glycogen degradation

By

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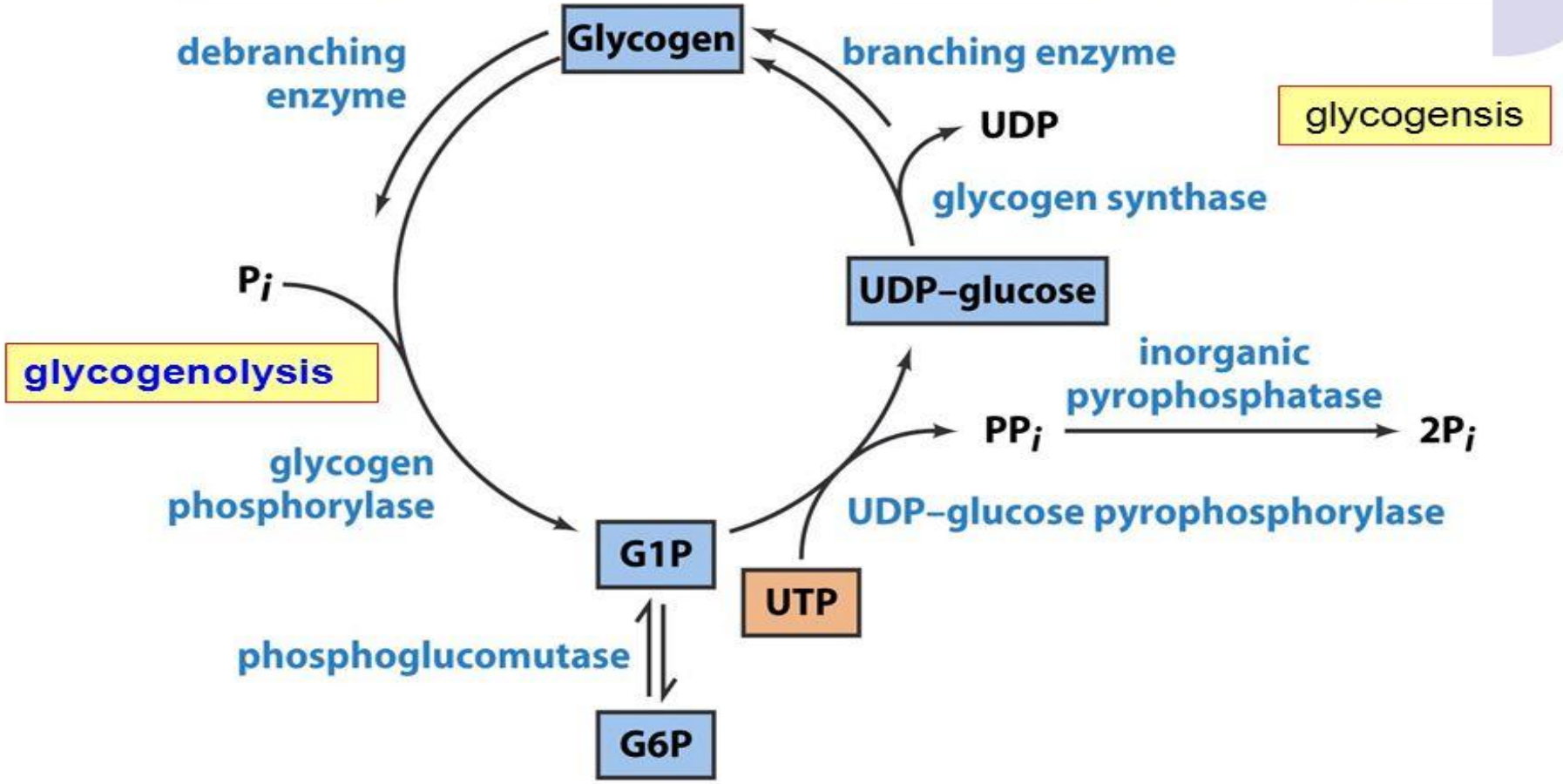
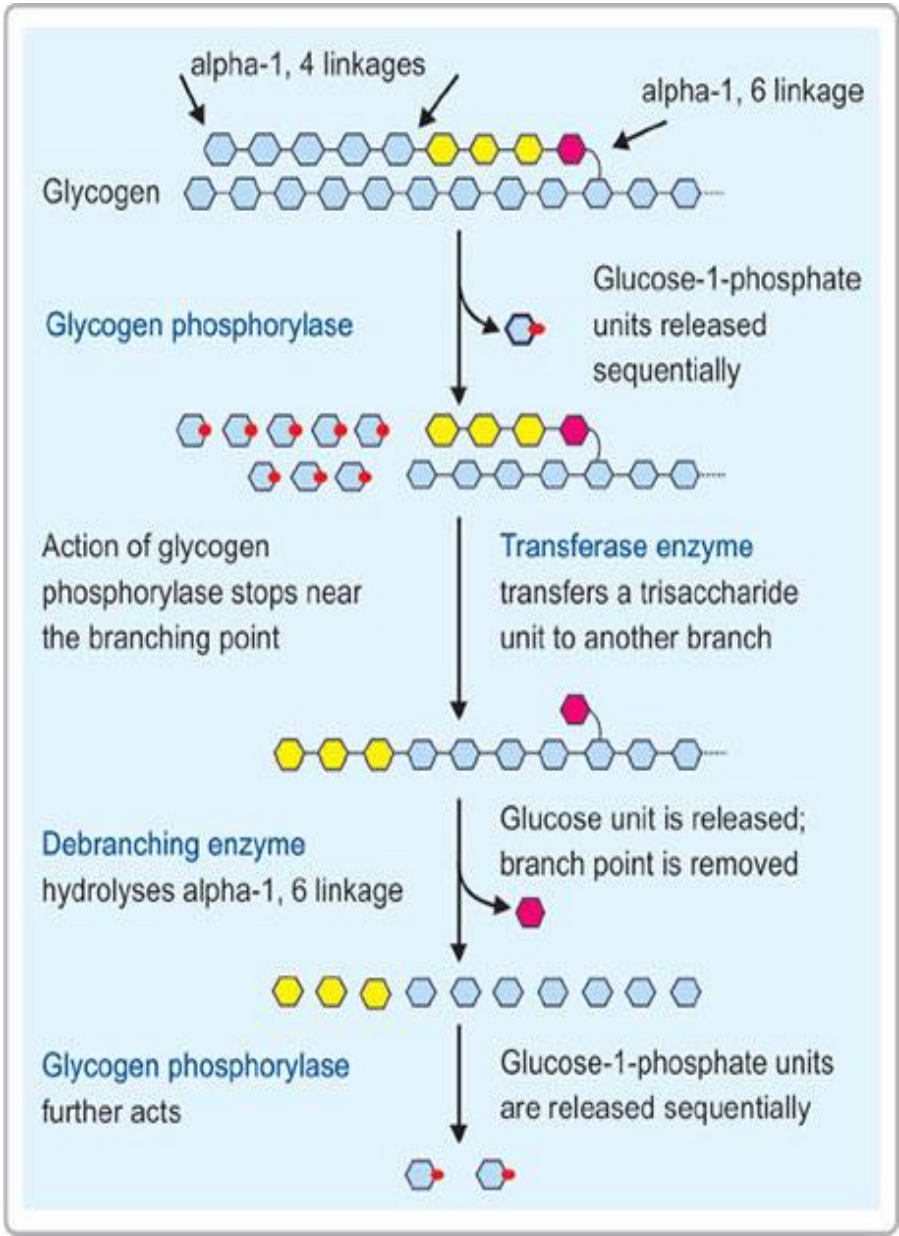
GLYCOGENOLYSIS PATHWAYS



- Degradation of glycogen to glucose -6 phosphate in muscles & to glucose in liver.
- It is a cytosolic process.

