CARBOHYDRATE METABOLISM

GLYCOGENOLYSIS AND GLYCOGENESIS

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Glycogen is a highly branched, very large polymer of glucose molecules, linked along its main line by α-1,4 glycosidic linkages, branches arise by α-1,6 glycosidic bonds at about every 10th residue.

The storage form of glucose is *glycogen* and the major storage sites are *liver* and *muscle*. Although the concentration of glycogen is higher in the liver, the much greater mass of skeletal muscle stores a greater total amount of glycogen. The function of muscle glycogen is to act as a readily available source of hexose units for glycolysis within muscle itself and muscle glycogen is significantly depleted after prolonged exercise. Liver glycogen is largely concerned with storage and export of hexose units for maintenance of the blood glucose, particularly between meals and after 12-18 hours of fasting, the liver glycogen is completely depleted.

After a meal, when there is a rise in blood glucose level, the synthesis of glycogen in liver and muscle is initiated. *This process is called glycogenesis*. This not only prevents excessive rise in blood glucose level, but also helps to store glycogen for future use.

In the liver, glycogen is metabolized to glucose and then released into the circulation in a fasting person. In the muscle, although glycogen cannot be converted into glucose it can still be used for obtaining energy during muscle contraction. This breakdown of glycogen in the liver (glycogen ⟶ glucose) and muscle (glycogen ⟶ glucose-1-phosphate) is called *glycogenolysis*.

Glycogen synthesis (glycogenesis) and glycogen usage (glycogenolysis) occur in separate pathways, which are discussed next.

