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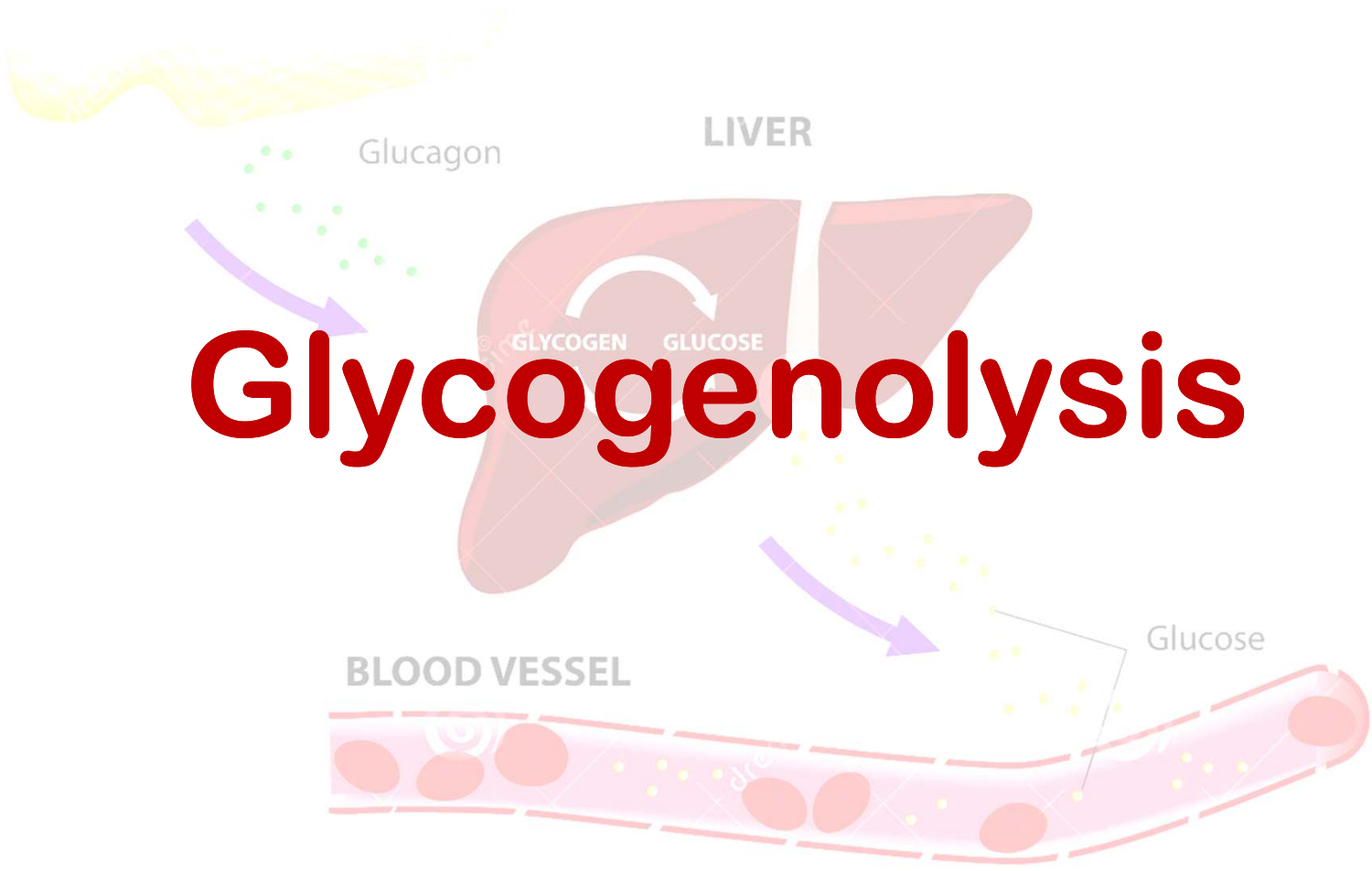

Glycogenolysis

Glycogenolysis

Glycogenolysis, process by which glycogen, the primary carbohydrate stored in the liver and muscle cells of animals, is **broken down into glucose to provide immediate energy** and to maintain blood glucose levels during fasting.