Glycogenolytic pathway

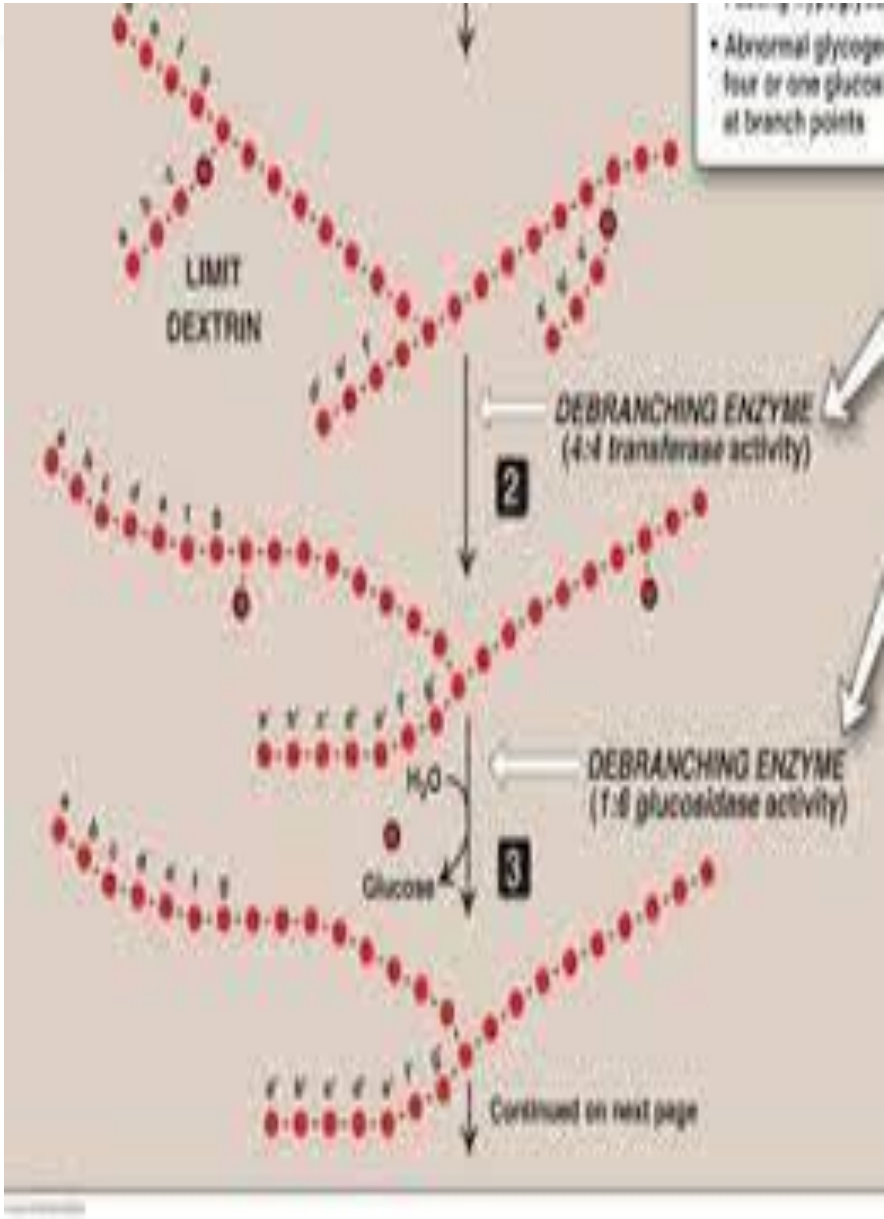
- Enzyme: **Phosphorylase**
- It brings about phosphorolytic cleavage of α1-4 glycosidic bonds to yield glucose-1-phosphate and residual glycogen molecule.



SHORTNING OF CHAINS:

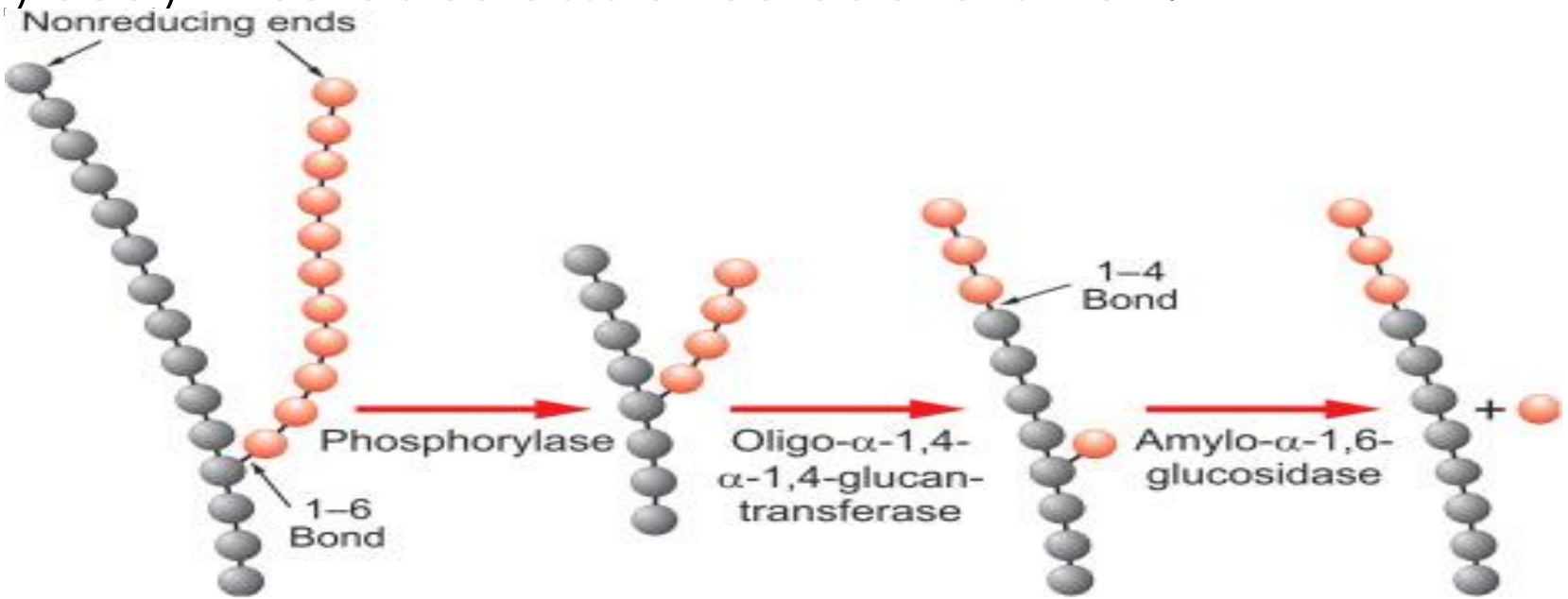
phosphorolysis continue until four glycosyl residues are left on each chain before a branch point. The resulting structure is called limit dextrin.

Pyridoxal phosphate is co-factor acting as a general acid catalyst,promoting attack by pi on the glycosidic bond.



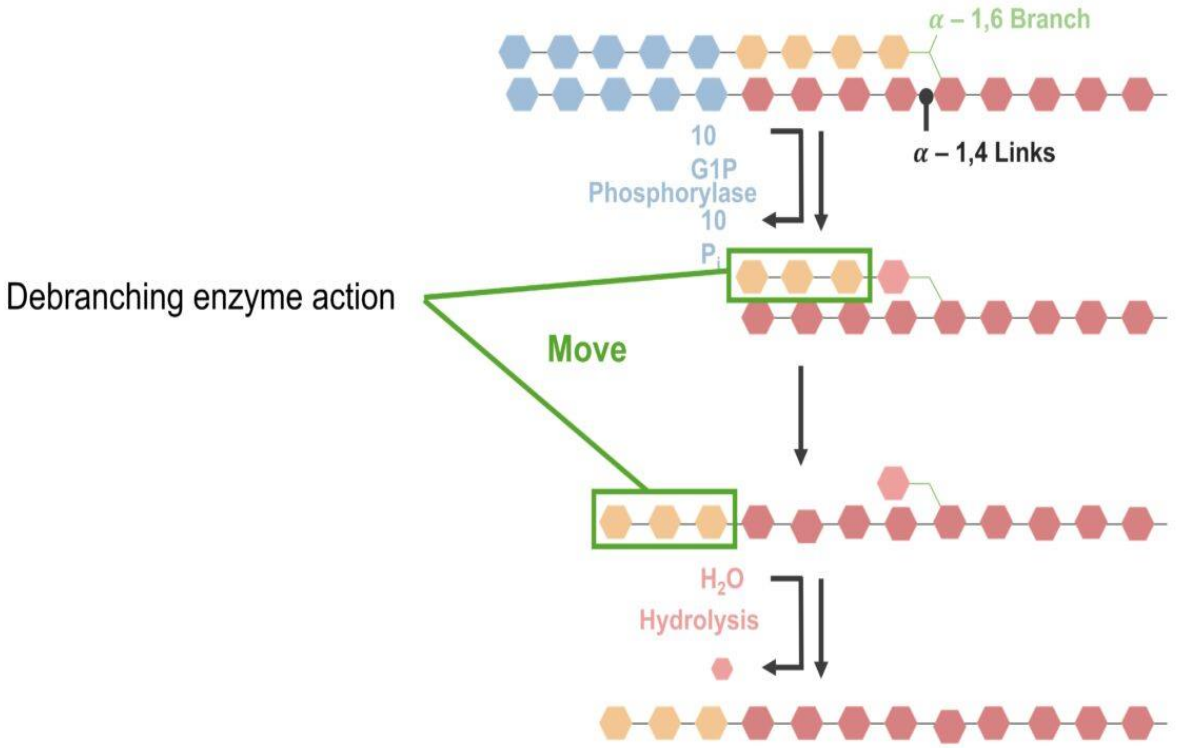
REMOVAL OF BRANCHES:

