SECTION

Chemical Nature, Physiology and Metabolism of Nutrition

CHAPTER

1

Carbohydrates

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INTRODUCTION

Carbohydrates, termed to reflect their chemical nature as hydrates of carbon, and are primarily composed of the elements carbon, hydrogen and oxygen. They are the most abundant organic molecules in nature occur widely in plants, animals and many microorganisms and serve both structural and metabolic functions. Glucose is synthesised from carbon dioxide and water by the process of photosynthesis in plants and is stored as starch or transformed into cellulose. Though animals can synthesise some carbohydrates from fat and protein, a major portion of their carbohydrate is obtained from plant sources.

Glucose is a simple sugar and plays the central role in the metabolic process. Other simple sugars like ribose and deoxyribose in nucleic acids, galactose in milk and hybrid molecules of carbohydrates with protein, like glycoprotein and proteoglycans, are important molecules. Fructose is the sweetest of all sugars and it occurs naturally in fruits and honey.

CHEMISTRY AND TYPES

Carbohydrates are aldehyde or ketone derivatives of polyhydric alcohols having an emperical formula with the ratio of C, H, O as 1:2:1 ($C_nH_{2n}O_n$). In some instances, the carbohydrates may contain nitrogen, phosphorus or sulphur. Broadly, there are 3 classes of carbohydrates: Monosaccharides, oligosaccharides and polysaccharides. Carbohydrates are broadly categorised as simple (monosaccharides and disaccharides) and complex carbohydrates (oligosaccharides, polysaccharides).

Monosaccharides consist of a single aldehyde or ketone unit and one are classified according to the chemical nature of their carbonyl group and the number of the C-atoms. If the carbonyl group is an aldehyde, the sugar is called aldose while the carbonyl group is a ketone, the sugar is a ketone. The smallest monosaccharides, those with three carbon atoms, are trioses and with four, five, six, seven, etc. are, tetroses, pentoses, hexoses, heptoses, respectively.

Oligosaccharides may have 2 (disaccharides) or 3–6 monosaccharide units bound together by covalent bonds (Table 1.1). Polysaccharides on hydrolysis yield many monosaccharides or their derivatives. Polysaccharides differ in the nature of their recurring monosaccharide units in terms of their length, degree of branching and type of bonding, e.g. starch, cellulose and glycogen.

Table 1.1: Classification of carbohydrates with important examples

No. of simple sugars				
Monosaccharides		**Disaccharides**	**Oligosaccharides**	**Polysaccharides**
1		**2**	**3–6**	**>6**
Aldose	Ketose			
Ribose	Ribulose	Sucrose (Glucose + Fructose)	Maltotriose (3 Glucose)	Inulin, glycogen Starch Cellulose
Glucose	Fructose	Lactose (Glucose + Galactose)		
Galactose	Maltose (2 Glucose)			

Sugars manifest different forms of isomerism, i.e. they have same structural formula, but differ in spatial organisation and are known to be stereoisomers. The presence of asymmetric carbon atoms attached with 4 different atoms or groups is responsible for this isomerism. The number of possible isomers will depend on the number of asymmetric carbon atoms (n) = 2^n. Glucose with 4 asymmetric carbon atoms has 16 isomers. The spatial orientation of H, and OH groups around carbon atoms adjacent to the terminal primary alcohol carbon (CH_2OH), determines whether they belong to D (–OH to the right) or L (–OH to the left) series (Fig. 1.1A).

Most of the mammalian monosaccharides are of D configuration. The presence of asymmetric carbon atoms also confers optical activity, i.e. the plane of polarized light is turned left or right making it laevo- or dextro-rotatory isomers, respectively. Although the structures of various sugars written in straight chain forms are correct, some of the physico-chemical properties can be explained only by ring structures as in Haworth projection in the pattern of pyranose or furanose. Stable ring structures of simple sugars are based on pyran or furan structure (Fig. 1.1B) and formation of ring structure introduces another form of isomerism in sugars, where the hydroxyl group on carbon 1 is on the same side (α) or on the opposite side (β) to that of primary alcoholic group.

There are several derivatives of monosaccharide, some of which are physiologically important such as sugar acids (formed upon oxidation) or sugar alcohols or polyols (formed by reduction of aldoses or ketoses). For instance, sorbitol is formed from glucose and mannitol from mannose. Amino sugars are monosaccharide derivatives formed by replacing of one of the hydroxyl groups by an amino group or substituted amino group. Three amino sugars are of physiological importance, namely glucosamine, galactosamine

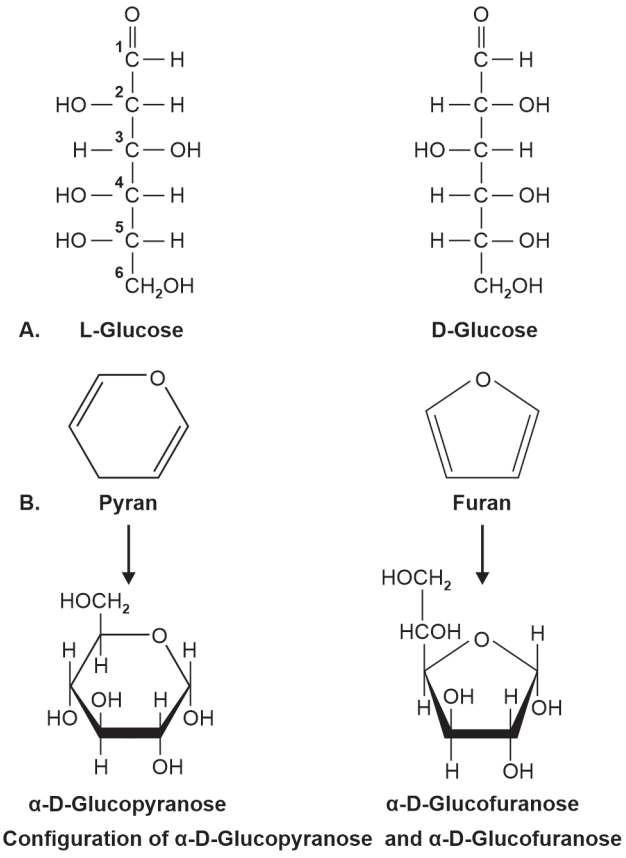


Fig. 1.1: Different configurations of simple sugars

and neuraminic acid. These are the sugars that contain one oxygen less than that present in the parent molecule. L-rhamnose and L-fucose are other important deoxy-sugars that occur in polysaccharides.

