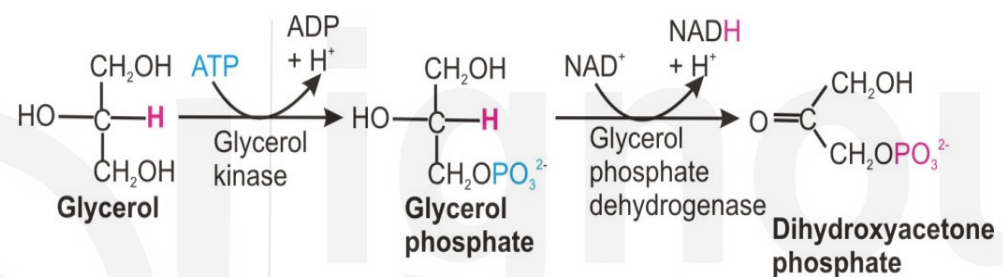


Fig. 3.16: The synthesis of DHAP from glycerol.

(c) Amino acids

The partial breakdown of most amino acids forms one or more gluconeogenic products ranging from pyruvate to intermediates of TCA cycle like succinyl CoA, fumarate or α -ketoglutarate. All these compounds can be converted to glucose once they are oxidised to OAA by TCA cycle. Such amino acids are called glucogenic. But in case of organisms that possess the glyoxylate cycle, all amino acids are glucogenic.

(d) Fatty acids and acetyl CoA

All organisms that possess the enzymes of the glyoxylate cycle are able to synthesise glucose from acetyl CoA, derived from degradation of few amino acids or fatty acids. The glyoxylate cycle produces 4C-TCA intermediate starting from two acetyl CoA molecules which is gluconeogenic.

SAQ 5

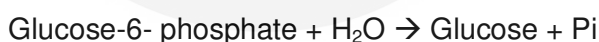
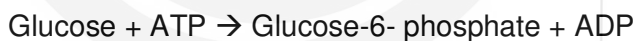
- a) Answer the following questions in brief:
 - i) Name the enzymes of gluconeogenesis unique to the pathway.
 - ii) Why has nature selected a complex and expensive route to produce glucose from pyruvate instead of a simple reversal of glycolysis?

- b) Fill in the blanks:
- i) is an allosteric activator of pyruvate carboxylase.
- ii) In animals, glucose cannot be synthesised from
- iii) A gluconeogenic enzyme bound to the ER membrane is
- iv) Propionyl CoA is produced by the partial breakdown of and
- v) Glycerol is converted to before it enters gluconeogenesis / glycolysis.

3.8 RECIPROCAL REGULATION OF GLYCOLYSIS AND GLUCONEOGENESIS

You have learnt in the previous section that glycolysis and gluconeogenesis share seven out of the ten reactions. These reactions are freely reversible and are catalyzed by the same enzymes. The three irreversible reactions of glycolysis which are highly exergonic are bypassed by alternate set of enzymes as explained earlier. The bypass reactions are also irreversible and are accompanied by a large negative free energy change.

This brings in an interesting scenario. If each of the irreversible reactions of both pathways takes place at the same time in the same cell, it will lead to release of usable energy without doing any useful biological or chemical work. For example, consider reactions catalyzed by hexokinase and glucose-6-phosphatase occurring simultaneously:



Net reaction: $\text{ATP} + \text{H}_2\text{O} \rightarrow \text{ADP} + \text{Pi} + \text{Heat}$

There is no useful product formed and energy released by ATP hydrolysis will be dissipated as heat. Such apparently wasteful set of reactions constitute a **futile cycle**. Similar cycles also operate with other two set of reactions of glycolysis and gluconeogenesis. You will be surprised to know that these cycles have an additional role of amplifying metabolic signals and are better described as **substrate cycles**. In order to exercise metabolic control, the opposing reactions occur at different rates to alter the net flux in response to signals.

The coordinated and reciprocal regulation of glycolysis and gluconeogenesis is mainly governed by energy status and blood glucose levels. The reciprocal regulation of both pathways is exercised at the three irreversible steps. The two opposing pathways are under both short and

Glycolysis and gluconeogenesis are not mere reversal of the same pathway. The two pathways are regulated at the three unique steps which are irreversible under cellular conditions.

