GLYCOGENOLYSIS

The degradation of stored glycogen in liver & muscle constitutes glycogenolysis

Introduction:

The synthesis & degradation of glycogen are not reversible.

An independent set of enzymes present in the cytosol carry out glycogenolysis

Glycogen is degraded by breaking α-l,4 & α-1,6- Glycosidic bonds.

Enzyme involved:

Action of glycogen phosphorylase

The α-1,4-glycosidic bonds (from the non- reducing ends) are cleaved sequentially by the enzyme *glycogen phosphorylase* to yield glucose 1–phosphate.

This process-called phosphorolysis- continues until four glucose residues remain on either side of branching point (α-1,6 -glycosidic link).

The glycogen so formed is known as limit dextrin which cannot be further degraded by phosphorylase. It is bound with one molecule of PLP(pyridoxal phosphate).

Action of de branching enzyme

The branches of glycogen are cleaved by two enzyme activities present on a single polypeptide called debranching enzyme, It is a bifunctional enzyme.

Glycosyl 4 : 4 transferase (oligo α-l,4 glucantransferase) activity removes a fragment of 3 or 4 glucose residues attached at a branch & transfers them to another chain.

One α -1,4 bond is cleaved & the same α -1,4 bond is made, places are different. Amylo α-1,6-Glucosidase breaks the α-1,6 bond at the branch with a single glucose residue & releases a free glucose.

The remaining molecule of glycogen is again available for the action of phosphorylase & debranching enzyme to repeat the reactions.

Formation of glucose 6-phosphate & glucose

Through the combined action of glycogen phosphorylase & debranching enzyme, glucose 1-phosphate & free glucose in a ratio of 8 : 1 are produced.

Glucose 1- phosphate is converted to glucose 6 – phosphate by phosphoglucomutase.

The fate of glucose 6-phosphate depends on the tissue.

Glucose-6-phosphatase in Liver

Hepatic glucose-6-phosphatase hydrolyses glucose-6-phosphate to glucose.

The free glucose is released to blood stream.

Muscle Lacks Glucose-6-phosphatase

Muscle will not release glucose to the blood stream, because muscle tissue does not contain glucose-6-phosphatase.

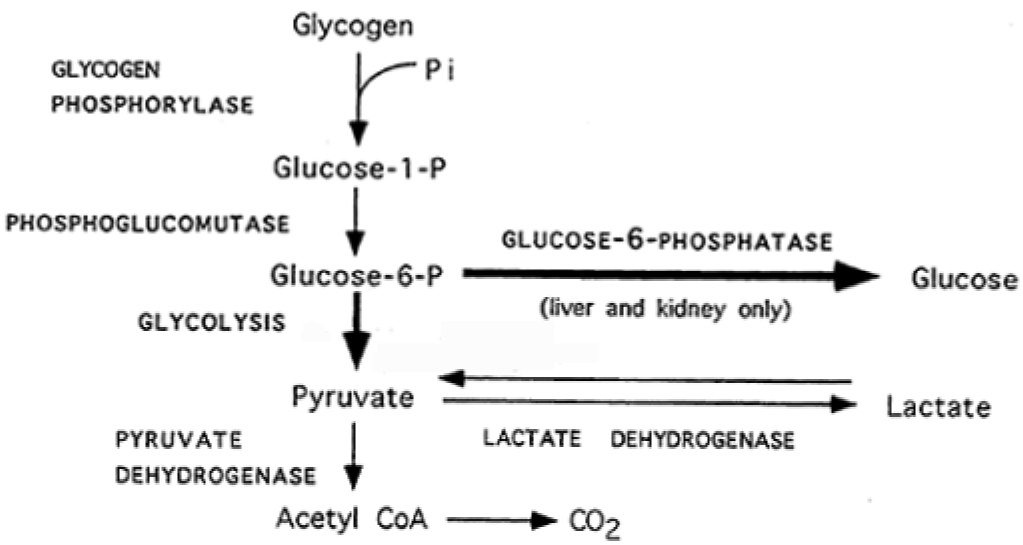
Provides ATP for muscle contraction via glycolysis.