Glycogenolysis occurs **primarily in the liver (in some extent in kidney but not in muscle)** and is **stimulated by the hormones glucagon and epinephrine (adrenaline).**

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In the liver

Glycogen (n glucose residues) + H_2O → Glycogen (n-1 glucose residues) + Glucose

In the muscle

Glycogen(n glucose residues) + 3 ADP + 3 Pi → Glycogen(n-1 glucose residues) + 2 Lactate + 3 ATP

Why Glycogenolysis ??

(Glycogen breakdown, releases glucose when it is needed)

- **In the fasted state, e.g. During the nocturnal fast**
- **Between meals**
- **During a high intensity physical activity**

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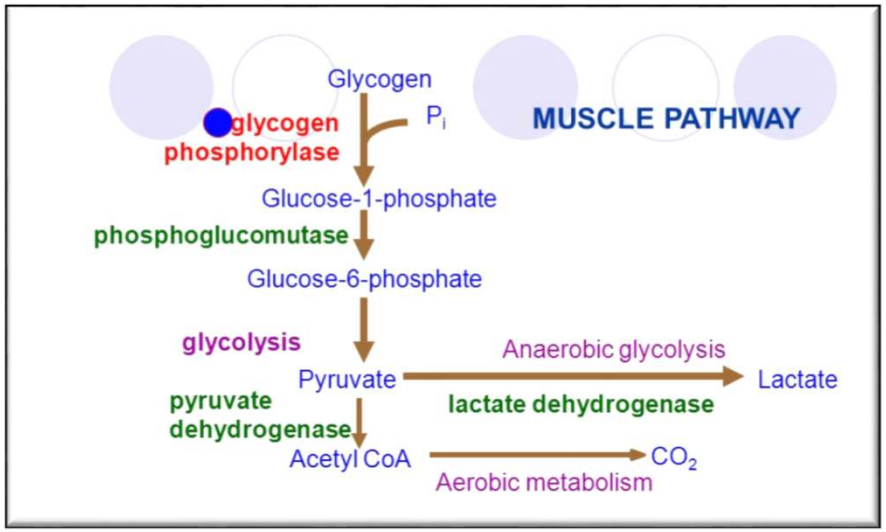
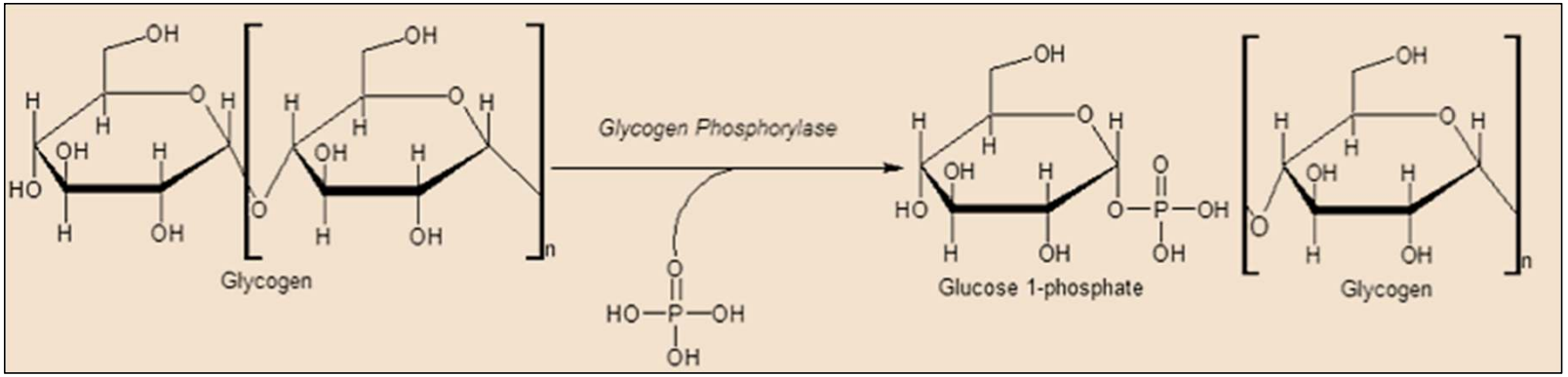


The liver breaks down glycogen to maintain adequate blood glucose levels, whereas, muscles break down glycogen to maintain energy for contraction.