- Phosphorolysis can not continue until branch is removed by debranching enzyme.
- It is bi functional enzyme.
- FIRST oligo alpha(1-4)->alpha(1-4) glucan transferase activity removes the outer three of four glycosyl residues attached at a branch.



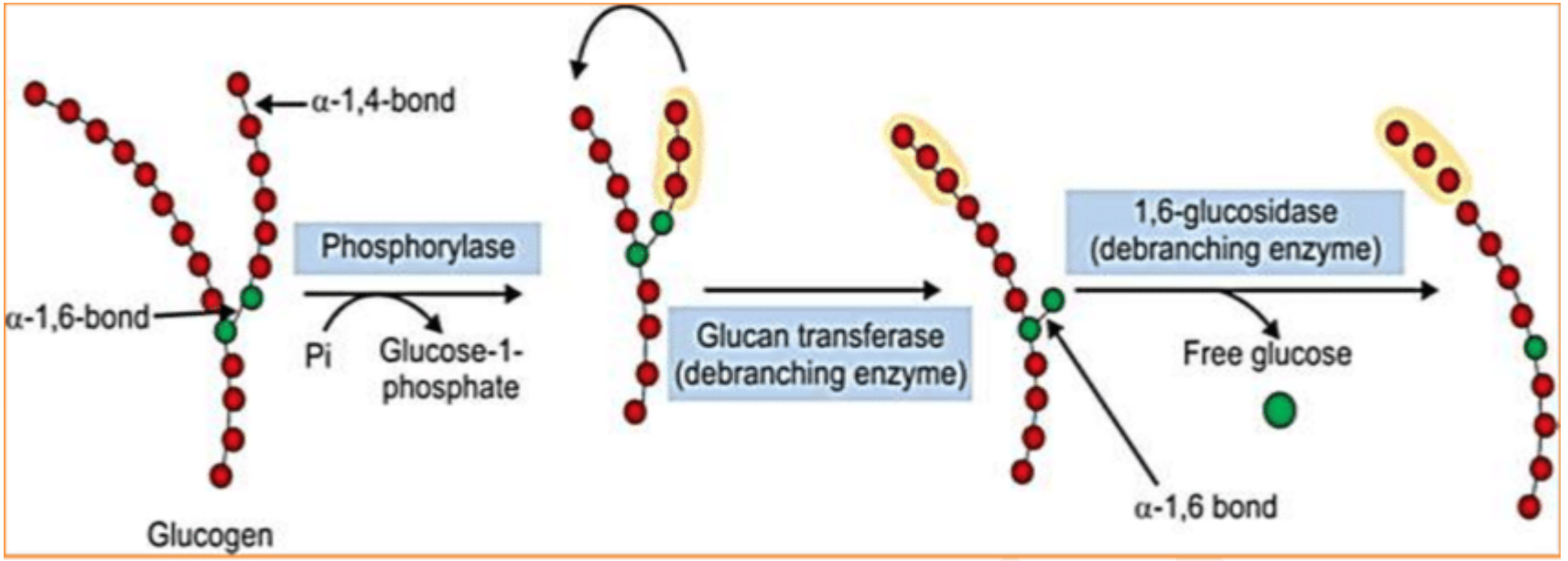
REMOVAL OF BRANCHES:

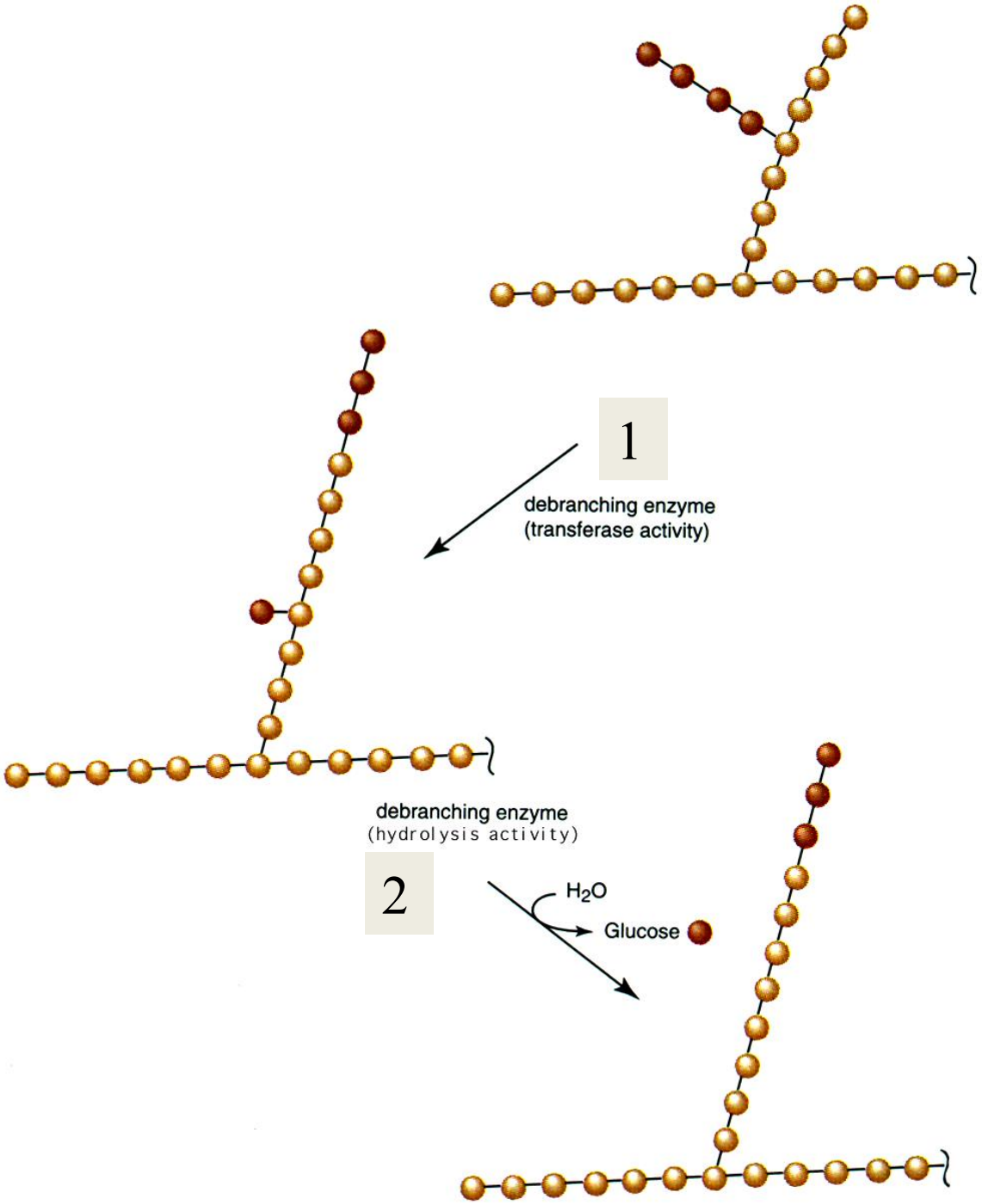
- NEXT it transfers them to the non reducing end of another chain , lengthening it accordingly.
- THUS alpha 1-4 bond is broken and alpha 1-4 bond is made, and the enzyme functions as 4:4 transferase.