The liver, kidney &intestine contain the enzyme glucose 6-phosphatase that cleaves glucose 6 – phosphate to glucose.

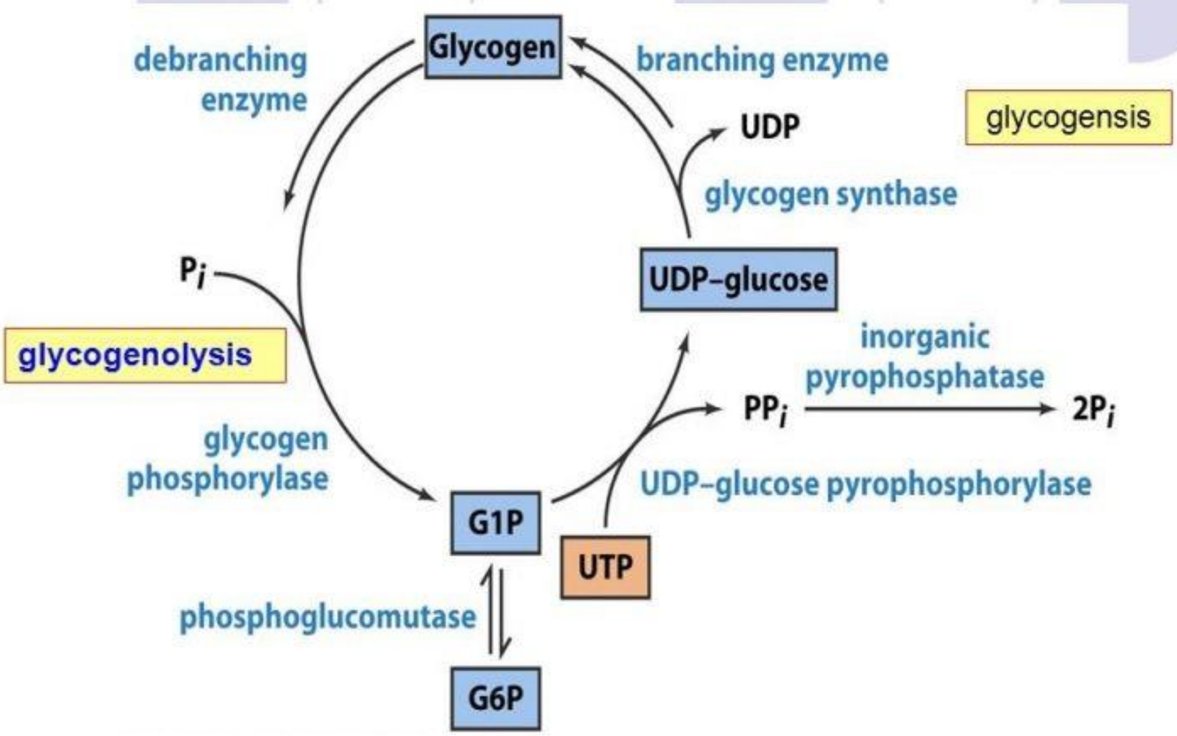
This enzyme is absent in muscle & brain, hence free glucose cannot be produced from glucose 6-phosphate in these tissues.

Liver is the major glycogen storage organ to provide glucose into the circulation to be utilized by various tissues.