Disaccharides consist of two monosaccharide units (similar or dissimilar) held together by a glycosidic bond. The disaccharides are of two types, reducing disaccharides with free aldehyde or keto group, e.g. maltose and lactose, non-reducing disaccharide with no free aldehyde or keto groups, e.g. sucrose, trehalose. Lactose occurs naturally only in milk is more commonly known as milk sugar. Lactose comprises D-galactose and D-glucose held together by β (1→4) glycosidic bond. Sucrose comprises D-glucose and D-fructose, where the two monosaccharides are held together by a glycosidic bond ($\alpha_1 \rightarrow \beta_2$). Sucrose is one of the major carbohydrates produced in photosynthesis. Sucrose is an important source of dietary carbohydrates.

Oligosaccharides are not relatively abundant in the diet compared to other more common carbohydrates. Common oligosaccharides include raffinose, stachyose, and verbascose. These oligosaccharides can be found in relatively abundant levels in legumes, whole grains, some cruciferous vegetables, and some fruits.

Polysaccharides are primarily concerned with two important functions—structural and storage of energy. The structural polysaccharides are cellulose and chitin, storage polysaccharides are starch and glycogen. Starch comprises α-glucosidic chain is found

in cereals, potatoes, legumes and other vegetables. It consists of two main constituents: amylose, which has a non-branching helical structure and amylopectin which features branched chains of 24–30 glucose residues linked by 1→4 linkages with 1→6, linkages at branch points (Fig. 1.2A). During the breakdown of starch, dextrins are formed. Glycogen, which is more branched than amylopectin, contains 10–18 glucopyranose units in 1→4 linkages in the backbone and 1→6 linkage at branch points (Fig. 1.2B). Cellulose, the primary carbohydrate in plants, is insoluble in ordinary solvents. It consists of units of β-D-glucopyranose in β-(1→4) bonds and many parallel chains are cross-linked by hydrogen bonds (Fig. 1.2C). In contrast, β-glucan is a linear unbranched polysaccharide with β-(1→3)- and β-(1→4)-D-glucopyranose units. It is found in the bran of grains such as barley, oats, and wheat. Both β-glucan and inulin are soluble polysaccharides that are important components of dietary fibre. They have been shown to be prebiotic, boost health-promoting microbial growth and aiding in the regulation of blood sugar and lipid levels.

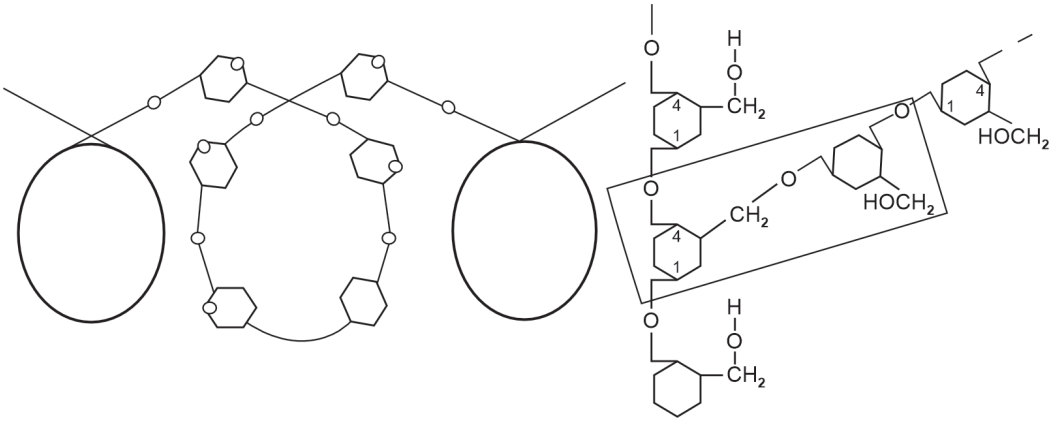
DIGESTION AND ABSORPTION

Polysaccharides such as starch and cellulose from plant foods and glycogen from foods of animal origin are the most abundant carbohydrates humans eat. Carbohydrates digestion begins briefly in mouth and primarily completed in the intestine. During heating, polysaccharides get hydrated, which is essential for their efficient digestion. The hydrolysis of glycosidic bonds is performed by a group of enzymes known as glycosidases which are specific to the bond, structure and configuration of monosaccharide units. Starch and glycogen are fully hydrolysed by enzyme action to yield free D-glucose.

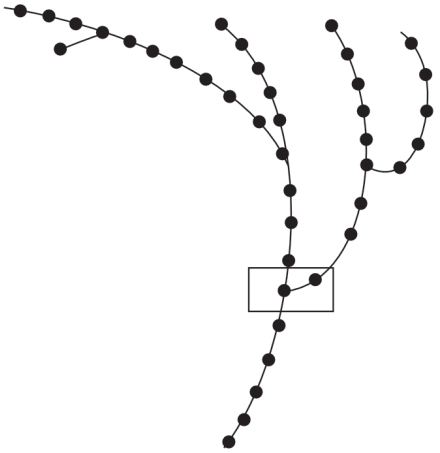
The digestive process starts in the mouth, where chewing and the action of salivary amylase break many α-(1→4) linkages in starch and glycogen, resulting in a mixture of maltose, glucose, and oligosaccharides. This process continues in the small intestine with the action of pancreatic amylase, which is secreted into the duodenum. Cellulose, on the other hand, cannot be hydrolyzed by most mammals because they lack the enzyme needed to break β-(1→4) linkages (Fig. 1.2C).

The undigested cellulose from plant foods constitutes the fibre that is essential for the bowel movement. Disaccharides are hydrolysed by specific disaccharidases like sucrase (sucrose), maltase (maltose) and lactase (lactose), which are released into the lumen from the epithelial cells, lining the walls of small intestine. A mixture of simple sugars mainly hexose is absorbed into the epithelial cells of the intestinal walls and brought *via* portal blood to liver. Simple process of diffusion and active transport of sugars (movement against concentration gradient, in energy derived process) are the mechanisms by which sugars are absorbed. The principal monosaccharides produced by the digestion of carbohydrates are glucose, fructose and galactose. Of these, glucose accounts for nearly 80% of the total monosaccharides. The absorption of sugars mostly takes place in the duodenum and upper jejunum of small intestine. There exists a considerable variation in the absorption of different monosaccharides. It is observed that hexoses are more rapidly absorbed than pentoses. Further, among the monosaccharides, galactose most efficiently absorbed followed by glucose and fructose.