GLYCOGENESIS

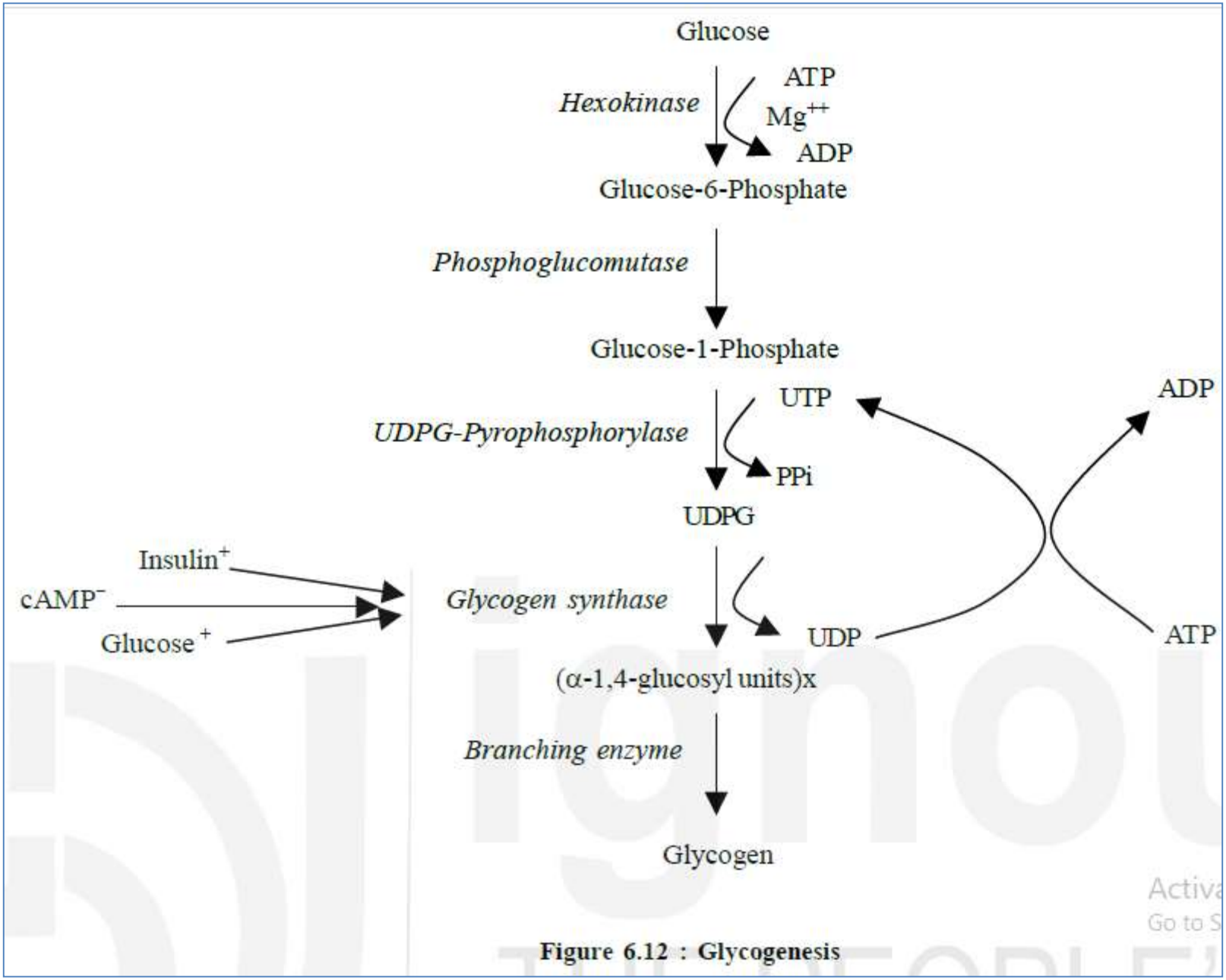

Figure 6.12 : Glycogenesis

The process is enumerated herewith:

1) Glucose is phosphorylated to glucose-6-phosphate by *hexokinase* (glucokinase in liver) in the presence of ATP and Mg^{++} ions. The action of glucokinase in liver is to remove glucose from the blood following a meal.

2) Glucose-6-phosphate is acted upon by *phosphoglucomutase* to form glucose-1-phosphate. This is a reversible reaction.

3) Glucose-1-phosphate reacts with uridine triphosphate (UTP) to form the active nucleotide uridine diphosphate glucose (UDPG) catalyzed by the enzyme *UDPG pyrophosphorylase*. The released pyrophosphate (PPi) is rapidly broken down by pyrophosphorylase to 2 inorganic phosphate (Pi) molecules, thereby rendering the reaction essentially irreversible.

4) The synthesis of new glycogen requires the presence of a glycogen primer (i.e. a preformed molecule) and α- glucosyl residues from UDP glucose. The residues are successively transferred to the C-4 terminus (non-reducing end) of an existing glycogen chain in α-1,4 glycosidic linkage. This process is repeated till about 10 to 12 molecules have been added. This reaction, which is the rate limiting step in glycogen synthesis, is catalyzed by *glycogen synthase* (glycogen synthetase).

5) After the chain has been lengthened to a minimum of 11 glucose residues, the branching enzyme (amylo [1→ 4]→[1→6] transglucosidase transfers a part of the 1→4 chain (minimum length of 6 glucose residue) to a neighbouring chain to form 1→6 linkage, thus, establishing a branch point in the molecule. The branches grow by further addition of 1→4 glucosyl units and further branching.

Glycogenolysis

Unlike glycogenesis, glycogenolysis is the breakdown of glycogen. Glycogen is broken down in the liver and muscle catalysed by the enzyme *glycogen phosphorylase*. Inorganic phosphate (Pi) is used for the lysis and hence is called phosphorolysis. Phosphorylase specifically acts upon α 1→4 linkage of glycogen to produce glucose-1-phosphate. The removal of α1,4 glucosyl residues continues until about 4 glucose residues remain on either side of α-1,6 branch, then the debranching enzyme (amylo α-1,6 glucosidase) causes the hydrolytic splitting of α 1,6 linkages. Here free glucose is formed (since no phosphate is used for lysis). However, since α-1,6 linkages are very few compared to α 1→4 linkages, the major end product of glycogenolysis is glucose with small amounts of glucose-1-phosphate. By the combined action of both the enzymes, glycogen is catabolized. The reversible reaction of *phosphoglucomutase* causes the conversion of glucose-1-phosphate to glucose-6-phosphate. In liver and kidney (but not in muscle), there is a specific enzyme glucose-6 phosphatase, which acts upon glucose-6-phosphate to release free glucose from the cell to the extracellular compartment as illustrated in Figure 6.14.