Liberation of Glucose 1 Phosphate with the help of Glycogen Phosphorylase



- **Glycogen phosphorylase** catalyzes the rate-limiting step in the degradation of glycogen in animals by **releasing glucose-1-phosphate** from the **terminal alpha-1,4-glycosidic bond (Phosphorolytic Cleavage).**
- Glycogen is left with one fewer glucose molecule, and the **free glucose molecule is in the form of glucose-1-phosphate.**

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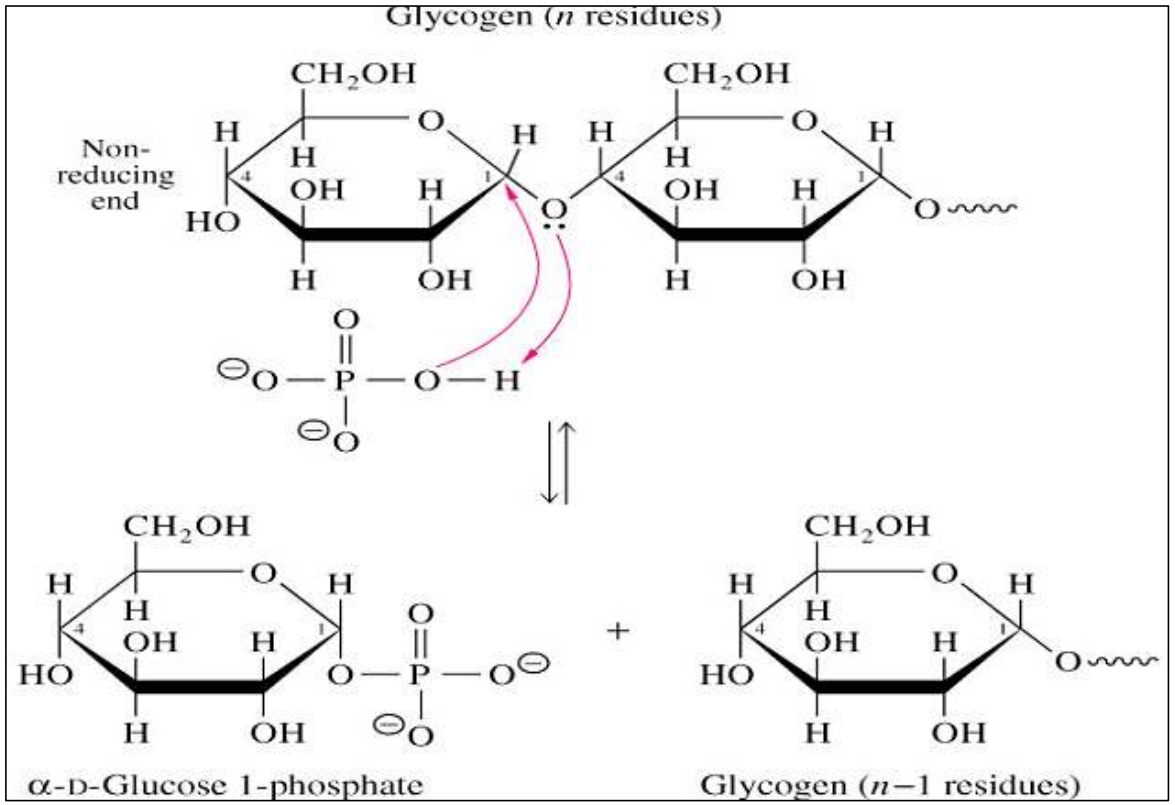
Cleavage of a glucose residue from the non-reducing end of glycogen