Allosteric regulation is quicker and reversible mechanism of control. It does not depend on net change in the amount of enzyme.

long term regulation. The former is through alteration of enzyme activity by negative and positive allosteric modulators, reversible covalent modifications and by binding of regulatory proteins while the latter is at the level of transcription and results in a net increase or decrease in the amount of enzymes. The short term regulation is a minute to minute reversible mechanism of control. On the other hand, long term regulation takes time to come into effect but also lasts longer. In multicellular organisms, various events are sensed and coordinated by release of appropriate hormones. In this section coordinated regulation of glycolysis and gluconeogenesis in mammalian liver is described.

3.8.1 Short Term Regulation

The **allosteric modulators** mediating short term regulation of glycolysis and gluconeogenesis are shown in Fig. 3.17. You can clearly notice that positive modulators in one pathway act as negative modulators for the other pathway and vice versa. Let's us discuss reciprocal allosteric regulation at each irreversible step.

(a) Conversion of glucose to glucose 6-phosphate and vice versa

Phosphorylation of glucose is catalysed by hexokinase. Generally, different isozymes are present in liver and muscles. They vary in their kinetic and regulatory properties, indicative of their role. You know muscle stores glycogen and takes up glucose from circulation only for its consumption while the liver has the major role of maintaining blood glucose levels.

Four isozymes (I-IV) of hexokinase are known in humans. The predominant form in muscles is hexokinase II that has high affinity for glucose (low K_m) and it is allosterically inhibited by its product, glucose 6-phosphate. This helps to balance the rate of formation of Glucose-6-phosphate with its utilisation. The liver on the other hand expresses hexokinase IV (glucokinase). It has a high K_m for glucose and it is active only when blood glucose levels are high and excess glucose is transported to the liver. Therefore at low glucose levels, glucose produced in the liver can easily be released into circulation. Hexokinase IV is not inhibited by its product.

The gluconeogenic hydrolytic enzyme, glucose 6-phosphatase is transcriptionally regulated. This mode of regulation will be discussed in long term regulation along with other enzymes of both pathways.

(b) Conversion of fructose 6 phosphate to fructose- 1,6- bisphosphate and vice versa. You have studied earlier that PFK-I catalyses the committed step of glycolysis. It is regulated by multiple of positive and negative modulators. The allosteric activators are AMP, ADP and Fructose 2,6- bisphosphate while allosteric inhibitors are ATP and citrate. ATP inhibits the enzyme by increasing K_m for its substrates and citrate further enhances the inhibitory effect of ATP. High levels of ATP and citrate signal abundance of energy. On the other hand ADP and AMP signal the need for more ATP and activate PFK-1. The reverse reaction catalysed by fructose 1,6 bisphosphatase-1 (FBPase –I) is allosterically inhibited by AMP, an indicator of low energy status of a cell.

In nutshell, glycolysis is favoured when AMP or ADP is high and gluconeogenesis occurs when ATP, citrate or other cellular indicators of abundance are high. The most important allosteric modulator of PFK-1 and FBPase-1 is fructose 2,6-bisphosphate. We will return to this compound while discussing the role of hormones in regulating its concentration and thereby dictating which of these two pathways should occur.

(c) Conversion of PEP to pyruvate and vice versa

In vertebrates multiple isozymes of the glycolytic enzyme pyruvate kinase have been reported. All of them are allosterically inhibited by high concentration of ATP, acetylCoA and fatty acids (indicators of high energy). When fatty acids are readily available as fuel, they are oxidized in mitochondria to acetyl CoA and so glycolysis is not required for energy. Acetyl CoA acts as positive modulator for pyruvate carboxylase that converts pyruvate to OAA and diverting it towards gluconeogenesis. Further, acetyl CoA is a negative allosteric modulator of PDH complex preventing conversion of pyruvate to acetyl CoA allowing excess of pyruvate towards gluconeogenesis. The regulation of PEP carboxykinase in mammals is at the level of synthesis and degradation in response to dietary and hormonal signals.

The survival of multicellular organisms is heavily dependent on inter organ / tissue cooperation. They have evolved by segregating specific roles to different organs. The division of labour calls for an efficient mechanism to relay information. This is accomplished via hormones, neurotransmitters or molecules that work at very short range.

