B.SC-4TH SEM
UNIT-2 (CC-410)

GLUCOGENOLYSIS

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Glycogenolysis

- The degradation of stored glycogen in liver & muscle constitutes glycogenolysis
- 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.

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.**

Action of debranching 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-,1,4 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

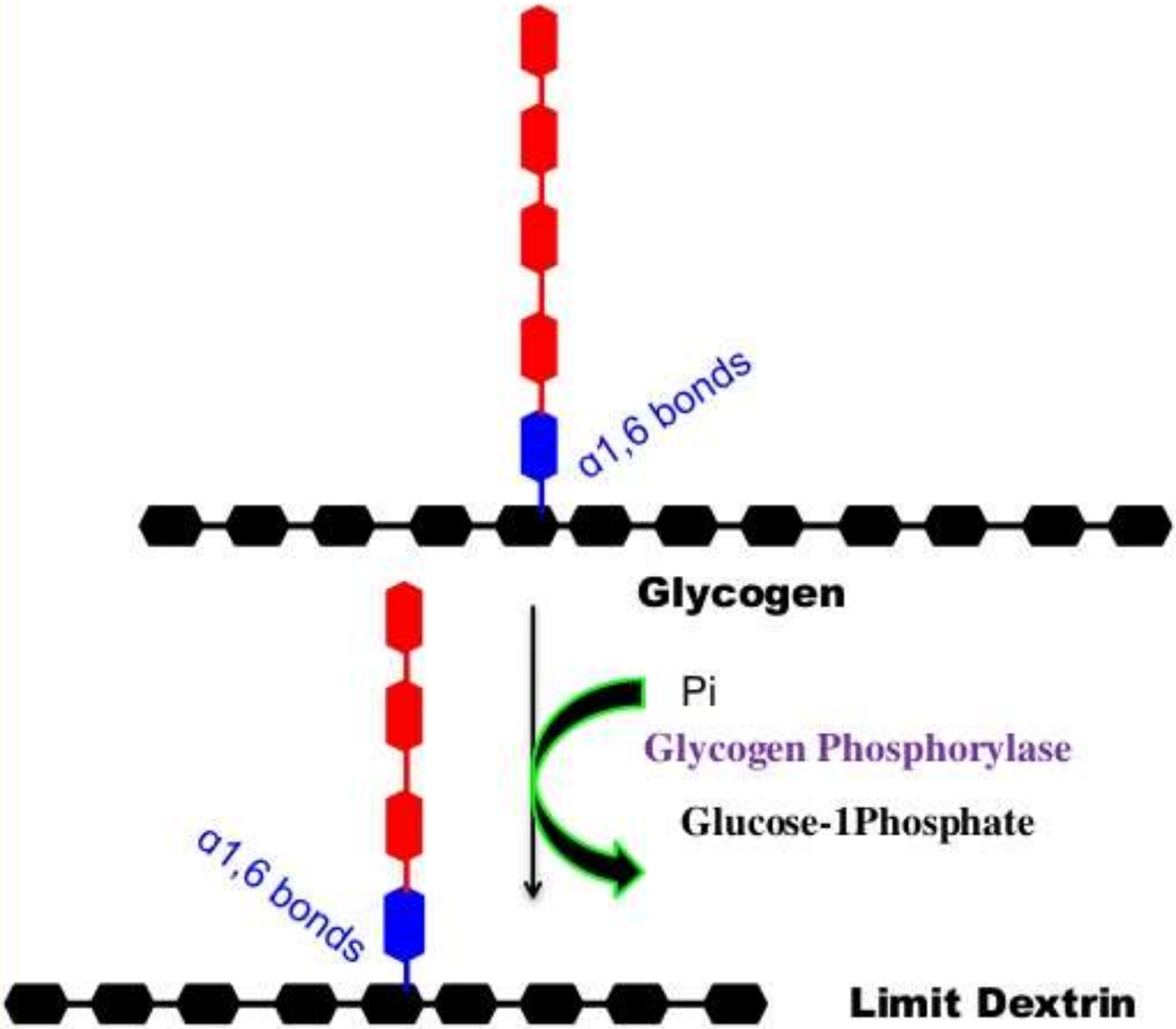
- Muscle will not release glucose to the blood stream, because muscle tissue does not contain glucose-6-phosphatase.
- Provides ATP for muscle contraction via glycolysis.