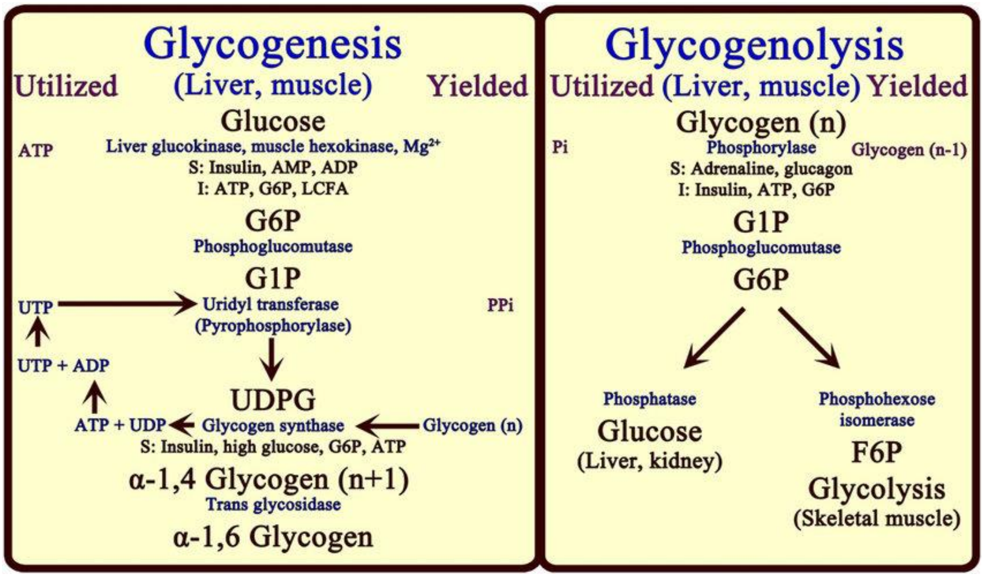
In the peripheral tissues, glucose 6 – phosphate produced by glycogenolysis will be used for glycolysis.


Glycogen
GLYCOGEN
PHOSPHORYLASE
P i
Glucose-1-P
PHOSPHOGLUCOMUTASE
Glucose-6-P
GLUCOSE-6-PHOSPHATASE
Glucose
(liver and kidney only)
GLYCOLYSIS
Pyruvate
Lactate
LACTATE DEHYDROGENASE
PYRUVATE
DEHYDROGENASE
Acetyl CoA
CO2

GLYCOGENOLYSIS PATHWAYS



REGULATION OF GLYCOGENESIS & GLYCOGENOLYSIS



Glycogenesis and glycogenolysis are, controlled by the enzymes glycogen synthase & glycogen phosphorylase.

Three mechanisms

- **Allosteric regulation**
- **Hormonal regulation**
- **Influence of calcium**

Allosteric regulation of glycogen metabolism

Certain metabolites that allosterically regulate the activities of glycogen synthase & glycogen phosphorylase. The glycogen synthesis is increased when substrate availability and energy levels are high.

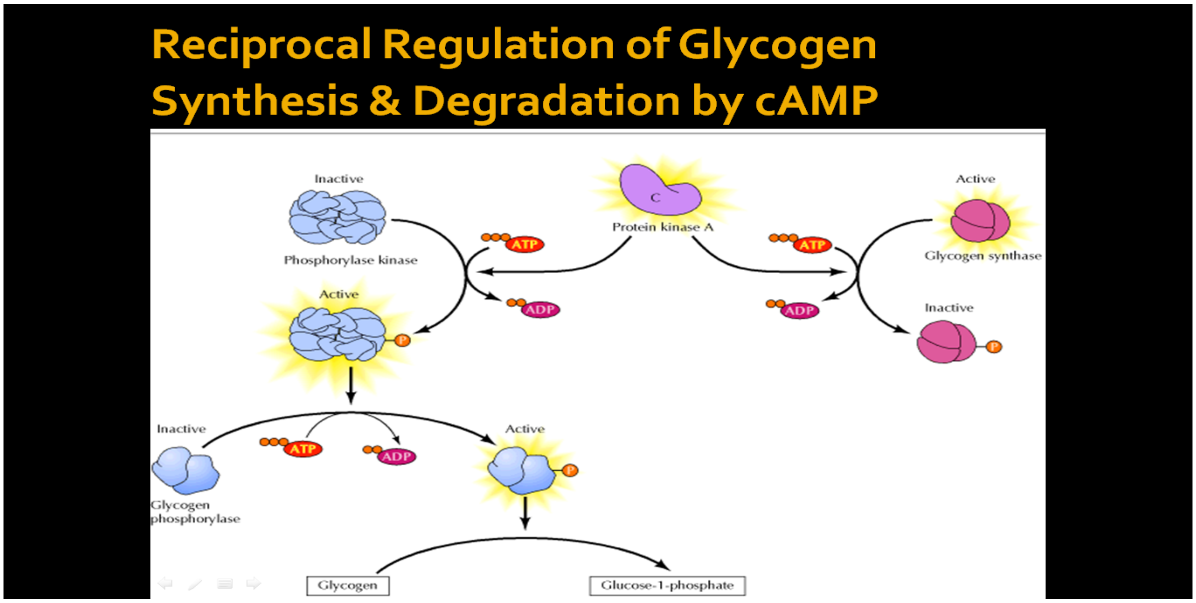
Glycogen breakdown is enhanced when glucose concentration & energy levels are low.