Activation of Glycogen Phosphorylase

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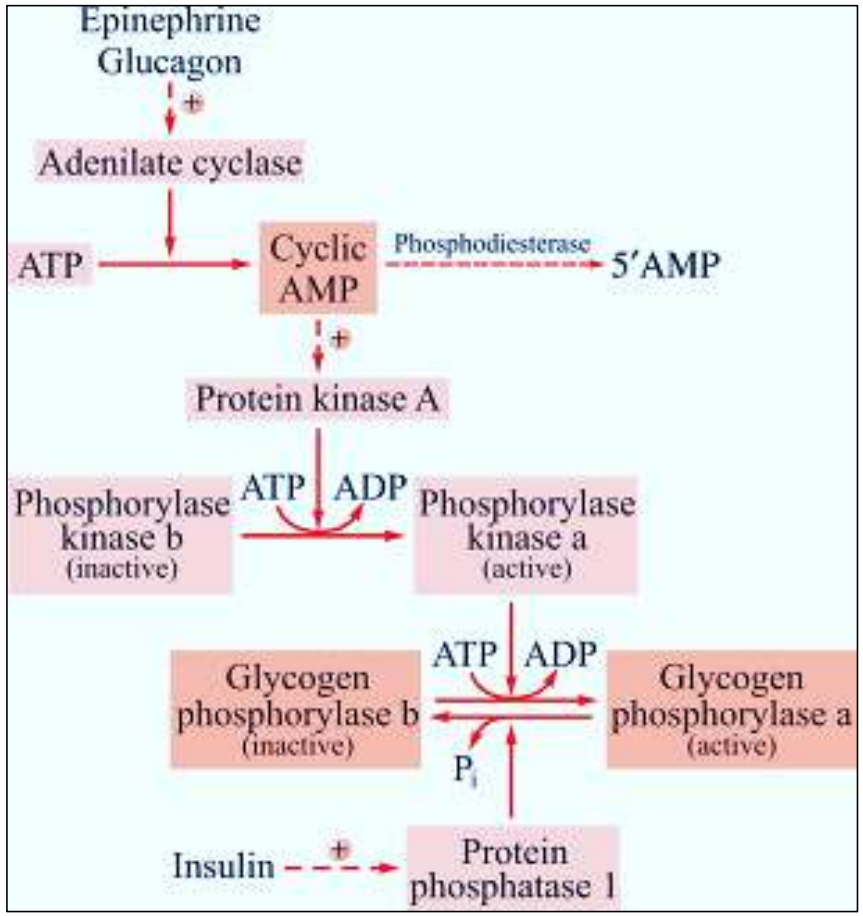

- **Epinephrine in muscle and glucagon in liver binds** to specific cell membrane receptors and **activates an enzyme called adenylate cyclase.**
- Adenylate cyclase catalyzes the conversion of intracellular ATP **into 3',5'-cyclic adenosine monophosphate.**
- The increased level of 3',5'-cyclic-AMP in the cytosol **activates protein kinase A.**
- Protein kinase A **phosphorylates the -OH of a serine residue on phosphorylase kinase.**
- This enzyme is also found in two forms, a and b, in the **dephosphorylated state (b) it is inactive.**
- Activated phosphorylase kinase (a), in turn, **catalyzes the transfer of phosphate from ATP to glycogen phosphorylase b converting it into a.**
- This **initiates the degradation of glycogen to glucose-1-phosphate.**

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Problem faced by glycogen phosphorylase

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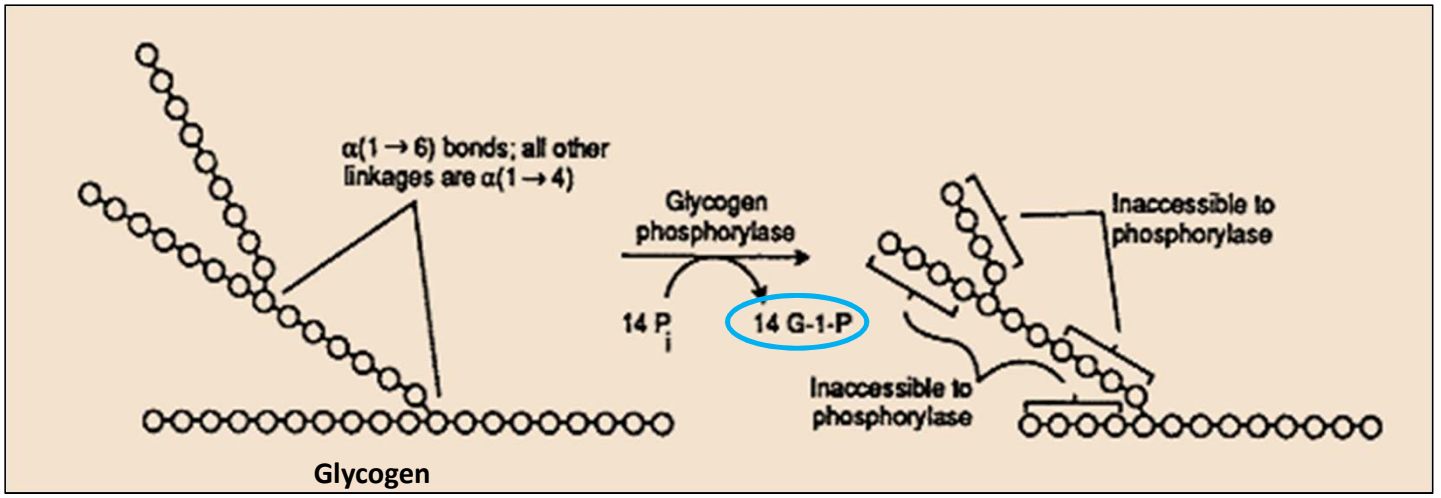

Glycogen phosphorylase catalyzes the **release of glucose-1-phosphate from the terminal residue of a nonreducing end of a glycogen branch**, by means of phosphorolysis.