Here we shall take the example of two hormones, glucagon and insulin which has opposite effects on glucose homeostasis. Both hormones can bring about rapid as well as long term effects. As mentioned earlier liver maintains blood glucose levels by coordinating the rate of glucose production and release with utilisation. When the levels of blood glucose fall; pancreas releases the hormone glucagon which signals the liver to release more glucose by adopting multiple strategies like increase breakdown of glycogen reserves, synthesis by gluconeogenesis and decrease consumption.

If the situation reverses insulin is released from the pancreas which stimulates glucose uptake by target tissues including liver. It utilizes it to synthesise glycogen and triacylglycerols and consume glucose as a fuel.

The short term rapid hormonal regulation of glycolysis and gluconeogenesis is mediated by changes in the concentration of **fructose 2,6-bisphosphate**. It has opposite effects on the activity of PFK-1 and FBPase -1. Recall from unit 2 on glycolysis that fructose 2,6 bisphosphate is the most potent positive modulator of glycolysis and a negative modulator of gluconeogenesis.

The levels of fructose 2,6 bisphosphate is dictated by the rate of its synthesis and degradation. It is synthesised from fructose 6-phosphate by phosphofructokinase-2 (PFK-2) and degraded by fructose 2,6 bisphosphatase (FBPase-2). PFK-2 / FBPase-2 is a bifunctional enzyme. Let us now try to understand how glucagon and insulin alter the levels of fructose 2,6

bisphosphate. These hormones bring about **reversible covalent modification**.

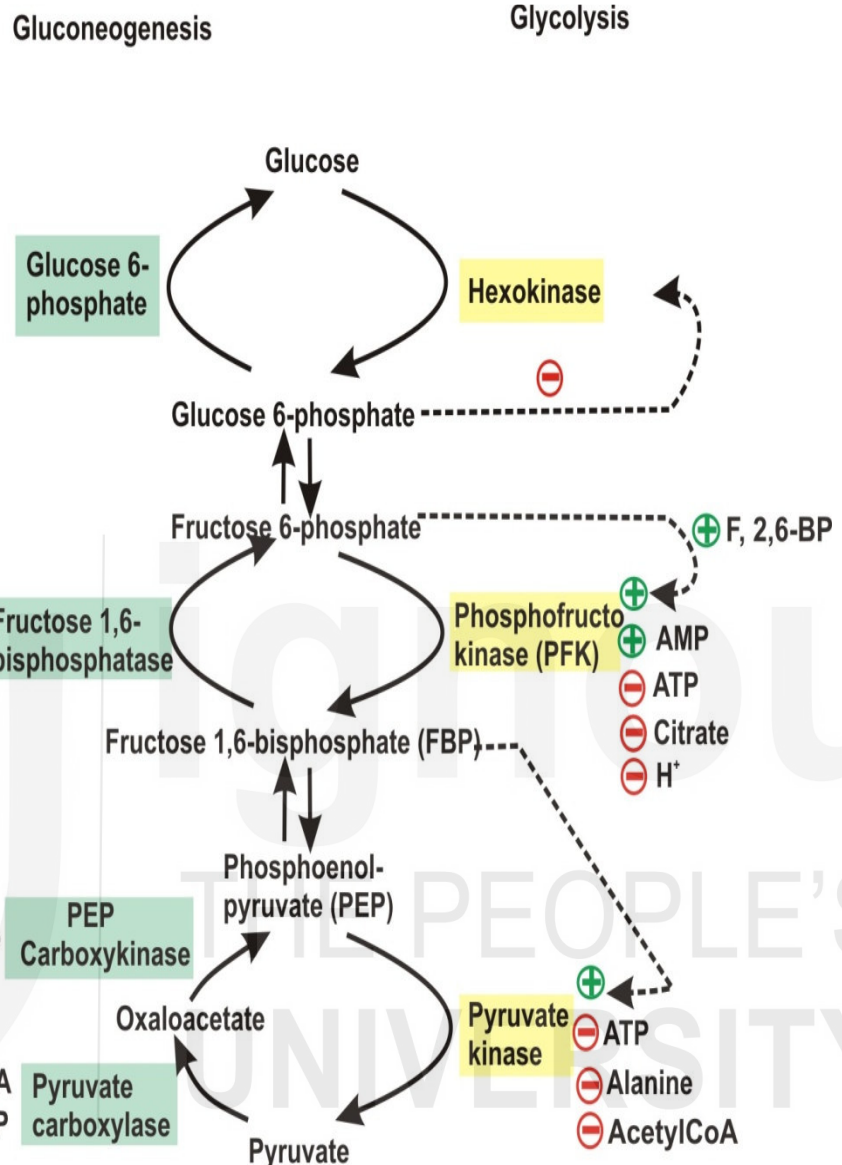


Fig. 3.17: Short term coordinated regulation of glycolysis and gluconeogenesis by allosteric modulators. Glycolysis is preferred when there is abundance of glucose and gluconeogenesis is the favoured when it is scarce.