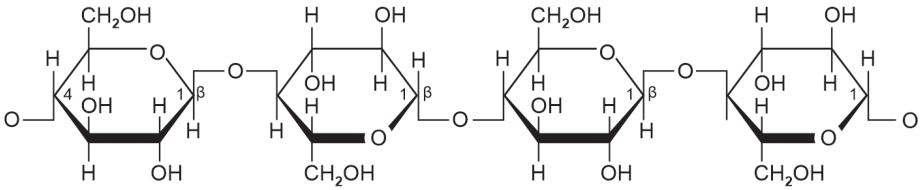
Diarrhoea and generation of gases due to fermentation of undigested lactose by intestinal microorganisms are results of lactose intolerance. Most adults of Asian and African races show lactose intolerance due to decreased expression of the enzyme—lactase, in the small intestine during infancy and childhood. Recent research suggests that



A. Starch: Amylose α (1→4) and amylopectin α (1→4) and (1→6) linkage of D-glucose



B. Glycogen: α (1→4) and α (1→6) D-glucose linkage



C. Cellulose: β (1→4) linkage of D-glucose

Fig. 1.2: Structure of some polysaccharides showing α (1→4) and (1→6) branching represented by structures in rectangle and β (1→4) linkage

'*genetic-epigenetic interactions*' as crucial in the regulation of lactase expression. Similarly, humans lack the ability to properly digest some oligosaccharides raffinose because they lack the digestive enzyme α-galactosidase, thus oligosaccharides are not hydrolyzed and are passed undigested into the lower gut. Here, the oligosaccharides are fermented and metabolized by anaerobic bacteria, which may result in the production of flatus gases.

METABOLISM

The major part of intermediary metabolism comprises catabolic reactions in which energy-yielding large molecules like carbohydrates, fats and proteins are converted into simple end products like NH_3, CO_2 and H_2O and in the process, the chemical energy is stored in the form of adenosine triphosphate (ATP) and NADPH. This chemical energy is used in biosynthetic pathways in which precursors like amino acids, sugars, fatty acids and nitrogen bases are converted to macromolecules like proteins, polysaccharides, lipids and nucleic acids. Glycolysis, tricarboxylic acid (TCA) cycle and hexose monophosphate (HMP) shunt are important pathways in which acetyl CoA is a common linking intermediate. Liver and muscle glycogen are converted to glucose by the process called glycogenolysis. Glycogen phosphorlylase breaks down the 1→4 linkages of liver and muscle glycogen by phosphorylytic cleavage to yield glucose 1 phosphate. A debranching enzyme splits up the 1–6 branch points.

Glycolysis

Carbohydrate metabolism is the synonymous with fate of glucose. There is a minimum requirement of glucose in all tissues and the requirement is substantial in some tissues like brain and erythrocytes. Glycolysis is the pathway by which glucose is metabolised to pyruvate and lactate (Fig. 1.3). The breakdown of 6-C glucose into 2 molecules of 3-C pyruvate is brought about by a sequential action of 10 cytosolic enzymes referred to as glycolytic enzymes. In most cells, the enzymes that catalyze glycolytic reactions are present in the extra-mitochondrial fraction of the cell in the cytosol. In the preparatory phase, the reactions are not redox reactions and do not release energy but instead lead to the production of a critical intermediate of the pathway. This phase consists of the first five steps of the glycolysis process. The last five reactions of glycolysis constitute phase II where redox reactions occur, energy is conserved in the form of ATP, and two molecules of pyruvate are formed.

Glucose is activated to phosphorylated glucose by the enzyme *glucokinase* (or *hexokinase*) and ATP to enter the pathway (Fig. 1.3). Glucose 6-phosphate forms a junction for many pathways involving glucose. By an isomerase action, this is converted to fructose 6-phosphate. Upon addition of another phosphate group in the presence of ATP, fructose 1,6-diphosphate is formed catalysed by the enzyme phosphofructokinase, which is an important regulatory step in glycolysis.

Aldolase breaks fructose 1,6-diphosphate to 2-triose phosphates which are inter-converted in the presence of an isomerase. Glycolysis further proceeds by oxidation and phosphorylation of glyceraldehyde 3-phosphate to 1,3-diphosphoglycerate (to form a high energy bond) by the action of glyceraldehyde 3-phosphate dehydrogenase, inorganic phosphorous (Pi) (substrate phosphorylation) and NAD. This high-energy phosphate bond can be captured as ATP by the action of *phosphoglycerate kinase*, yielding 3-phosphoglycerate as a product. Phosphoglyceromutase converts 3-phosphoglycerate to 2-phosphoglycerate. *Enolase*, an enzyme inhibited by fluoride ion, catalyses the conversion of 2 phosphoglycerate into a high energy compound, phosphoenol pyruvate. The high energy phosphate can next be transferred to ADP in the presence of pyruvate kinase to form ATP and pyruvate.

Pyruvate represents an important junction point under aerobic conditions, it is a product of glycolysis in aerobic conditions and the NADH formed in the cycle is reoxidised to NAD by respiratory chain. Under anaerobic conditions, (for example, in active muscles),