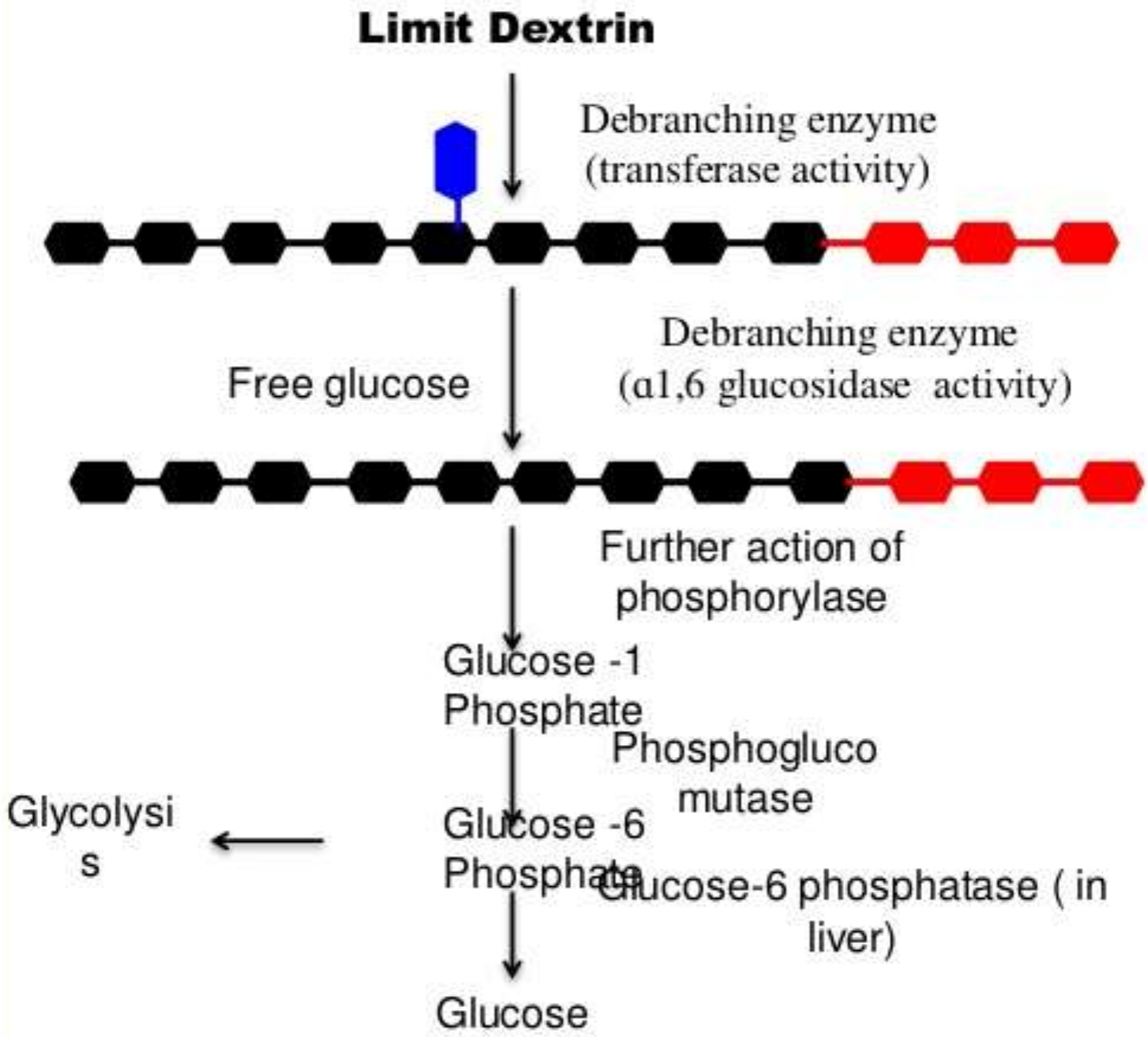
- The liver, kidney & intestine contain the enzyme glucose 6-phosphatase that cleaves glucose 6 –phosphate to glucose.
- This enzyme is absent in muscle & brain, hence free glucose cannot be produced from glucose 6-phosphate in these tissues.

- **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.**

Degradation by lysosomal acid maltase

- Acid maltase or α-1,4-glucosidase degrades small quantity of glycogen.
- Deficiency of this α-1,4-glucosidase results in glycogen accumulation, causing glycogen storage disease type II (Pompe's disease)


α1,6 bonds
Glycogen
Pi
Glycogen Phosphorylase
Glucose-1Phosphate
α1,6 bonds
Limit Dextrin


Limit Dextrin
Debranching enzyme
(transferase activity)
Free glucose
Debranching enzyme
(α1,6 glucosidase activity)
Further action of
phosphorylase
Glucose -1
Phosphate
Phosphogluco
mutase
Glycolysi
s
Glucose -6
Phosphate
Glucose-6 phosphatase (in
liver)
Glucose

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.