REMOVAL OF BRANCHES:

- The remaining glucose residue attached in an alpha 1-6 linkage is hydrolytically removed by amylo alpha 1-6 glucosidase activity , releasing free glucose.
- The glycosyl chain is now available again for degradation by glycogen phosphorylase until four glycosyl units in the next branch are reached.





1. α-1,4->1,4 Glucosyl transferase

transfers three residues to another chain

2. Amylo α-1->6 Glucosidase

hydrolytic activity releases Glc

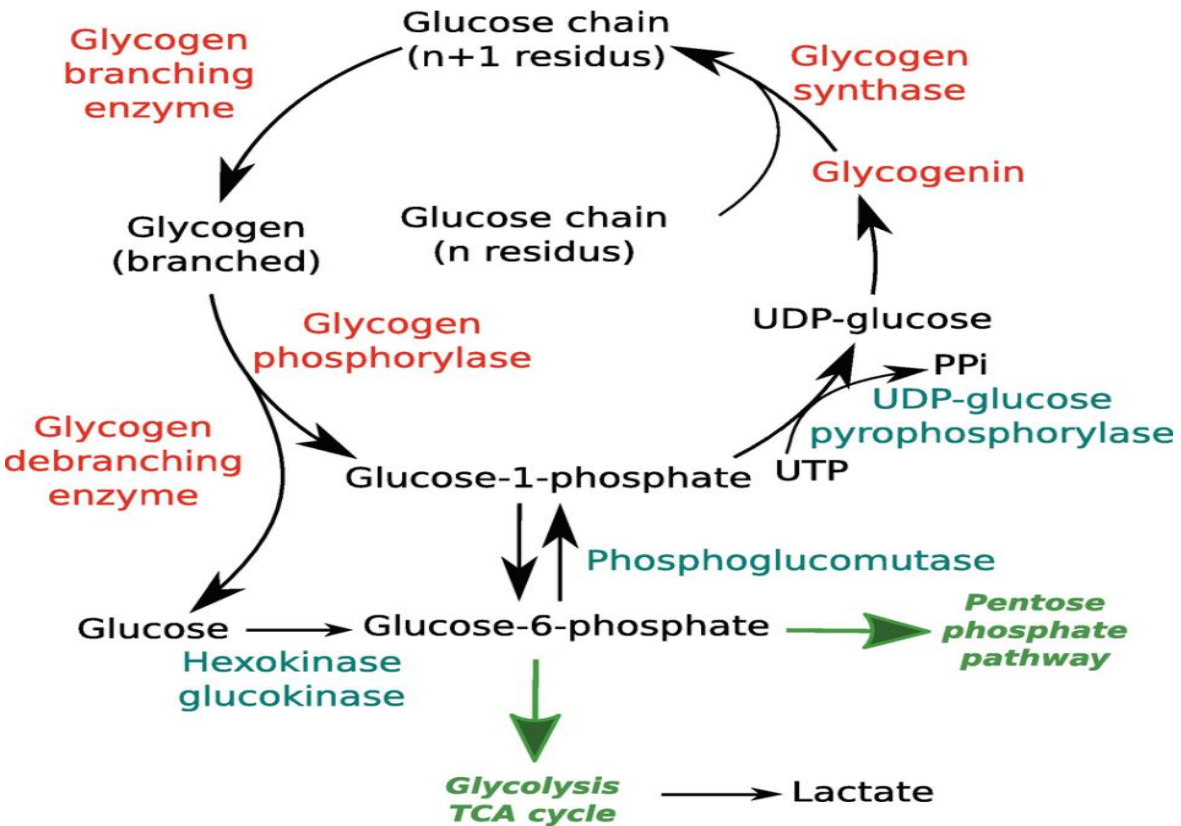
Major Final Product

Glc-1-P

In muscle… immediate energy source

Phosphoglucomutase

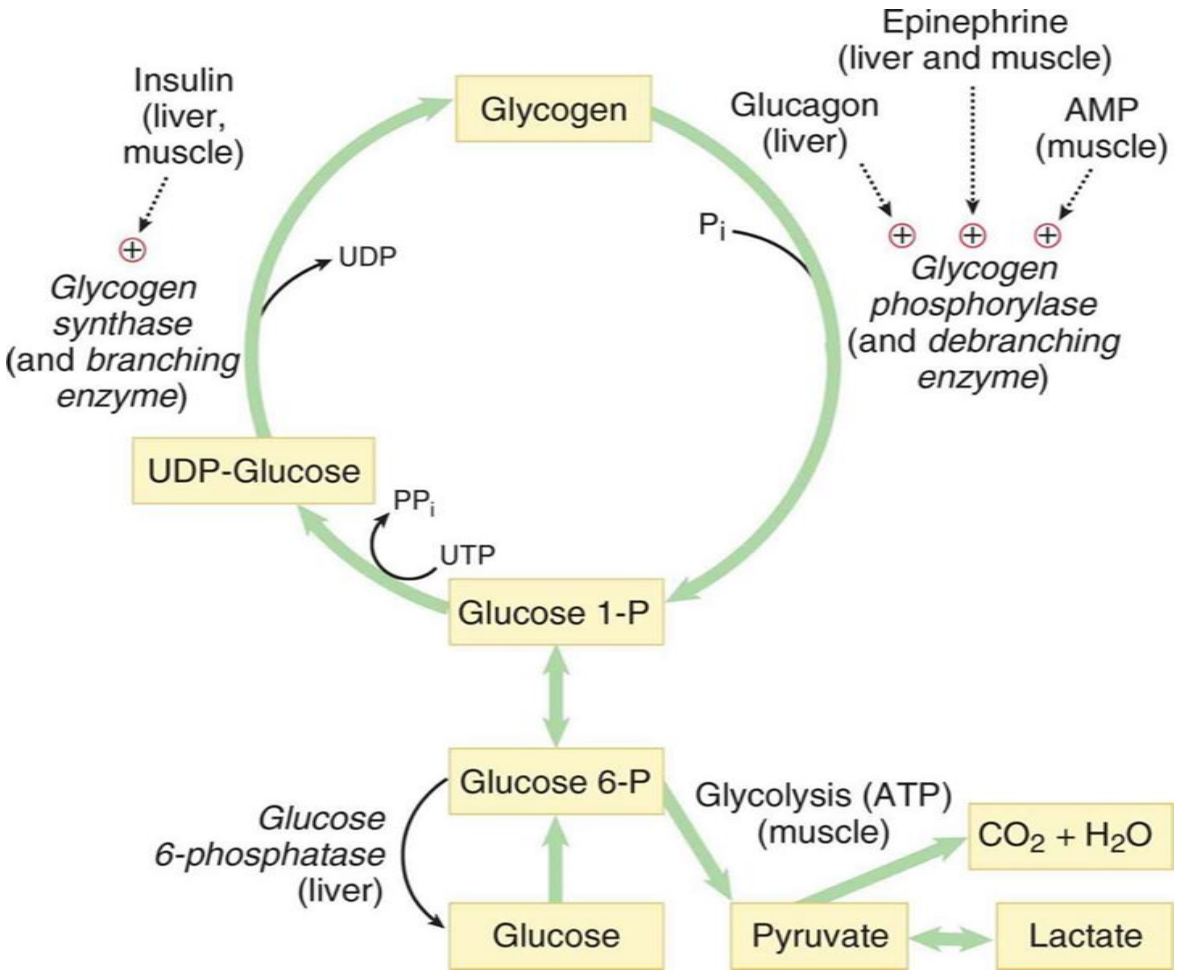
Glc-1-P <----------> Glc-6-P ------> Glycolysis