Glycogen phosphorylase sequentially **removes the glucosyl residues** from a glycogen branch **until further action is sterically hindered by a branch point.** This occurs when the **branch is four residues long from the branch point.**

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Function of debranching enzymes

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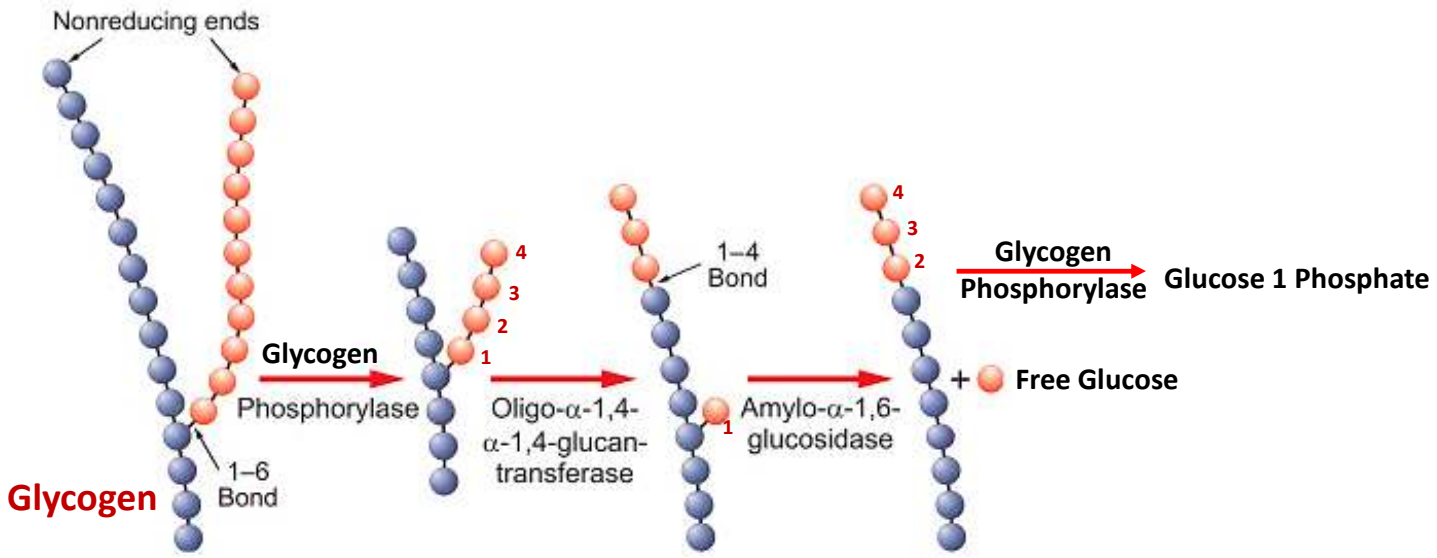


Debranching enzyme, a **multifunctional protein**, first removes the **trisaccharide "stump" on the branch and then removes the branch point itself.**