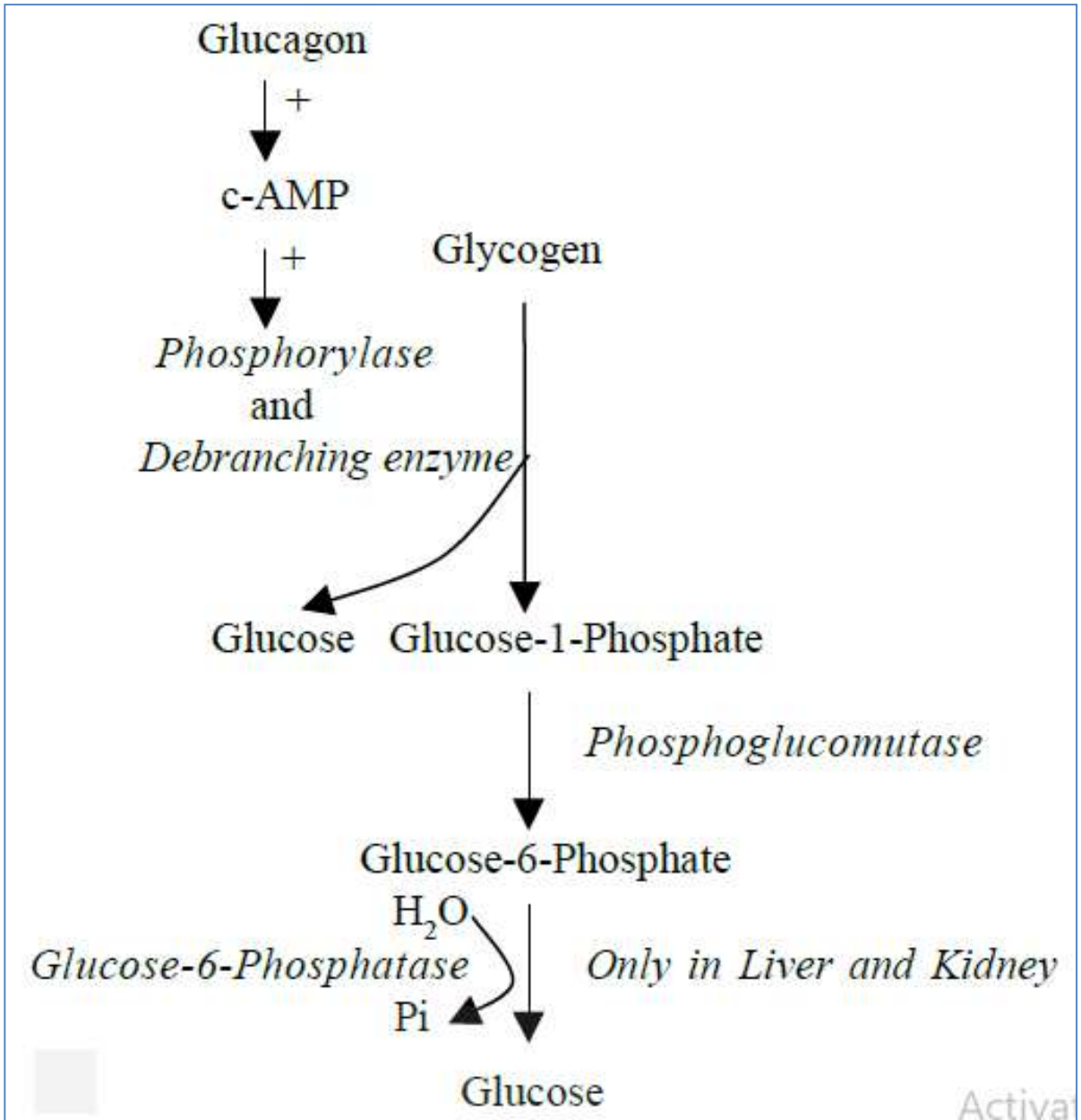

Figure 6.14 : Glycogenolysis

Glycogen phosphorylase is a dimeric (2 polypeptide) enzyme that utilizes pyridoxal phosphate as a prosthetic group. Different isozymes of glycogen phosphorylase are present in different tissues. Phosphorylase from liver is activated by glucagon stimulated cAMP levels whereas muscle phosphorylase is activated only by epinephrine via cAMP. In lysosomes, another enzyme α-1,4 glucosidase is involved in debranching.