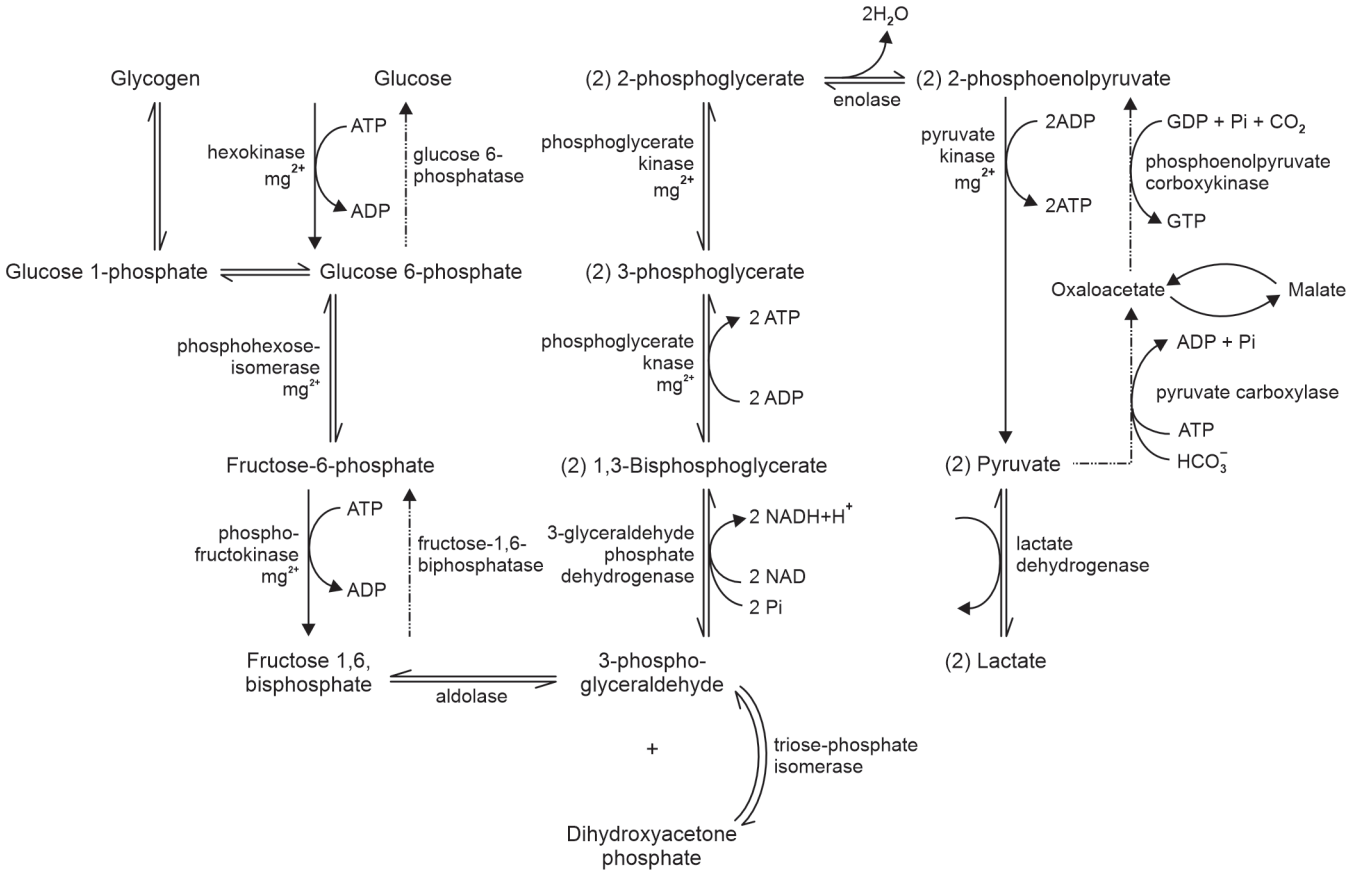


Fig. 1.3: Reactions of glycolysis. Bypass steps operating in the reversal gluconeogenic pathway are shown by discontinuous arrows

NADH generated by glycolysis cannot be reoxidised by oxygen and therefore, must be reoxidised to NAD by pyruvate, converting itself into lactate under the action of lactate dehydrogenase (LDH). Thus, in the overall process of glycolysis, D-glucose is either converted into 2 molecules of lactate along with the 2 ATP (4 – 2 = 2) or to 2 molecules of pyruvate + 2 ATP and 2 NADH. The 2 molecules of NADH when reoxidised produce *via* respiratory chain are 6 moles of ATP. Thus, the complete oxidation of glucose to pyruvate yields 8 moles of ATP.

Together with glucose, the hexoses—fructose, galactose and mannose are the prominent metabolic fueles. After digestion, these are converted to glycolytic intermediates that are then metabolised by glycolytic pathway.

Tricarboxylic Acid (TCA) Cycle

Pyruvate enters into mitochnondria and is then converted into acetyl CoA, before it is further oxidised in TCA cycle. Pyruvate dehydrogenase (or decarboxylase) complex contains *thiamine pyrophosphate* as coenzyme. In the presence of lipoic acid, NAD and CoA, it oxidises pyruvate to acetyl CoA.

The TCA cycle (Kreb's cycle or citric acid cycle) is constituted by a series of reactions occurring in mitochondria and forms the final common pathway for oxidation of acetyl groups into which major fuel molecules converge during catabolism to CO_2 and H_2O generating NADH. Liver is the only tissue in which all the reactions occur at an appreciable level.

The cycle is initiated by the condensation of acetyl CoA with oxaloacetate to form the 6C citric acid (Fig. 1.4). Citrate is converted into isocitrate through *aconitase*. Isocitrate dehydrogenase catalyses the next reaction to α-ketoglutarate involving the liberation of CO_2 and generation of reduced NAD. Oxalosuccinate is an intermediate in the reaction. Oxidative decarboxylation of α-ketoglutarate by α-ketoglutarate dehydrogenase in a manner analogous to pyruvate decarboxylase, produces succinyl CoA. In the next reaction catalysed by *succinate thiokinase*, there is substrate level phosphorylation and one molecule of GDP or IDP is converted into GTP or ITP, which can be converted to ATP, subsequently.

Succinate is metabolised to fumarate by undergoing dehydrogenation. This is the only reaction in which hydrogen is directly transferred from the substrate to a flavoprotein (FAD), without the involvement of NAD. Fumarate is hydrated to malate and further oxidised to oxaloacetate (malate dehydrogenase) with the release of NADH.

The overall oxidative reactions of citric acid cycle yield 3 moles of NADH and 1 of $FADH_2$ from a molecule of acetyl CoA. When oxidised in the respiratory chain, NADH generates 3 ATP and $FADH_2$ produces 2 ATP. One ATP is released at substrate level accounting for a total of 12 ATP in each turn of TCA cycle. In addition, as mentioned earlier, 1 NADH is formed during the conversion of pyruvate to acetyl CoA. Thus 15 ATP are formed per mole of pyruvate oxidized, i.e. 30 per mole of glucose through mitochondrial respiration.

TCA cycle takes part in integrating other pathways like gluconeogenesis, trans-amination, deamination and fatty acid synthesis reactions.