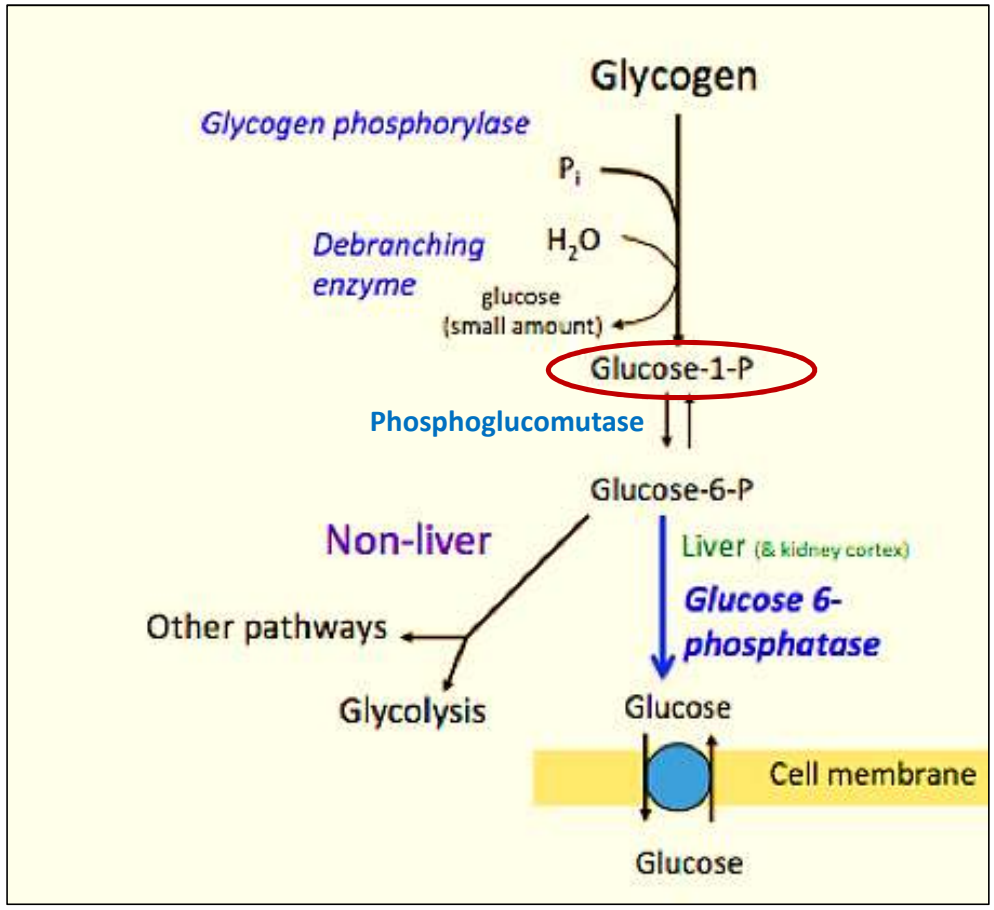
The α(1 → 4) glycosidic bond linking the trisaccharide to the branch point residue is first cleaved, and the **trisaccharide is transferred to the nonreducing end of an adjacent branch**.

This **elongated branch can now be cleaved, one residue at a time, by glycogen phosphorylase**.

The **glucose residue** that remains, **linked by an α(1 → 6) glycosidic bond, is then cleaved by hydrolysis to yield free glucose.**

Thus, **one molecule of glucose is released for each branch point removed.**

Formation of Glucose 6 Phosphate and release of free glucose



Cleavage of glycogen by glycogen phosphorylase yields **glucose 1-phosphate, which is converted into glucose-6-phosphate by phosphoglucomutase.**

Glucose-6-phosphate cannot exit the cell, and so, in the liver, glucose 6-phosphate is transported into the endoplasmic reticulum, where it is **converted into glucose by glucose 6-phosphatase.**

Glucose then **exits the cell through the Glut-2 transporter.**

Muscle lacks glucose-6-phosphatase and therefore **cannot contribute to maintenance of blood glucose levels**. Instead, it is used as a rapidly mobilizable source of oxidizable glucose for ATP production.

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Steps involved

- Glycogen phosphorylase cleaves the bond linking a terminal glucose residue to a glycogen branch by substitution of a phosphoryl group for the α-[1→4] linkage.
- **Glucose-1-phosphate is converted to glucose-6-phosphate by the enzyme phosphoglucomutase.**
- Glucose residues are phosphorolysed from branches of glycogen until four residues before a glucose that is branched with a α-[1→6] linkage.
- Glycogen **debranching enzyme then transfers three of the remaining four glucose units to the end of another glycogen branch.**
- This **exposes the α-[1→6] branching point, which is hydrolyzed by α[1→6] glucosidase,** removing the final glucose residue of the branch as a molecule of glucose and eliminating the branch.
- This is the only case in which a glycogen metabolite is not glucose-1-phosphate.
- The **glucose is subsequently phosphorylated to glucose-6-phosphate by hexokinase in liver.**
- **With the help of glucose 6 phosphatase**, glucose 6 phosphate converts into free glucose.