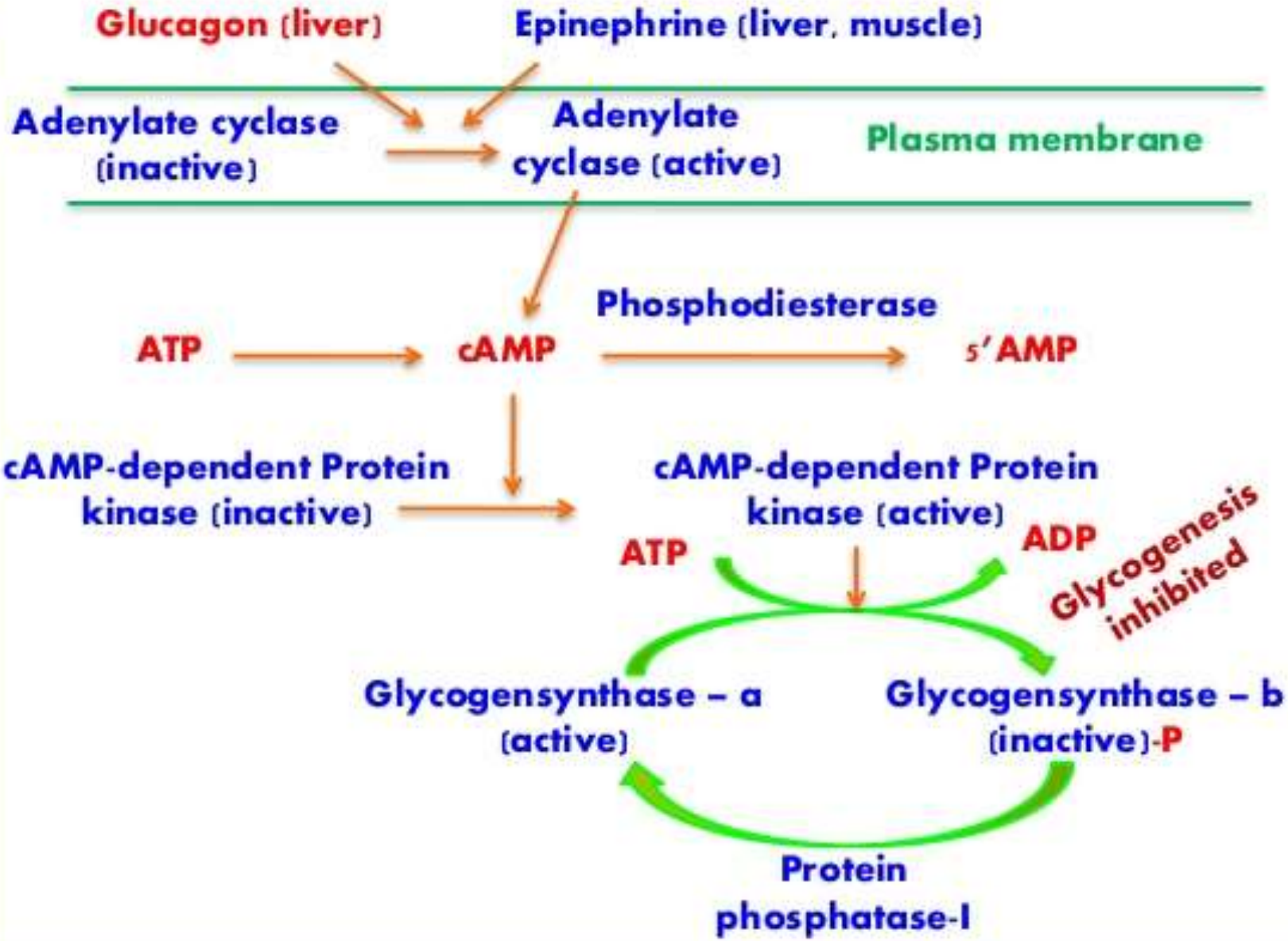
Regulation of glycogenesis by cAMP

- 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 I.