Calorific Value

It is the amount of energy in food or fuel that is measured by measuring the heat produced by full combustion with a given amount of oxygen. The energy value of carbohydrates

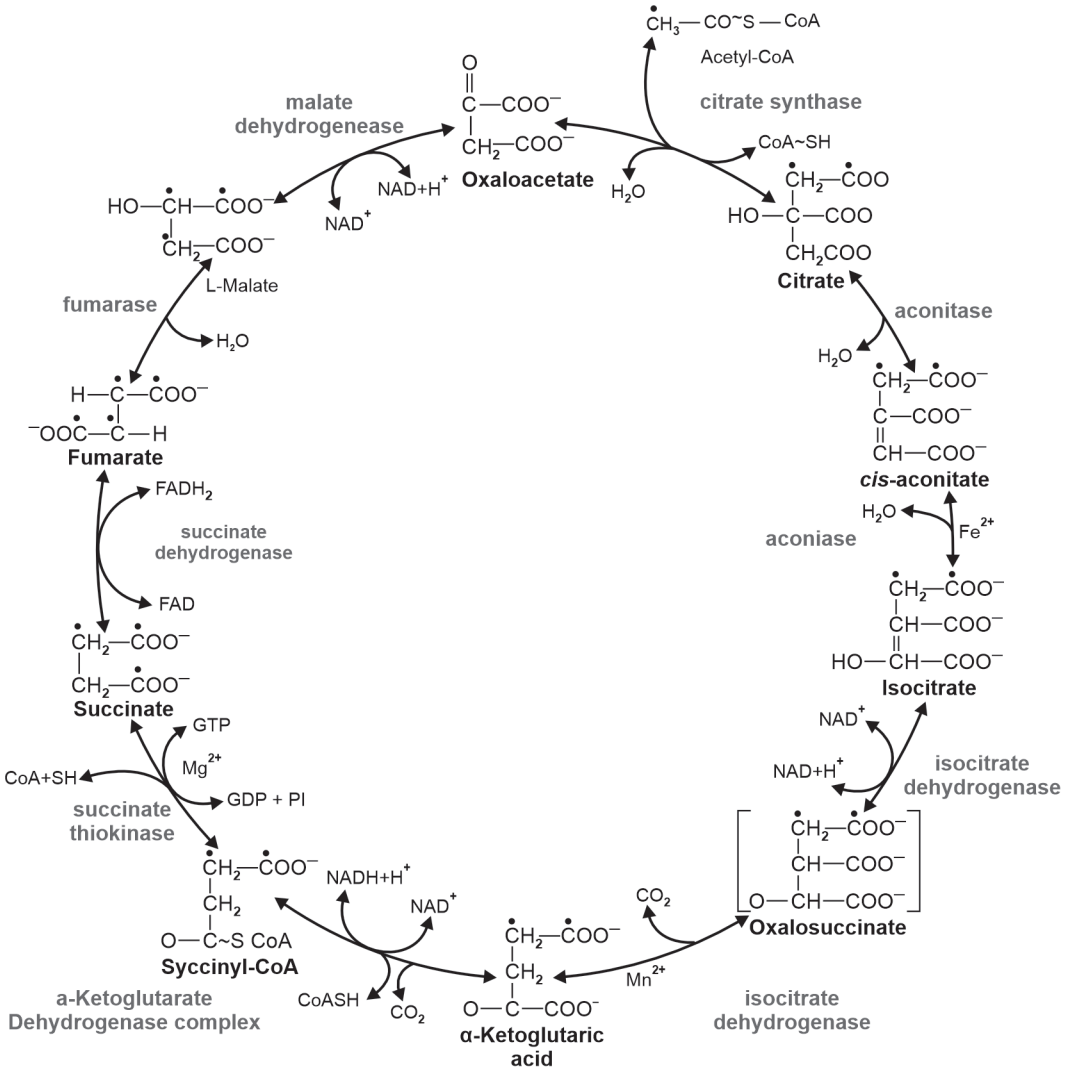


Fig. 1.4: TCA cycle

derived either *in vitro* as on heat of combustion in a bomb calorimeter (or in human oxidation) is found to be 4.1 kcal/g. This is also referred to as calorific value of the carbohydrates.

Pentose-Phosphate Pathway

The HMP shunt pathway or pentose-phosphate pathway arises from the intermediates of glycolysis and is a direct source of the reducing equivalents necessary for biosynthetic reactions (NADPH). This is also the source of producing ribose, which is important for the synthesis of nucleotides and nucleic acids. This cycle is not meant to or does not produce any ATP.

The first phase comprises the oxidative phase, where dehydrogenation of glucose 6-phosphate to 6-phosphogluconate occurs through the formation of 6-phosphoglucono-lactone (Fig. 1.5). In the next oxidative step, 3-keto 6-phosphogluconate is formed which

