Glycogenolysis, or glycogen breakdown, releases glucose when it is needed.

In the liver, glycogen is a glucose reserve for the maintenance of normal blood glucose levels, and its breakdown occurs primarily:

- in the fasted state, e.g. during the nocturnal fast;
- between meals;
- during a high intensity physical activity.

In hepatocytes, glycogenolysis is stimulated by glucagon and adrenalin, inhibited by insulin, and subject to negative allosteric regulation by glucose as well (see below).

In the muscle, glycogen is an energy source for muscular activity;
therefore, glycogen breakdown occurs during contraction, and only in muscles involved in the activity.
In muscle cells, glycogenolysis is stimulated by adrenaline, and regulated by positive and negative allosteric effectors, AMP and calcium ion (Ca^{2+}), and ATP and glucose 6-phosphate, respectively (see below).

The steps of glycogenolysis

Glycogenolysis begins by the action of **glycogen phosphorylase** (EC 2.4.1.1), a homodimer that for its activity requires the presence of pyridoxal-5-phosphate, a derivative of pyridoxine or vitamin B6. The enzyme catalyzes the phosphorolytic cleavage of α-(1,4) glycosidic bond, releasing glucose molecules one at a time from the non-reducing ends, that is, the ends with a free 4'-OH group, of the external branches. This reaction, which does not consume ATP but an orthophosphate, yields **glucose 1-phosphate**.

$$\text{Glycogen}_{(\text{n glucose residues})} + P_i \rightarrow \text{Glucose 1-Phosphate} + \text{Glycogen}_{(\text{n-1 glucose residues})}$$

Note: in the small intestine, pancreatic α-amylase (EC 3.2.1.1) catalyzes the hydrolytic cleavage of the α-(1,4) glycosidic bonds of the starch, and yields glucose molecules.

In vivo, glycogen phosphorylase catalyzes an irreversible phosphorolysis, a particularly advantageous reaction for skeletal muscle and heart (see below). The irreversibility of the reaction is ensured by the ratio $[P_i]/[\text{glucose 1-phosphate}]$, which is usually greater than 100. Conversely, the reaction is easily reversible *in vitro*. Glycogen phosphorylase acts repetitively on the non-reducing ends of branches, coming to a halt when the glucose unit that is 4 residues away from the branch point is reached: this is the outer limit of the **limit dextrin**. At this point, two enzymatic activities, present on the same polypeptide chain, complete glycogen breakdown: the **α-(1,4)-glucan-6-glycosyltransferase** (EC 2.4.1.24) and the **amylo-α-(1,6)-glucosidase or debranching enzyme** (EC 3.2.1.33). The first enzymatic activity transfers three of the remaining four glucose units from the branch to the non-reducing end of another branch, leaving in the first chain only a single glucose unit, that is attached to the chain by an α-(1,6)-glycosidic bond. The second enzymatic

activity hydrolyzes this α-(1,6)-glycosidic bond, releasing glucose and an unbranched chain of α-(1,4)-linked glucose units.
Without the branch, glycogen phosphorylase can continue to remove glucose units until it reaches the next limit dextrin.