- **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 glycogen synthesis by cAMP

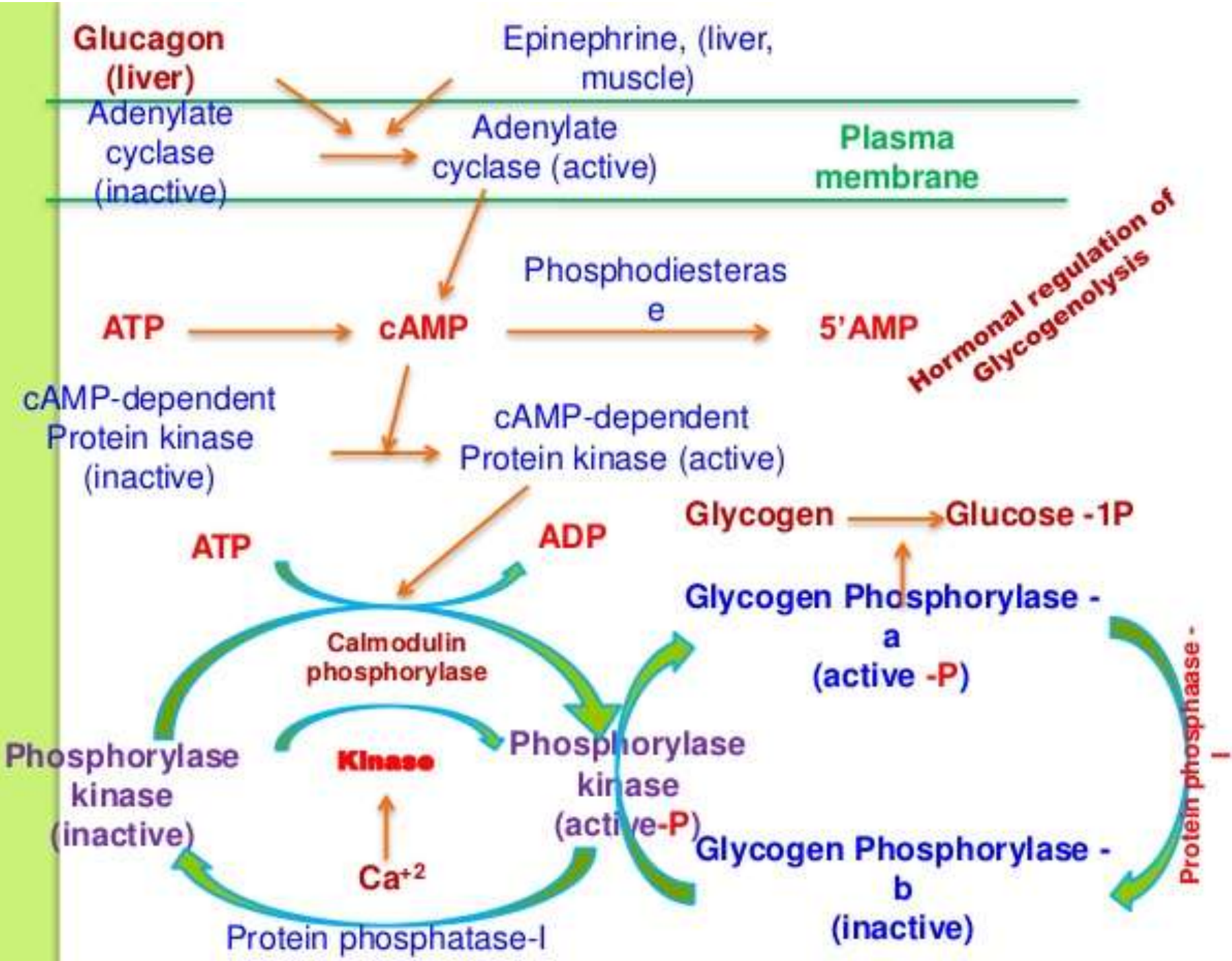


Regulation of glycogenolysis by cAMP

- 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 cAMP dependent 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.


Glucagon (liver)
Epinephrine, (liver, muscle)
Adenylate cyclase (inactive)
Adenylate cyclase (active)
Plasma membrane
Phosphodiesteras e
ATP
cAMP
5'AMP
Hormonal regulation of Glycogenolysis
cAMP-dependent Protein kinase (inactive)
cAMP-dependent Protein kinase (active)
ATP
ADP
Glycogen
Glucose -1P
Glycogen Phosphorylase - a (active -P)
Calmodulin phosphorylase
Phosphorylase kinase (inactive)
Kinase
Phosphorylase kinase (active-P)
Ca+2
Protein phosphatase-I
Glycogen Phosphorylase - b (inactive)
Protein phosphaase - I

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 an elevated insulin results in increased glycogen synthesis.