The hormone glucagon binds to cell surface receptor and activates adenyl cyclase that converts ATP to an intracellular second messenger, cAMP. Cyclic AMP in turn activates protein kinase A (PKA) which phosphorylates PFK-2/ FBPase-2, activating the phosphatase (Fig. 3.18) and simultaneously inhibiting PFK-2. The net effect is a decrease in fructose 2,6 bisphosphate level, creating conditions for gluconeogenesis and generating more glucose needed to replenish the blood glucose levels.

When blood glucose levels are high such as after meals, insulin is secreted which acts in just the opposite way of glucagon by activating phosphoprotein phosphatase. The phosphatase removes phosphate group from the bifunctional enzyme, activating PFK-2 and inhibiting FBPase-2. The increase in

3.8.2 Long Term Regulation

The effect of hormonal regulation is also seen at transcriptional level. It results in a net increase or decrease in the amount of enzymes and the effect persists as long as the altered levels are maintained. Glucagon and insulin act antagonistically to activate specific transcriptional factors (TF). In many cases the activation/ inactivation of TF is dependent on whether it is phosphorylated or dephosphorylated. The promoters of genes coding for enzymes of glycolysis or gluconeogenesis generally have multiple sites to bind these TF and their combinatorial binding will signal the assembly of transcription machinery. Such a mechanism helps to fine tune the level of expression required to coordinate opposing pathways.

Insulin stimulates the transcription of genes encoding hexokinase II and IV, PFK-1, pyruvate kinase and PFK-2/ FBPase-2. At the same time it decreases the expression of PEP carboxykinase and glucose 6-phosphatase. In response to glucagon one of the TF activated by a cAMP dependent kinase is CREB (cyclic AMP response element binding protein) that induces the synthesis of PEP carboxykinase and glucose 6-phosphatase.

SAQ 6

- a) Match the enzymes in the left column with the appropriate control mechanism in the right column.

i) F1,6BPase	a) Allosteric inhibition by citrate
ii) PEP carboxykinase	b) Allosteric inhibition by ADP
iii) PFK1	c) Not regulated
iv) Glyceraldehyde-3-phosphate dehydrogenase	d) Allosteric activation by citrate
v) F2,6BPase	e) Inactivation by phosphorylation in response to glucagon
vi) Pyruvate kinase	f) Activation by phosphorylation in response to glucagon

- b) Acetyl CoA is not a substrate for gluconeogenesis in animals however its production largely by fatty acid oxidation is an important signal for gluconeogenesis. Justify.

3.9 GLUCURONATE PATHWAY

The glucuronate pathway, also known as the uronic acid pathway, is a metabolic route that primarily helps in the detoxification and excretion of various substances. It involves the conversion of glucose into UDP-glucuronic

acid, which then acts as a conjugation agent to help the body process and eliminate waste products, toxins, and drugs. The pathway also synthesizes glycosaminoglycans and is involved in vitamin C synthesis in many animals. Key steps include the conversion of glucose-6-phosphate to UDP-glucuronate and the subsequent production of L-gulonate, a precursor for ascorbic acid synthesis. Certain genetic disorders can cause excess excretion of metabolites from this pathway such as L-xylulose in essential pentosuria. Moreover, it is a minor pathway for glucose oxidation, primary goal of which is to provide important biosynthetic precursors and interconvert some less common sugars to ones that can be metabolized. Fig. 3.19 gives an overview of glucuronate pathway.