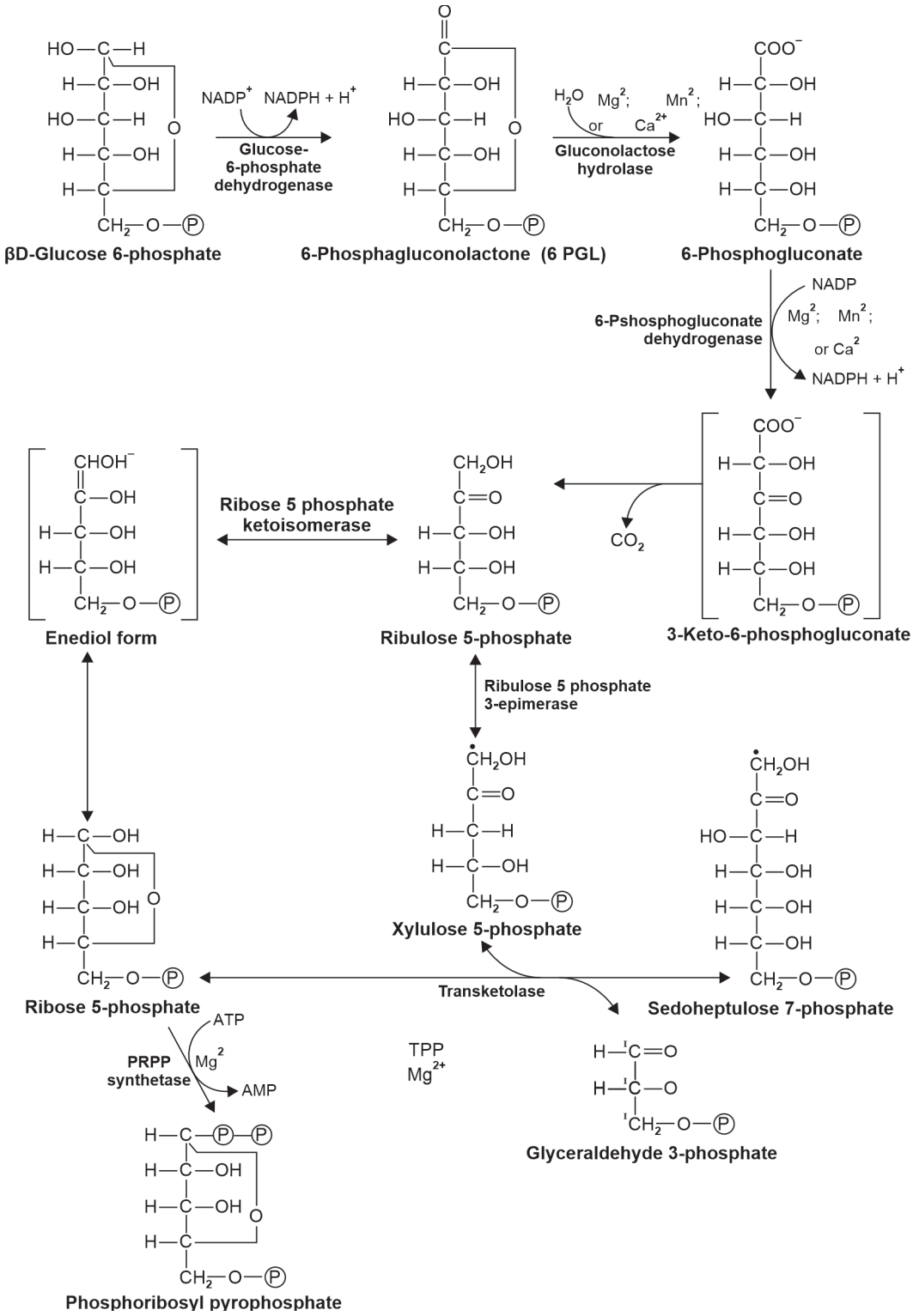


Fig. 1.5: Pentose-phosphate pathways

on decarboxylation yields a ketopentose, ribulose 5-phosphate. Ribulose 5-phosphate can be converted into its epimer, xylose 5-phosphate or the corresponding aldopentose, ribose 5-phosphate.

Uronic Acid Pathway

Transketolase, containing TPP, transfers 2 carbon unit of a ketose to the aldehyde carbon of an aldose sugar. The net result of this reaction is the simultaneous change of a ketosugar into an aldose with 2 carbon atoms less and an aldose into ketose with 2 carbon atoms more. Sedoheptulose 7-phosphate and glyceraldehydes-3-phosphate are the products in the case of glucose as a starting hexose substrate of this cycle. From sedoheptulose 7-phosphate, by the action of an aldolase, two other ketose derivatives, erythrose 4-phosphate and fructose 6-phosphate are formed. Thus, many ketoses and aldoses could be inter-converted through the action of these two enzymes.

Another secondary pathway for glucose in animal tissues yields 2 important compounds, D glucuronate, that participates in detoxification of foreign compounds, and L ascorbic acid or vitamin C (Fig. 1.6). Glucose 6-phosphate is converted into glucose 1-phosphate by a mutase. This reacts with UTP to form UDP glucose and this is required for many synthetic reactions involving the transfer of glucose moiety. By oxidation, UDP glucose is changed to UDP glucuronate, an active form of glucuronate. This compound is important as it is incorporated into various proteoglycans or could be used in the conjugation of substrates such as steroids and bilurubin. In a reduction reaction, this is reduced to L gulonate, which subsequently yields L ascorbic acid through an intermediary lactone step. This pathway helps all plants and animals except human beings, monkeys, guinea pigs and some birds and fishes to synthesise vitamin C. In most of these species, gluonolactone oxidase is missing.

Biosynthesis Reactions

All pathways leading to the formation of glucose or glycogen synthesis are anabolic pathways. Gluconeogenesis refers to the conversion of pyruvate, lactate and amino acids into glucose, which involves 7 steps, common to glycolysis. This pathway is not just a reversal of glycolysis. Citric acid cycle intermediates could also be used for synthesis of glucose. Biosynthesis reactions in carbohydrate metabolism play critical roles in maintaining energy balance, cellular structure, and metabolic homeostasis across all forms of life

Gluconeogenesis

The liver is the major site for producing glucose to be transported to other tissues. Three reactions of glycolysis, which are essentially irreversible, are catalyzed by hexokinase, phosphofructokinase and pyruvate kinase (Fig. 1.3). Glucose 6-phosphatase and Fructose 2, 6-bisphosphatase are the enzymes employed to bypass the first two reactions (Fig. 1.3). Reversal of the third reaction is achieved by the action of two mitochondrial enzymes—pyruvate carboxylase and phosphoenol-pyruvate carboxykinase. By a series of transamination steps and interconversion reactions in TCA cycle, all amino acids are converted to pyruvate or lactate.

In view of the mitochondrial localization of pyruvate cabroxylase, pyruvate is either locally generated from the deamination of alanine or transported from cytosol. This