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Regulation of Glycogenolysis

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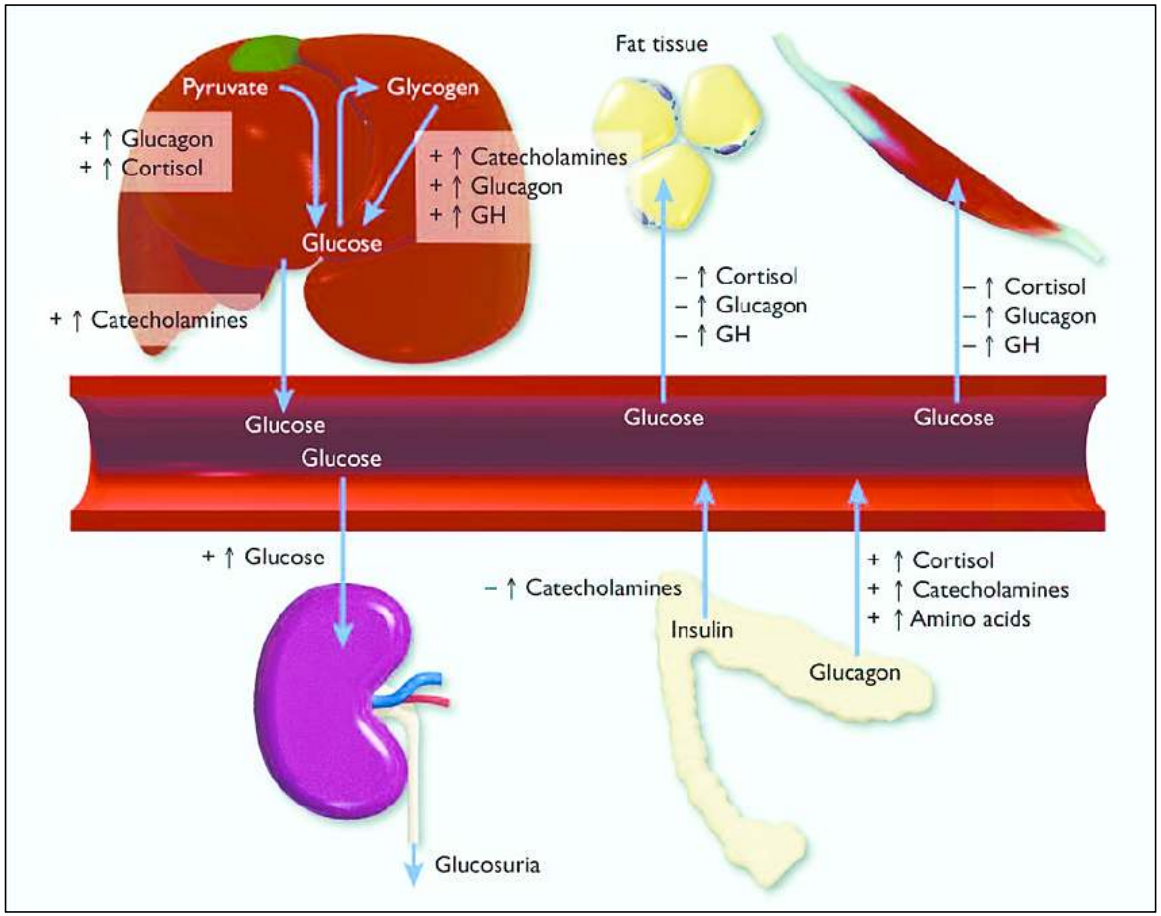

- Pancreatic **glucagon, adrenal medullary adrenalin promote glycogenolysis by activating glycogen phosphorylase**.
- **Glucocorticoides** of adreanal cortex and **thyroxin promote glycogenolysis by stimulating glucose 6 phosphatase activity.**
- **Gene mutation** may lead to inborn failure of glycogenolysis leading to **high hepatic glycogen concentration and Hypoglycemia**. The condition is called as **Glycogenosis.**
- **Cori Disease:** Deficiency of debranching enzyme (amylo-1,6-glucosidase) is called as Type III or limit dextrinosis.
- **Von Gierke disease:** Deficiency of Glucose 6 Phosphatase is known as Type I Glycogenosis.
- **Type V or McArdle disease:** Myophosphorylase deficiency or glycogen phosphorylase activity is effected.
- **Pompe disease,** also known as glycogen storage disease type II or acid maltase deficiency, leading to lysosomal accumulation of glycogen in various tissues, but mostly affecting cardiac and skeletal muscles.