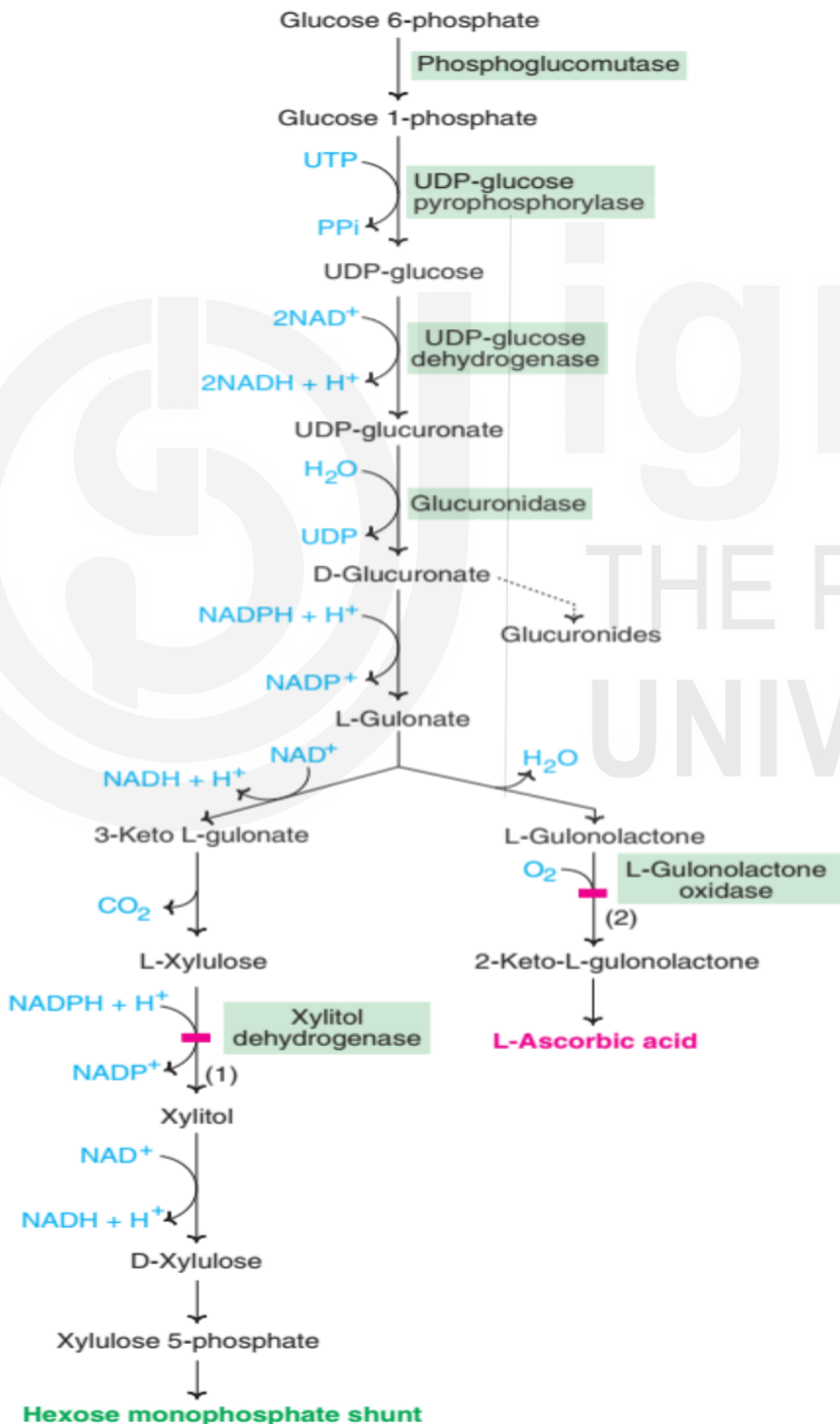


Fig. 3.19: Glucuronate pathway.

Step 1: Formation of UDP glucuronate

Glucose 6 phosphate is first converted to glucose 1-phosphate which serves as substrate for UDP-glucose synthesis catalyzed by enzyme UDP glucose pyrophosphorylase. Till this step, it is same as glycogenesis. UDP glucose dehydrogenase oxidizes UDP-glucose to UDP-glucuronate in the next reaction. UDP-glucuronate is a metabolically active form of glucuronate which is utilized from the conjugation of many substances like bilirubin, steroid hormones, and drugs. It is also required for the synthesis of glycosaminoglycans and proteoglycans

Step 2 Conversion of UDP-glucuronate to L-gulonate

UDP glucuronate loses its UDP moiety in a hydrolytic reaction and releases D-glucuronate which is reduced to L-gulonate by an NADPH reaction.