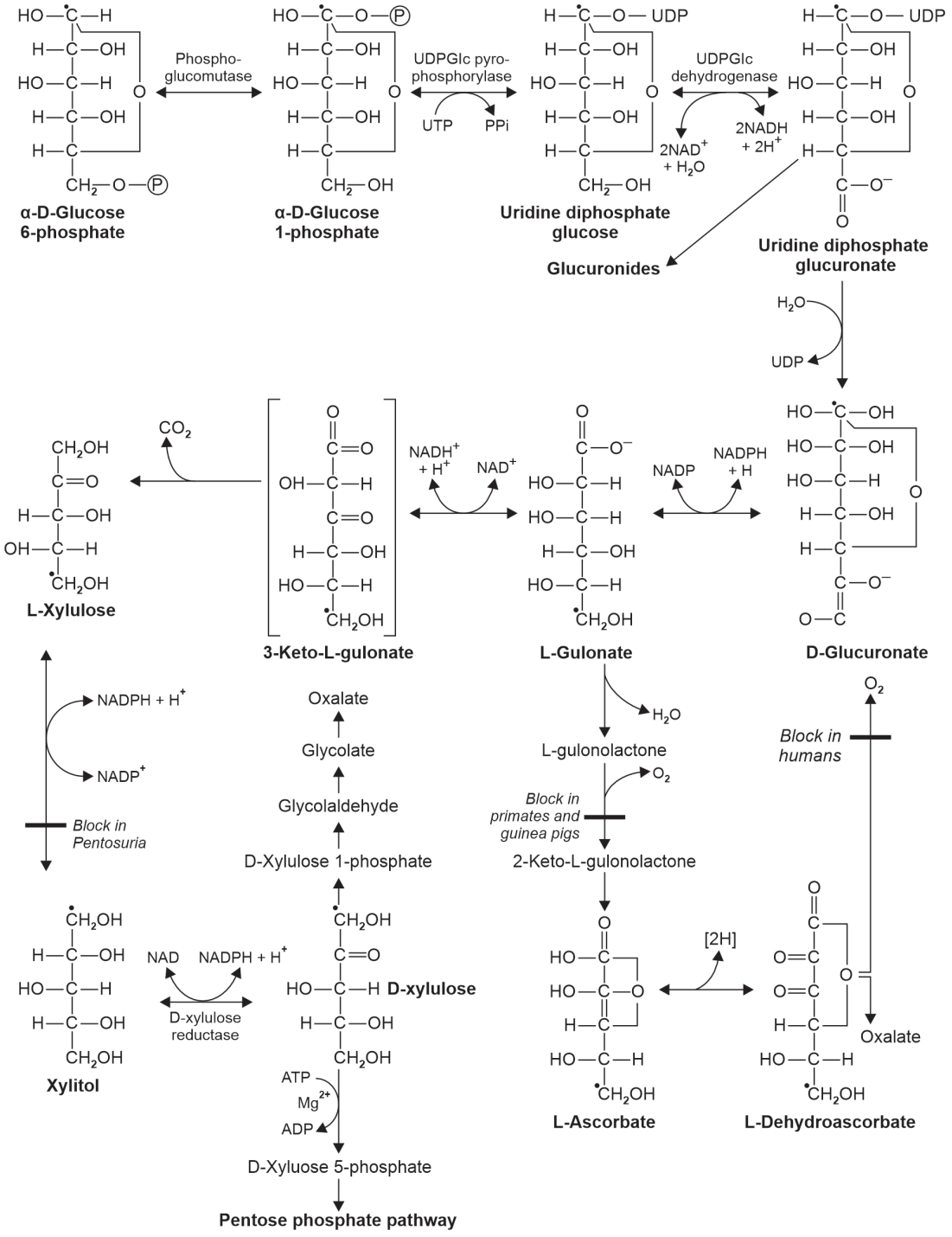


Fig. 1.6: Uronic acid pathway (*indicates the fate of carbon 1 of glucose)

is converted to oxaloacetate by fixation of carbon dioxide derived from bicarbonate ion, under the influence of pyruvate carboxylase, a biotin-requiring enzyme. This is the first regulatory step in the gluconeogenic pathway. Oxaloacetate moves out of the mitochondria through the oxaloacetate malate shuttle catalysed by malic dehydrogenase on the mitochondrial membrane (oxaloacetate is converted to malate on the inner side and this comes out and is converted back to oxaloacetate on the outer side of the mitochondria). Cytosolic phosphoenolpyruvate carboxykinase catalyzes the conversion of oxaloacetate to phosphoenolpyruvate. This is a Mg^{++}-dependent reaction that requires GTP as the phosphate donor and the same carbon atom which was incorporated by pyruvate carboxylase earlier, is released during this reaction. On the other hand, lactate follows a shorter route avoiding the malate shuttle and the oxaloacetate generated in the mitochondria is acted upon directly by a mitochondrial phosphoenolpyruvate carboxy-kinase to release phospho-enolpyruvate which comes out into cytosol.

These two sets of reactions are aimed at maintaining the balance of NADH expended in the cytosol during gluconeogenesis. For each mole of glucose produced from 2 moles of pyruvate, six high energy phosphate groups are used up (4 ATP + 2 GTP), in addition to the 2 NADH required for the reduction of 2 moles of 1,3-bisphosphoglycerate. Simultaneous operation of glycolysis and gluconeogenesis resulting in the degradation of ATP through dissipation of heat is called a 'futile cycle'. However, under normal conditions, operation of futile cycles is prevented by the reciprocal regulation brought about by common allosteric regulators. For example, fructose 2, 6 bisphosphate is a potent activator of liver phospho-fructokinase and thus glycolysis, but is also an inhibitor of fructose bisphosphatase retarding gluconeogenesis. Similarly, AMP is a strong inhibitor of fructose 1,6-bisphosphatase while the corresponding glycolytic enzyme phospho-fructokinase is stimulated by ATP.

Glycogen Synthesis

Glucose 6-phosphate can be inter-converted to glucose-1 phosphate by a mutase action. Glucose 1-phosphate is activated with the formation of uridine diphosphate glucose or UDP glucose (an intermediate of HMP shunt) by the action of a uridyl transferase enzyme yielding pyrophosphate. Glycogen synthase enzyme promotes the transfer of the glycosyl moiety from UDP glucose to a non-reducing end of the branched glycogen, establishing a new (1→4) linkage of carbon atom 1 of incoming glucose and carbon atom 4 of the terminal glucose residue of glycogen branch. Glycogen synthase cannot make the alpha (1→6) bonds found at branch points. Glycosyl (1→6) transferase catalyses the transfer of a terminal oligosaccharide fragment to another such fragment.

REGULATION OF CARBOHYDRATE METABOLISM

General Mechanisms

For regulating the concentration of blood glucose within a narrow range of 4–5 mmol/L, three levels of regulation of metabolic pathways are known. The concentrations of enzymes, (which at any time depend upon the balance of their rates of synthesis and degradation), determine the activity of the pathway and the flux of metabolites. This is a slow-responding control and is influenced by the changes in nutritional status. Some enzymes in a pathway (like phosphofructokinase) are known to be regulatory enzymes and are very sensitive to the stimulatory (AMP) and inhibitory (citric acid) effects of

molecules derived from the same pathway or another pathway. This is known as feedback regulation.