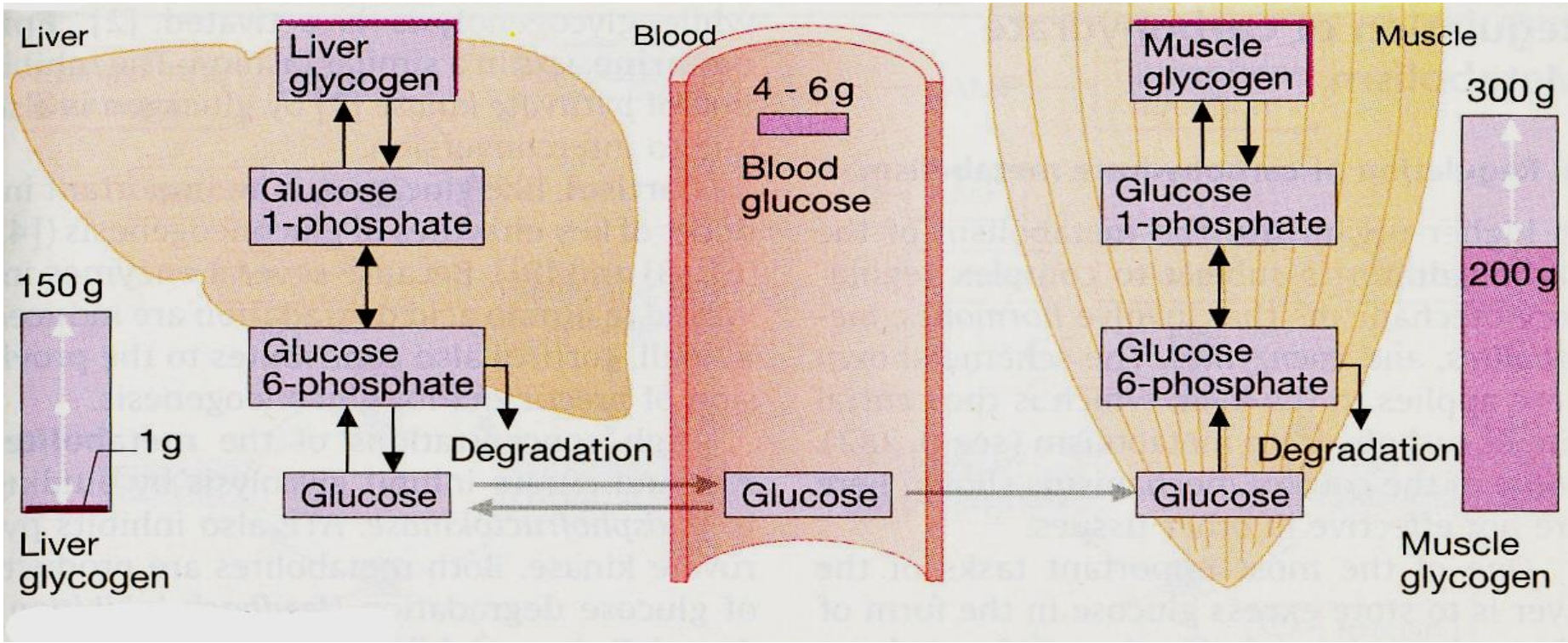
In liver……provide Glc to peripheral tissues

Phosphoglucomutase **Glucose-6-Phosphatase**

Glc-1-P ----------> Glc-6-P -----> Glucose



The role of glycogen in muscles and liver:



Decrease in glucose in the blood

→ glycogen degradation

→ release of glucose to the blood

Glucose 6-phosphatase (only in liver)

High ATP demand

→ glycogen degradation

→ anaerobic glycolysis

Regulation

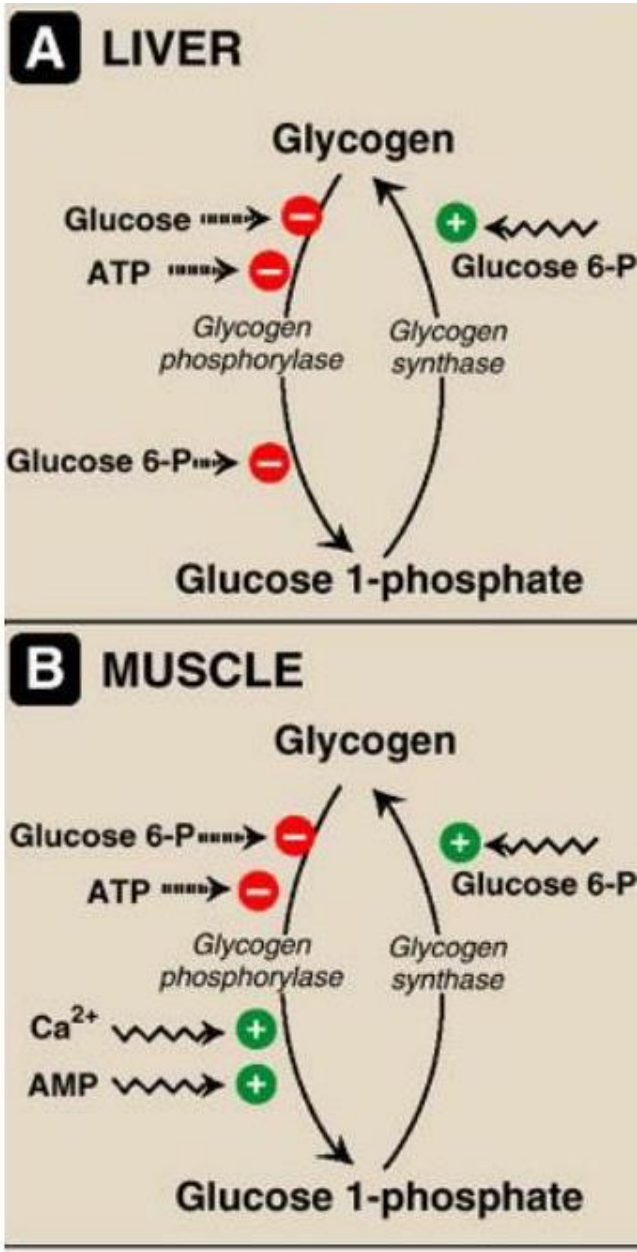
Glycogen phosphorylaseis key regulatory enzyme

regulated by

1) Allosteric regulation
2) Hormonal regulation
3) Influence of calcium

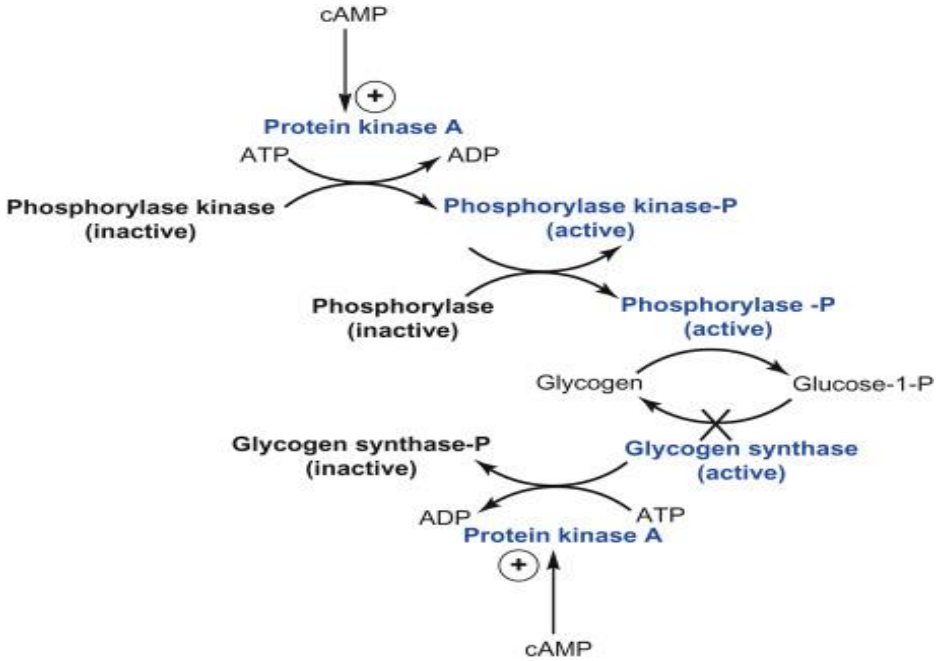
Allosteric regulation

- In well fed state Glucose -6-phosphate availability is high which allosterically activates Glycogen synthase.
- In contrast Glycogen phosphorylase is allosterically inhibited by glucose-6-phosphate & ATP.
- In liver free glucose is allosteric inhibitor of glycogen phosphorylase.