Fate of L-gulonic acid: Fate of L-Gulonic acid is different according to the animals. It may serve as the direct precursor of vitamin C (ascorbic acid), in those animals which are capable of synthesizing this vitamin. In humans and other primates as well as guinea pig can not synthesize vitamin C as the enzyme L-gulonolactone oxidase which converts gulonate to ascorbic acid is absent. Therefore, vitamin C has to be supplemented in the diet for these animals.

L-Gulonic acid is oxidized to 3-ketoglulonate, which is then decarboxylated to the pentose L-xylulose. L-xylulose is converted to a D-xylulose via xylitol by a reduction followed by oxidation. The D-xylulose can enter pentose phosphate pathway.

Deficiency of NADP dependent enzymes xylitol dehydrogenase and xylulose reductase results in a rare genetic disorder (1 in 2500 births) known as essential pentosuria. Due to defect in any of these enzymes xylulose cannot be converted to xylitol. These patients secrete large amounts of L-xylulose in urine that gives a positive Benedict's test. Essential pentosuria is asymptomatic and the individuals suffer from no ill-effects, but it should be differentiated from diabetes mellitus.

Overall, the glucuronate pathway is crucial for maintaining metabolic balance, detoxifying the body, and enabling the efficient excretion of various compounds.

Let us summarize what we have learnt in this unit.

3.10 SUMMARY

- In vertebrates and many microorganisms excess glucose is stored as glycogen. It is distributed in the cytosol as dense granules in liver and muscles. The granules also have enzymes of synthesis and degradation.
- Liver glycogen is primarily responsible for maintaining blood glucose levels whereas muscle glycogen stores are meant to meet the energy demands of the muscle itself.

- Glycogenesis (synthesis of glycogen) is catalyzed by the enzyme glycogen synthase which add glucose residues to a primer of at least 8 glucose residues linked by α -1, 4 linkages synthesised by an autocatalytic protein glycogenin. It is stimulated by insulin in response to high glucose levels especially after a carbohydrate rich meal.
- UDP- glucose is the activated glucose donor for glycogen synthesis. Both glycogenin and synthase add glucose residues from the non-reducing end of primer / glycogen.
- Branches in glycogen are introduced by the action of branching enzyme.
- Glycogenolysis is the process of breakdown of stored glycogen to glucose 1-phosphate. It is initiated by glycogen phosphorylase. It catalyses phosphorolytic cleavage from the non- reducing ends until four glucose residues remain on either side of the branch point. The structure so formed is called limit dextrin. The enzyme is pyridoxal phosphate dependent. .
- The highly branched limit dextrin is a substrate of bifunctional debranching enzyme. First it transfers a fragment of 3 or 4 glucose residues from an outer branch to another branch or to an interior position of the same branch. Then Amylo α - 1,6-glucosidase hydrolyses the α - 1,6 bond at the branch point releasing free glucose.
- Glucose-1-phosphate is converted into glucose-6-phosphate by phosphoglucomutase before it can enter different routes.
- Both glycogenesis and glycogenolysis are regulated by hormones primarily glucagon, epinephrine and insulin. The key enzymes regulated are glycogen phosphorylase and glycogen synthase. These are also under allosteric control.
- Gluconeogenesis refers to synthesis of glucose from non-carbohydrate precursors such as lactate, pyruvate, glycerol, and products derived from glucogenic amino acids. Most of its reactions take place in cytosol, though some take place in mitochondria.
- It helps meet basal requirements of the body for glucose during fasting conditions; remove certain metabolites which are harmful if accumulated in the blood e.g. lactate, glycerol etc. and ensure continuous supply of glucose to the brain.
- Glycolysis and gluconeogenesis share seven out of the ten reactions. These reactions are freely reversible and are catalyzed by same enzymes. Three irreversible reactions of glycolysis which are highly exergonic are bypassed by alternate set of enzymes.
- The coordinated and reciprocal regulation of glycolysis and gluconeogenesis is mainly governed by energy status and blood glucose levels.

- The glucuronate pathway, also known as the uronic acid pathway, is a metabolic route that primarily helps in the detoxification and excretion of various substances. It involves the conversion of glucose into UDP-glucuronic acid, which then acts as a conjugation agent to help the body process and eliminate waste products, toxins, and drugs. The pathway also synthesizes glycosaminoglycans and is involved in vitamin C synthesis in many animals.