Hormonal Regulation

The last type of control mechanism depends on the involvement of hormones, which are directly secreted into circulation, responding to the needs of the organism. This control is also a rapid one and is mediated through the binding of hormones to specific molecules in the cell, called the receptors. The activation of one cycle is always in concert with corresponding changes in another cycle, for example, glycolysis and TCA cycle. Cyclic AMP (cAMP) is one of the second messengers (the hormone being the first messenger) in cytosol that mediates the metabolic changes in response to protein hormones.

Hormones like glucagon (from α-cells of pancreas) and epinephrine (adrenal medulla) promote the formation of blood glucose and reduce its catabolism by activating glycogen phosphorylase and inhibiting glycogen synthase. Glucocorticoids like cortisol (adrenal cortex) have a permissive role in increasing plasma glucose concentration. Insulin, produced by beta cells of pancreas brings about hypoglycaemia and its secretion is stimulated by hyperglycaemia. Insulin plays a key role in controlling blood glucose concentration. Insulin also promotes the uptake of glucose into both liver and peripheral tissues. The ratio of insulin to glucagon concentration determines the blood glucose concentration. Insulin exerts some of its effects through enhanced cellular uptake of glucose through increased 'glucose transporters' in the sensitive tissues.

In addition, a group of hormones called incretins also play a crucial role in the regulation of glucose metabolism, particularly in response to food intake. The two main incretins involved are glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). GLP-1 is primarily secreted by the intestinal L-cells in response to nutrient ingestion, especially carbohydrates. It enhances glucose-stimulated insulin secretion from pancreatic beta cells in a glucose-dependent manner. This means that GLP-1 stimulates insulin release when blood glucose levels are elevated after a meal, helping to lower blood sugar levels. GLP-1 suppresses the secretion of glucagon from pancreatic α-cells, it delays gastric emptying, which slows the absorption of nutrients, including glucose, from the intestines into the bloodstream. This delay contributes to more stable postprandial (after-meal) glucose levels and helps prevent rapid spikes in blood sugar. GIP is secreted by the intestinal K-cells in response to nutrient ingestion, particularly fats and carbohydrates. It also stimulates glucose-stimulated insulin secretion from pancreatic beta cells, though its role in this regard is generally considered weaker compared to GLP-1. GIP promotes lipid synthesis and storage in adipose tissues, which can contribute to increased fat accumulation in the body.

Blood Glucose Homeostasis

Maintenance of a relatively constant blood glucose level near 4–5 mmol/L is made possible by a coordinated action of hormones like insulin, glucagon and epinephrine in the target organs (Fig. 1.7). While glucagon carries the message that blood glucose is too low, blood insulin signals the high glucose level message. The tissues respond accordingly by cutting down or increasing glucose production or breakdown. Releasing and oxidizing fats is another effort made to reduce the use of glucose and this is also regulated by the above hormones. Release from adrenal medulla of epinephrine or

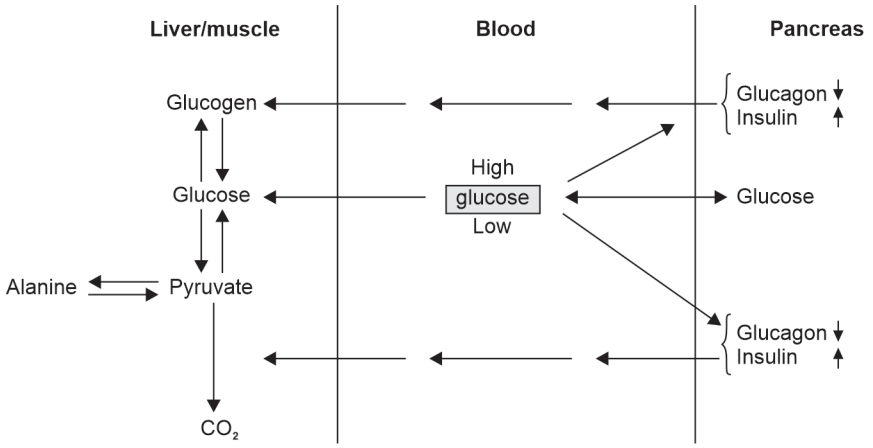


Fig. 1.7: Hormonal control of blood glucose. The changes indicated by continuous arrows are brought about by high blood glucose and discontinuous arrows by low blood glucose concentration

norepinephrine, in response to a neuronal signal from brain as a result of stressful stimulation, prepares the muscle, lungs and heart for a spurt of activity. Norepinephrine activates glycogen phosphorylase and inactivates glycogen synthase through cAMP dependent phosphorylation of the enzymes, by protein kinase, thus enhancing the conversion of glycogen into blood glucose. Like epinephrine, glucagon stimulates the net breakdown of liver glycogen through increased levels of cAMP. Insulin interaction with its receptor regulates the glucose metabolism in a slightly different manner. The receptor has a protein kinase activity and its activation phosphorylates tyrosine residues of the receptor and in turn other kinases. Insulin also activates the phosphodiesterase that degrades cAMP and thus decreases cellular levels of cAMP. Consumption of a diet rich in carbohydrates causes increased blood glucose which in turn causes a surge in insulin and a drop in glucagon secretions from the pancreas. Insulin stimulates glucose uptake by muscle tissue and activates glycogen synthase and inactivates glycogen phosphorylase, accelerates withdrawal of glucose from blood till the normal levels are reached. This slows down the release of insulin. Opposite changes are brought about by a decrease in blood glucose triggering the secretion of glucagon and inhibition of insulin release.

DIABETES MELLITUS

It is an important example of metabolic disorder in which the ability of the body to utilize glucose is reduced (impaired glucose tolerance). This condition arises due to either insufficient production of insulin by the pancreas or the body's ineffective use of insulin or both. When hyperglycaemia is associated with glycosuria (excretion glucose in urine), induces reduced insulin secretion and ketoacidosis, it is diagnosed as type-1 diabetes (insulin dependent diabetes mellitus, IDDM). In this condition, insulin therapy is needed for survival. Similar metabolic changes occur even in type-2 diabetes (non-insulin dependent diabetes mellitus, NIDDM) wherein the body becomes resistant to insulin or does not produce enough insulin to maintain normal blood glucose levels. It can often be managed with lifestyle changes such as diet and exercise, oral medications, and sometimes insulin therapy. For a detailed discussion, refer to Chapter 22—*Diet and Diabetes Mellitus*.

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