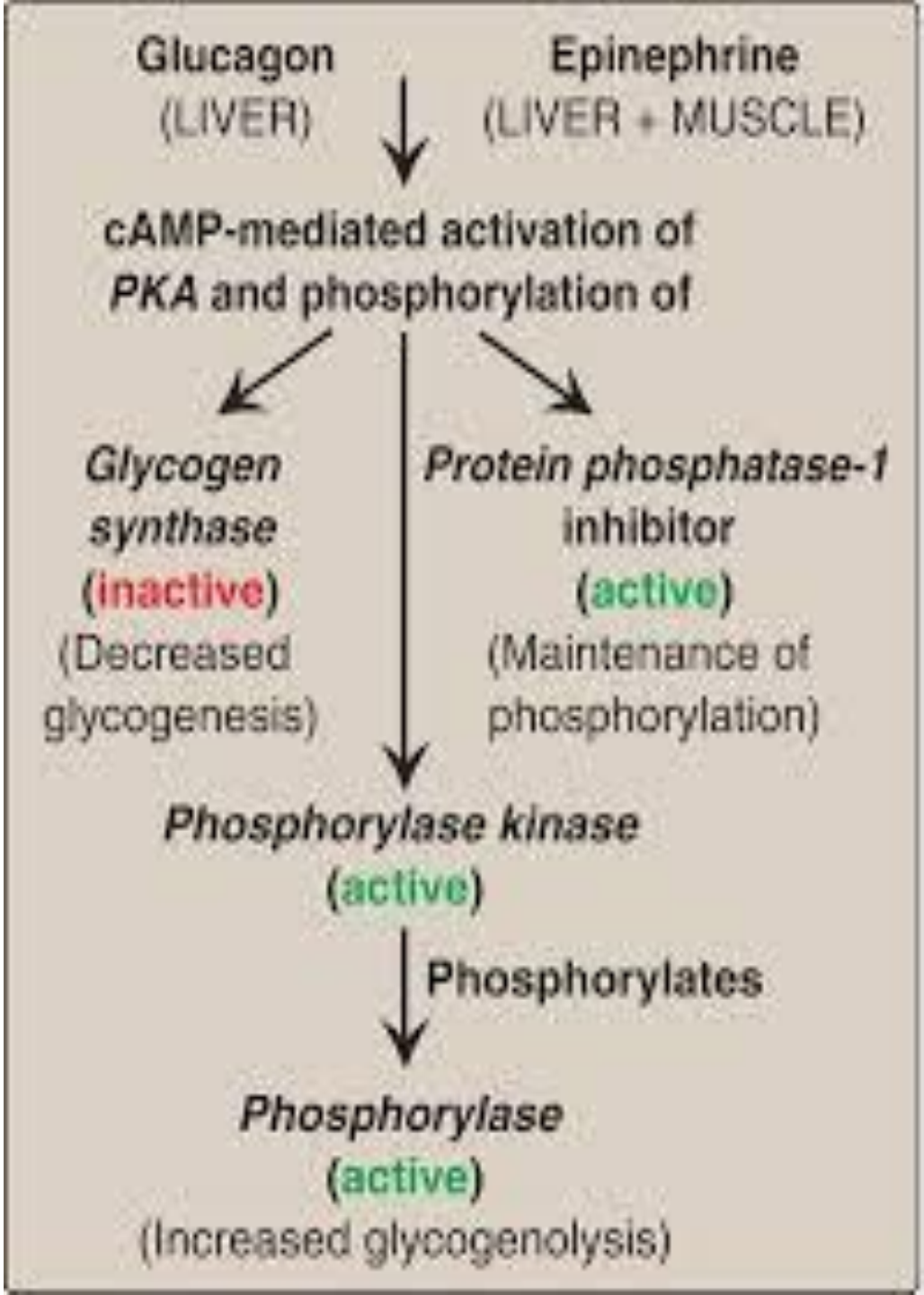


Hormonal regulation

- Activation of phosphorylase kinase enzyme is brought about by activated protein kinase(activated through cAMP) .
- Activated phosphorylase kinase eventually activates inactive glycogen phosphorylase ‘b’ to its active form,which stimulates the breakdown of glycogen.

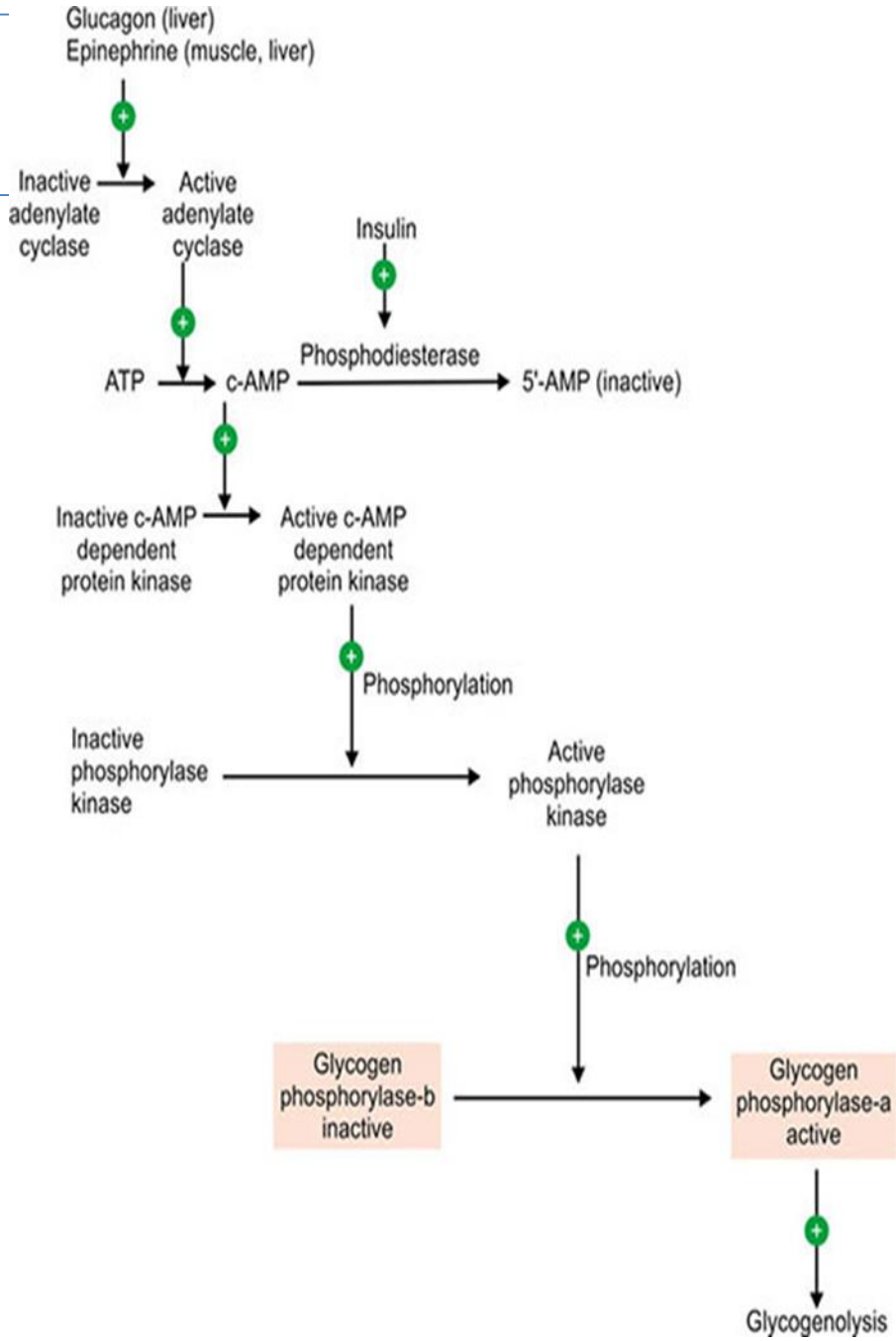


- Epinephrine (in liver & muscles) and Glucagon (in liver) stimulates glycogen breakdown & inhibits glycogen synthesis.