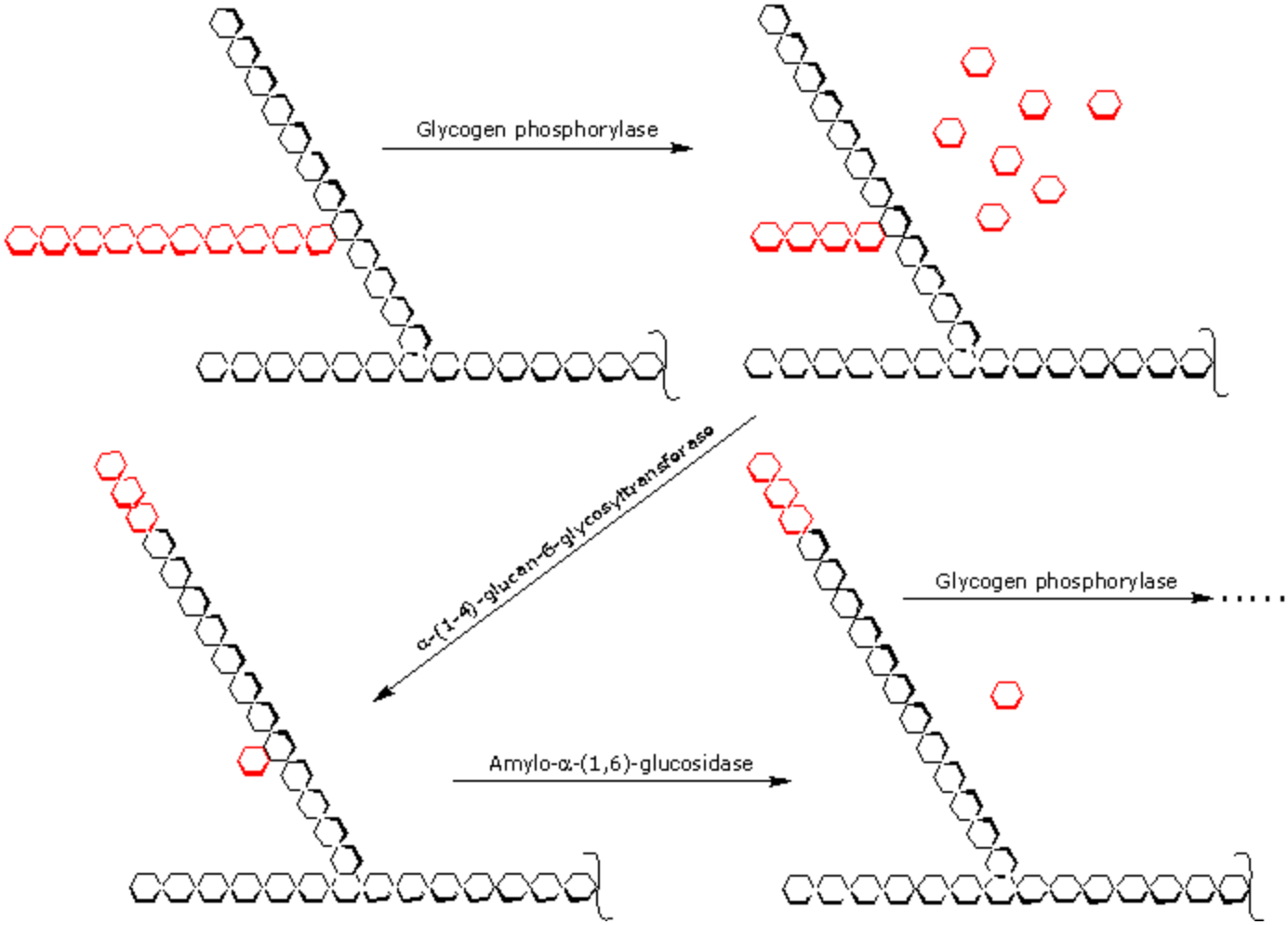

Fig. 1 – Glycogen Breakdown
Therefore, the products of the reactions catalyzed by the three enzymatic activities are:

- glucose 1-phosphate (about 90% of the glucose molecules released);
- a small amount of free glucose, the remaining 10% [these are the 1,6 linked residues; in the muscle, hexokinase activity (EC 2.7.1.1) is so high that any free glucose molecule is phosphorylated to glucose 6-phosphate, and therefore activated, and metabolized within the cell];
- a smaller and less branched glycogen molecule.

Metabolic fate of glucose 1-phosphate in muscle and liver

Glucose 1-phosphate is a charged molecule, and therefore it is trapped within the cell.
It is converted to glucose 6-phosphate in the reaction catalyzed by phosphoglucomutase (EC 5.4.2.2), the same enzyme that also intervenes in glycogen

synthesis converting glucose 6-phosphate to glucose 1-phosphate. This enzyme catalyses a reversible reaction: the direction is determined by the relative concentrations of the two molecules, and in this case moves the phosphate group from C1 to C6.

$$\text{Glucose 1-Phosphate} \rightleftarrows \text{Glucose 6-Phosphate}$$

In the muscle, and in most of the other organs and tissues, glucose from glycogenolysis enters the glycolytic pathway as glucose 6-phosphate, bypassing the activation step catalyzed by hexokinase. Therefore, glycogen phosphorylase, releasing an already "activated" glucose molecule, saves an ATP. An ATP molecule is required to synthesize another glycolytic intermediate, the fructose 1,6-bisphosphate. In this way, some of the activation energy required for glycogen synthesis is conserved: the net yield of ATP per glucose molecule by glycolysis to lactate is 3 rather than 2, an advantage for the working muscle. The overall equation is:

$$\text{Glycogen}_{(\text{n glucose residues})} + 3\ \text{ADP} + 3\ P_i \rightarrow \text{Glycogen}_{(\text{n-1 glucose residues})} + 2\ \text{Lactate} + 3\ \text{ATP}$$

In the liver, glucose 6-phosphate from glycogen is dephosphorylated by glucose 6-phosphatase (EC 3.1.3.9), and then released into the bloodstream. These are the steps in the removal of glucose units, in the form of phosphorylated glucose, by hepatic glycogenolysis:

$$\text{Glycogen}_{(\text{n glucose residues})} + P_i \rightarrow \text{Glucose 1-Phosphate} + \text{Glycogen}_{(\text{n-1 glucose residues})}$$

$$\text{glucose-1-phosphate} \rightarrow \text{glucose-6-phosphate}$$

$$\text{glucose-6-phosphate} + H_2O \rightarrow \text{glucose} + P_i$$

The overall equation is:

$$\text{Glycogen}_{(\text{n glucose residues})} + H_2O \rightarrow \text{Glycogen}_{(\text{n-1 glucose residues})} + \text{Gglucose}$$