3.11 TERMINAL QUESTIONS

1. What is glycogenesis? Explain its steps.
2. Is glycogenolysis a reversal of glycogenesis? Explain.
3. Describe the reciprocal regulation glycogenesis and glycogenolysis in the liver.
4. Calculate the net ATP yield from the breakdown of sugar released from glycogen to pyruvate?
5. Write the reactions which differ in gluconeogenesis from pyruvate from glycolysis.
6. What sources other than pyruvate are used for gluconeogenesis?
7. Describe factors involved in short term coordinated regulation of gluconeogenesis and glycolysis.
8. Explain the importance of glucuronate pathway.

3.12 ANSWERS

Self-Assessment Questions

1. Branching increases the number of non-reducing ends. Since synthesis and degradation of glycogen occurs from the non-reducing ends so a branched structure will allow reactions to take place simultaneously at multiple ends thereby increasing the overall rate. In addition branching increases solubility.
2. a) Glycogenin is a glycosyl transferase that can initiate glycogen synthesis. It can add up to eight glucose residues; the first one is attached covalently to the phenolic hydroxyl of tyrosine.

Glycogen synthase is a chain elongating enzyme that adds glucose residues from the non-reducing end of a primer. The polymer has approx. 6×10^5 glucose residues.
- b) i) Liver and muscle;
ii) Glucokinase (hexokinase IV);
iii) Non-reducing;
iv) Glycogenin

- v) Glucose 1-phosphate, UTP, UDP pyrophosphorylase
- vi) 3
3. i) Glycosyl 4: 4 transferase and ii) amylo α - 1,6-glucosidase.
4. i) Active
ii) Inactive
iii) Inactive
5. a) i) 1. A) i) Pyruvate carboxylase and PEP carboxykinase; Fructose 1,6-bisphosphatase; (iii) Glucose 6-phosphatase
- ii) Most metabolic pathways are catalysed by completely separate set of enzymes for synthesis and degradation. But in case of glycolysis and gluconeogenesis majority of the steps are catalysed by freely reversible enzymes. Only three steps are unique to each pathway. These reactions are responsible for giving directionality to the pathways; one set of enzymes favour glycolysis and the other gluconeogenesis. By having irreversible reactions the two pathways can be independently regulated in response to cellular signals.
- b) i) Acetyl CoA
ii) Fatty acids or acetyl CoA
iii) Glucose-6- phosphatase
iv) Odd chain fatty acids and methionine
v) DHAP
6. a) i) d ii) b iii) a iv) c v) f vi) e.
- b) Gluconeogenesis occurs at the time of starvation, when protein and lipids are utilized. Acetyl CoA formed by fatty acid oxidation inhibits PDH complex and act as positive allosteric modulator of pyruvate carboxylase diverting pyruvate into gluconeogenesis.

Terminal Questions

- The synthesis of glycogen from glucose is known as glycogenesis. It is activated by insulin in response to high glucose levels especially after a carbohydrate rich meal. Although present in all tissues, it primarily takes place in cytosol of liver and skeletal muscles. Refer to section 3.3 for details.
- Glycogenolysis is not a reversal of glycogenesis. Both pathways use a different set of enzymes. Separate pathways allow greater flexibility and control. Refer to section 3.3 and 3.4 for details of the pathways.
- Glycogenesis and glycogenolysis are regulated by three hormones; insulin, glucagon and epinephrine. Refer to section 3.8 for details.

4. The breakdown of glycogen by phosphorylase releases glucose 1-phosphate as the major product. It can enter the glycolytic pathway once it is converted to glucose 6-phosphate by PGM. The breakdown of Glucose 6-phosphate to two molecules of pyruvate generates 4 ATP and consumes only one. The net ATP yield is 3.
5. i) Pyruvate carboxylase and PEP carboxykinase; Fructose 1,6-bisphosphatase; (iii) Glucose 6-phosphatase are the three enzymes unique to gluconeogenesis. Refer to the section 3.8 for more details.
6. Lactate, glycerol and products derived from glucogenic amino acids in addition to pyruvate are used for gluconeogenesis. Refer to the section 3.7 for more details.
7. Allosteric modulators are involved in short term coordinated regulation of glycolysis and gluconeogenesis. Refer to section 3.8.1 for more details.
8. Glucuronate pathway is involved in detoxification of drugs, toxins and waste products. It is also involved in synthesis of vitamin C and glycosaminoglycans. Refer to section 3.9 for more details.



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