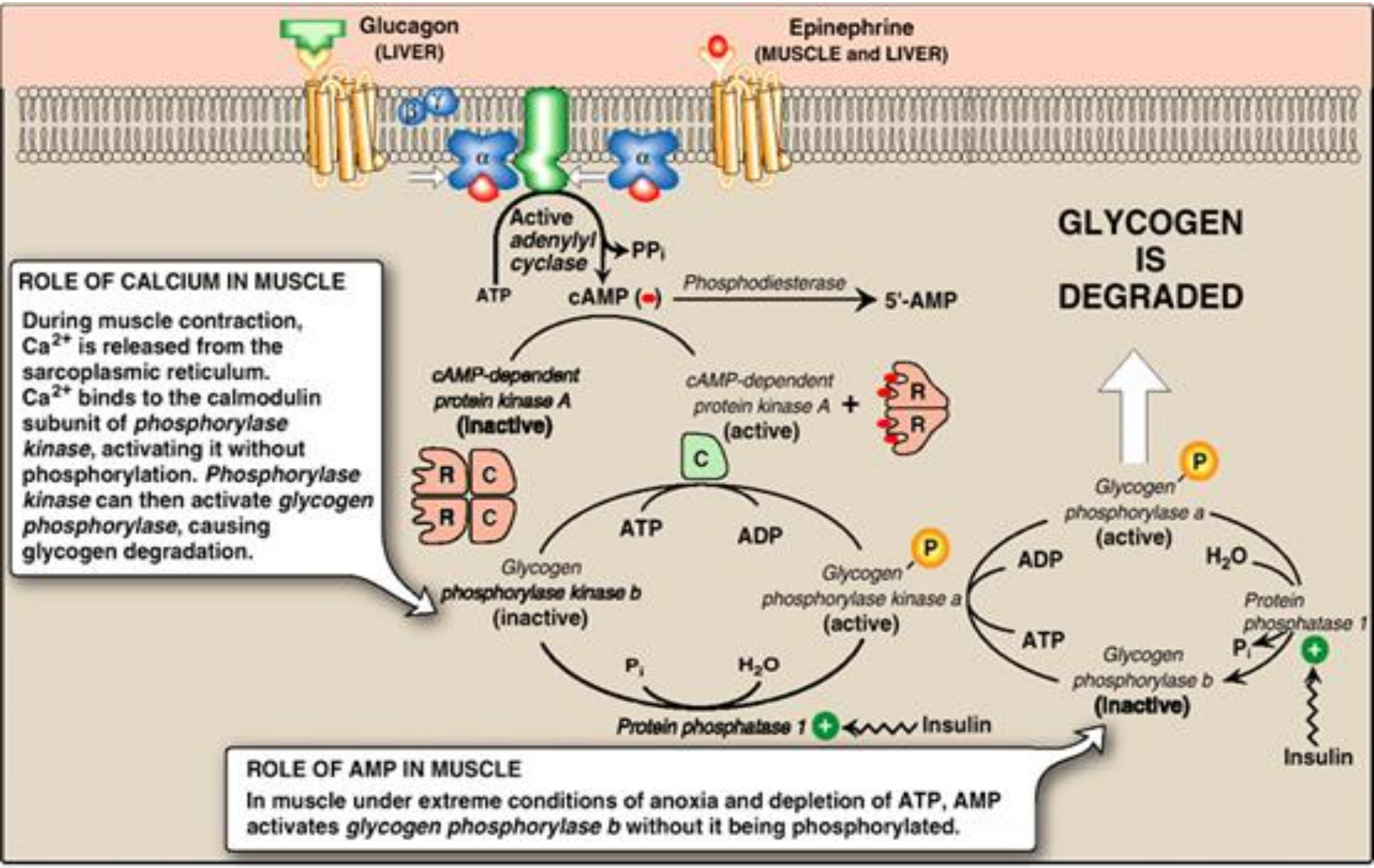


Hormonal regulation

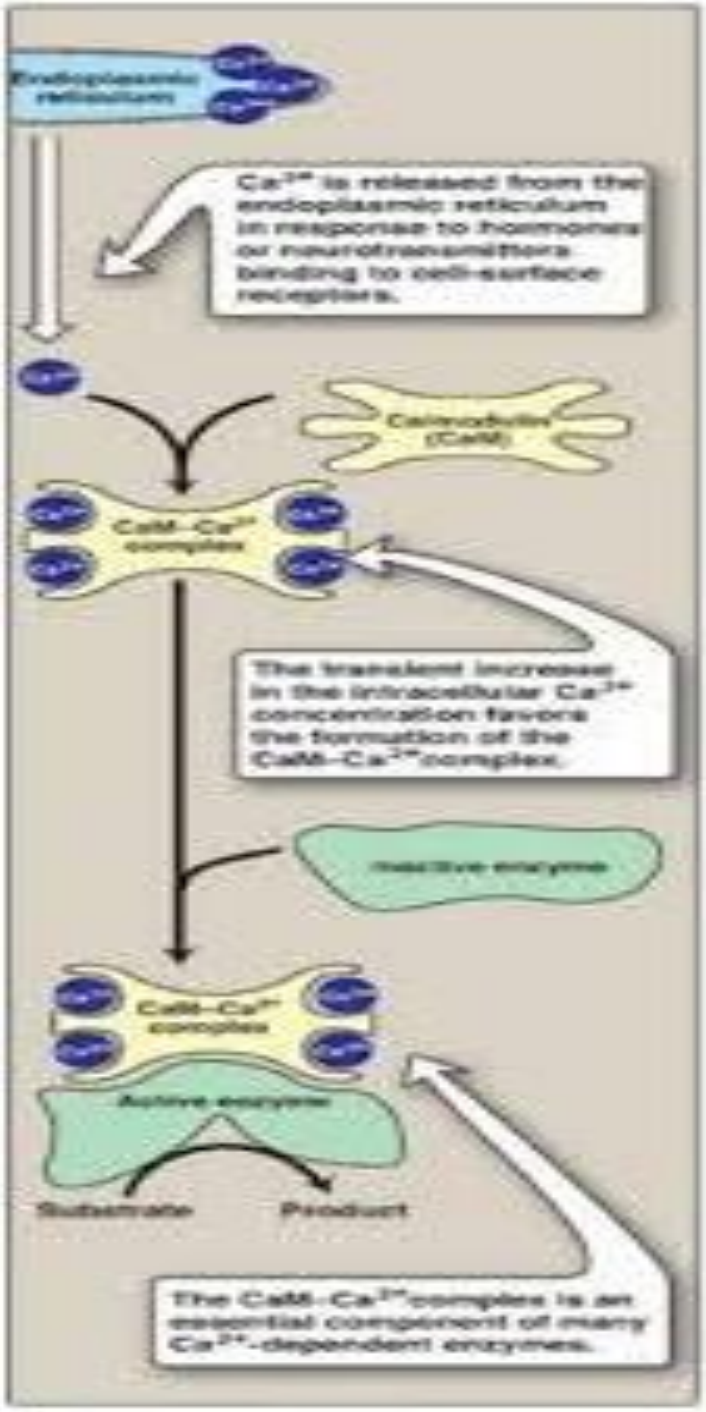
- Catecholamines cause breakdown of liver & muscle glycogen through β-adrenergic receptors.
- Glucagon breakdowns only liver glycogen as β-adrenergic receptors for glucagon are not present on muscles.