In a well-fed state, the availability of glucose 6 – phosphate is high which allosterically activates glycogen synthase for more glycogen synthesis.

Glucose 6-phosphate & ATP allosterically inhibit glycogen phosphorylase.

Free glucose in liver also acts as an allosteric inhibitor of glycagen phosphorylase.

Hormonal regulation of glycogen metabolism



The hormones, through a complex series of reactions, bring about covalent modification, namely phosphorylation and dephosphorylation of enzyme proteins which, ultimately control Glycogen synthesis or its degradation.

The hormones like epinephrine, norepinephrine and glucagon (in liver) activate adenylate cyclase to increase the production of cAMP. The enzyme phosphodiesterase breaks down cAMP.

The hormone insulin increases the phosphodiesterase activity in liver & lowers the cAMP levels.

Regulation of glycogenesis by cAMP

Regulated by glycogen synthase.

It exist in two forms glycogen synthase - a -not phosphorylated & most active.

Glycogen synthase - b - phosphorylated inactive form.

Glycogen synthase - a can be converted to 'b' form (inactive) by phsophorylation.

Phosphorylation is catalysed by a cAMP dependent protein kinase.

Protein kinase phosphorylates & inactivates glycogen synthase by converting 'a' form to 'b' form.

The glycogen synthase 'b' can be converted back to synthase' a' by protein phosphatase

The inhibition of glycogen synthesis brought by epinephrine (also norepinephrine) & glucagon through cAMP by converting active glycogen synthase 'a' to inactive synthase 'b'.

Regulation of glycogenolysis by cAMP

The hormones like epinephrine & glucagon bring about glycogenolysis by their action on glycogen phosphorylase through cAMP.

Glycogen phosphorylase exists in two forms

An active 'a' form – phosphorylated ,Inactive form 'b' - dephosphorylated

The cAMP - activates cAMPdependent protein kinase.

Protein kinase phosphorylates inactive form of glycogen phsophorylase kinase to active form.

The enzyme protein phosphatase removes phosphate & inactivates phosphorylase kinase.

The Phosphorylase kinase phosphorylates inactive glycogen phosphorylase 'b' to active glycogen phosphorylase 'a' which degrades glycogen.

The enzyme protein phosphatase I can dephosphorylate & convert active glycogen phosphorylase 'a' to inactive 'b' form.

Effect of Ca^{2+} ions on glycogenolysis

When the muscle contracts, Ca^{2+} ions are released from the sarcoplasmic reticulum.Ca^{2+} binds to calmodulin- calcium modulating protein & directly activates phosphorylase kinase without the involvement of cAMP-dependent protein kinase.

An elevated glucagon or epinephrine level increases glycogen degradation whereas elevated insulin results in increased glycogen synthesis.

Energetics:

- 1 glucose residue derived from glycogen yield 3 ATP molecules as no ATP is required for initial phosphorylation.
- If glycolysis starts from free glucose - 2 ATP molecules produced.