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Significances of Glycogenolysis

- Glycogenolysis plays an important role in the **fight-or-flight response**.
- It contributes to the **regulation of glucose levels in the blood**.
- The metabolism of glycogen polymers becomes important **during fasting.**
- In **myocytes (muscle cells),** glycogen degradation serves to provide an **immediate source of glucose-6-phosphate for glycolysis, to provide energy for muscle contraction.**
- In hepatocytes, the main purpose of the breakdown of glycogen is for the **release of glucose into the bloodstream for uptake by other cells.**

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Cori cycle or Glucose-Lactate cycle

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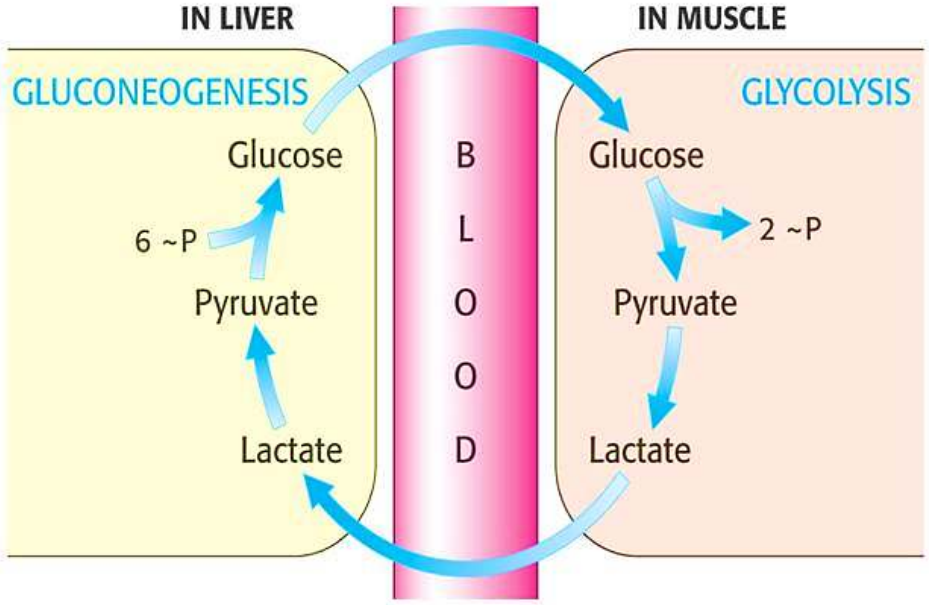
The Cori cycle refers to the metabolic pathway in which lactate produced by anaerobic glycolysis in the muscles move via the blood stream to the liver where it is converted into blood glucose and glycogen.

- The conversion of glucose to lactic acid, or lactate, by anaerobic glycolysis in skeletal muscle cells;
- The diffusion of lactate from muscle cells into the bloodstream, by which it is transported to the liver;
- the conversion of lactate to glucose by hepatic gluconeogenesis;
- The diffusion of glucose from the hepatocytes into the bloodstream, by which it is transported back to the skeletal muscle cells, thereby closing the cycle.



Significances

- Prevent lactic acidosis in the muscle under anaerobic conditions.
- The cycle is important in producing ATP, an energy source during muscle activity.
- Cori cycle functions ,more sufficiently when the muscle activity has ceased thus allowing the oxygen debt to be repaid.

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Glucose –Alanine cycle

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Alanine is one of the major amino acid metabolized by the body. The amino group of glutamic acid is transferred to pyruvate resulting in the formation of alanine and α-ketoglutarate. The reaction is carried by the enzyme known as alanine transaminase. As the levels of alanine increases in the muscle cells, it would be transferred to the liver via blood.

- Alanine is synthesized in muscle by transamination of glucose-derived pyruvate, and released into the bloodstream.
- In the liver, the carbon skeleton of alanine is reconverted to glucose, and released into the bloodstream where it is available for uptake by muscle and re-synthesis of alanine.

Significance

- Toxic ammonia can be transferred to the liver in the neutral form for urea synthesis.
- Distribution of metabolic burden between the muscle and liver cells.
- ATP molecules meant for muscular contraction are not used up in the elimination of ammonia from the cells.