Role of calcium



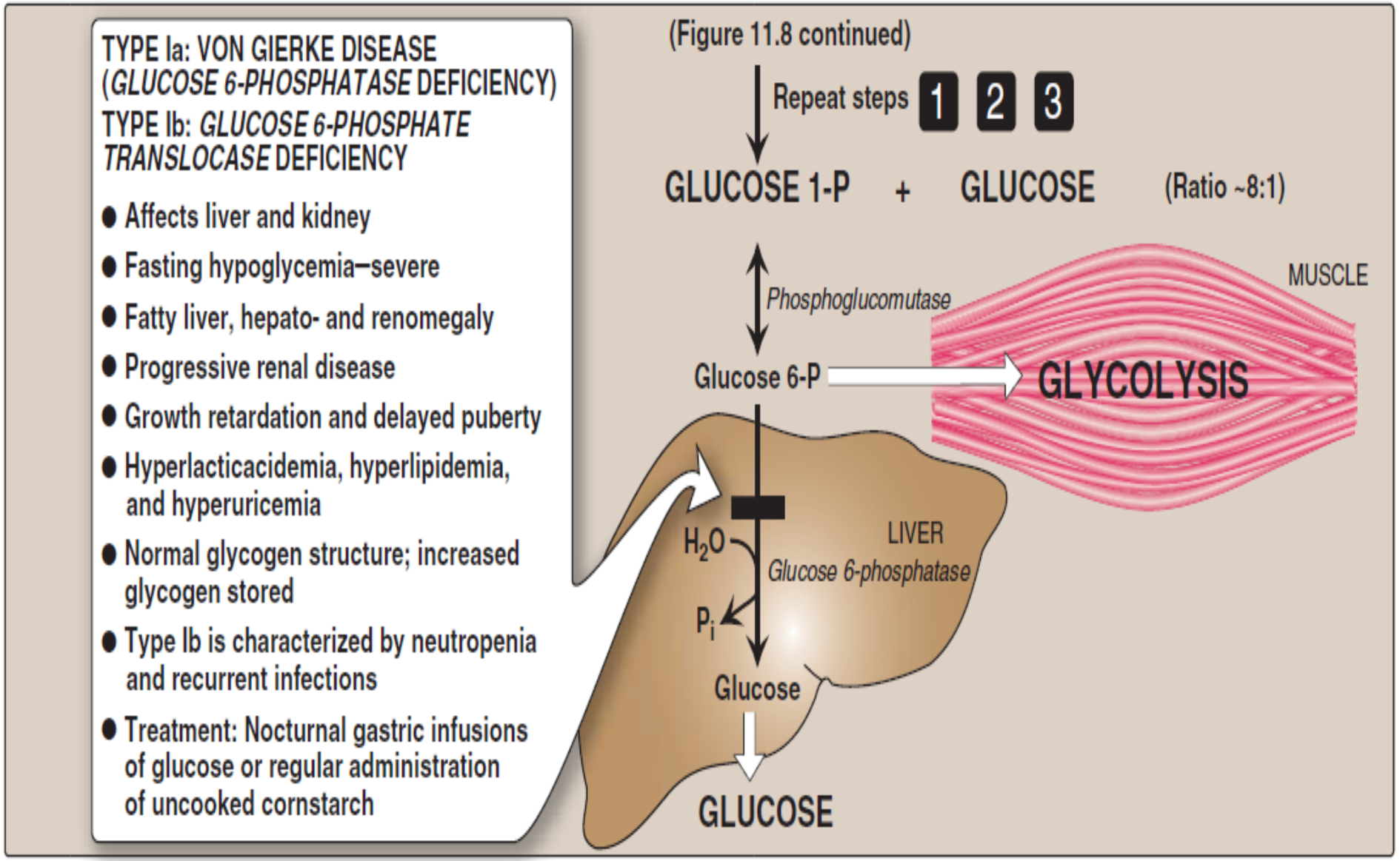
Calmodulin are calcium modulating proteins and directly activates phosphorylase kinase without involvement of cAMP.



Regulation of liver and muscle glycogen metabolism:

State	Regulators	Response
Liver		
Fasting	Glucagon ↑, Insulin ↓ cAMP ↑	Glycogen degradation ↑ Glycogen synthesis ↓
Carbohydrate meal	Glu ↑, Glucagon ↓, Insulin ↑ cAMP ↓	Glycogen degradation ↓ Glycogen synthesis ↑
Exercise and stress	Adrenalin ↑ cAMP ↑, Ca^{2+}-calmodulin ↑	Glycogen degradation ↑ Glycogen synthesis ↓
Muscle		
Fasting (rest)	Insulin ↓	Glycogen synthesis ↓ Glucose transport ↓
Carbohydrate meal (rest)	Insulin ↑	Glycogen synthesis ↑ Glucose transport ↑
Exercise	Epinephrine ↑ AMP ↑, Ca^{2+}-calmodulin ↑, cAMP ↑	Glycogen synthesis ↓ Glycogen degradation ↑ Glycolysis ↑

GLYCOGEN STORAGE DISEASES



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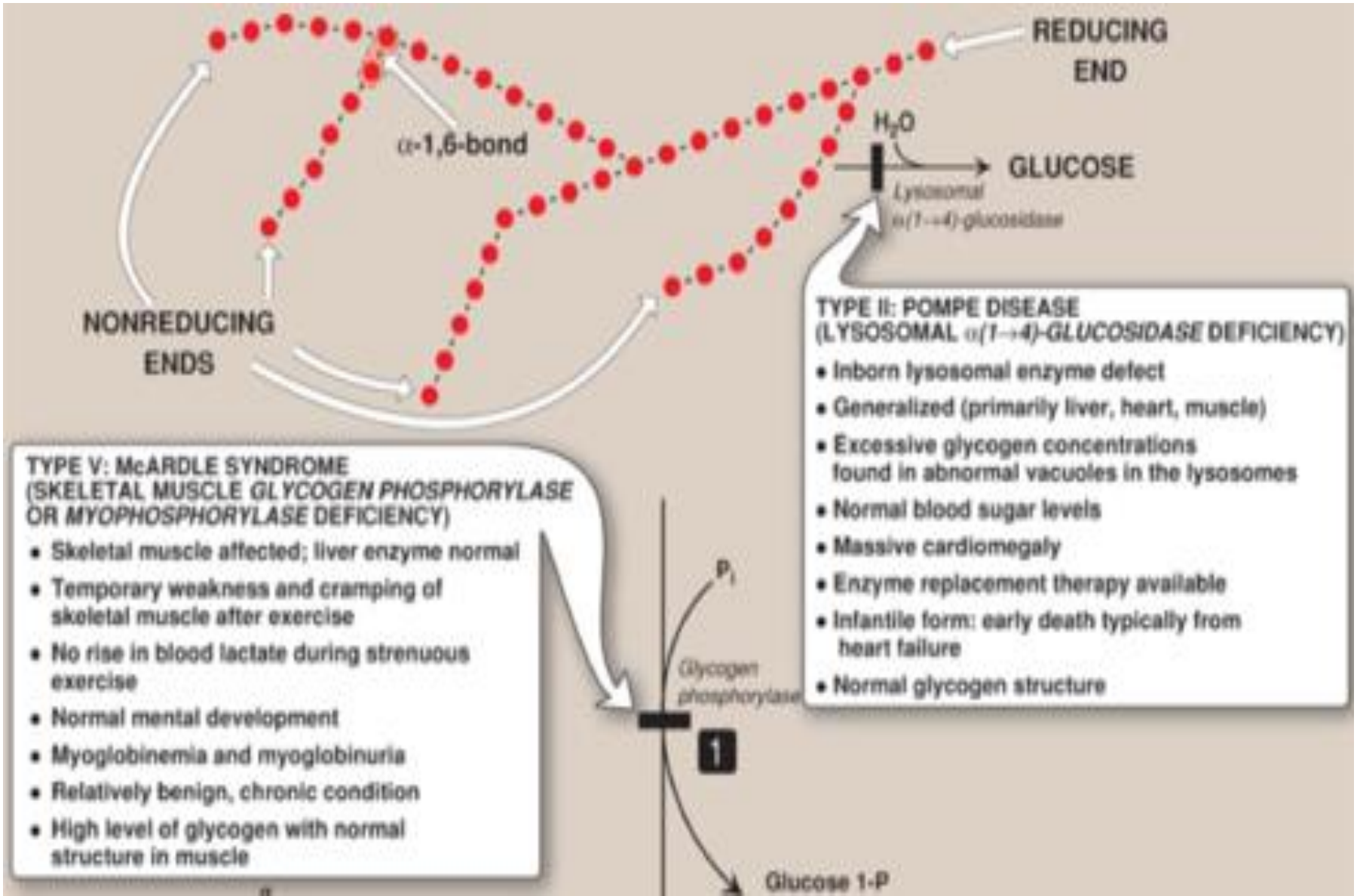
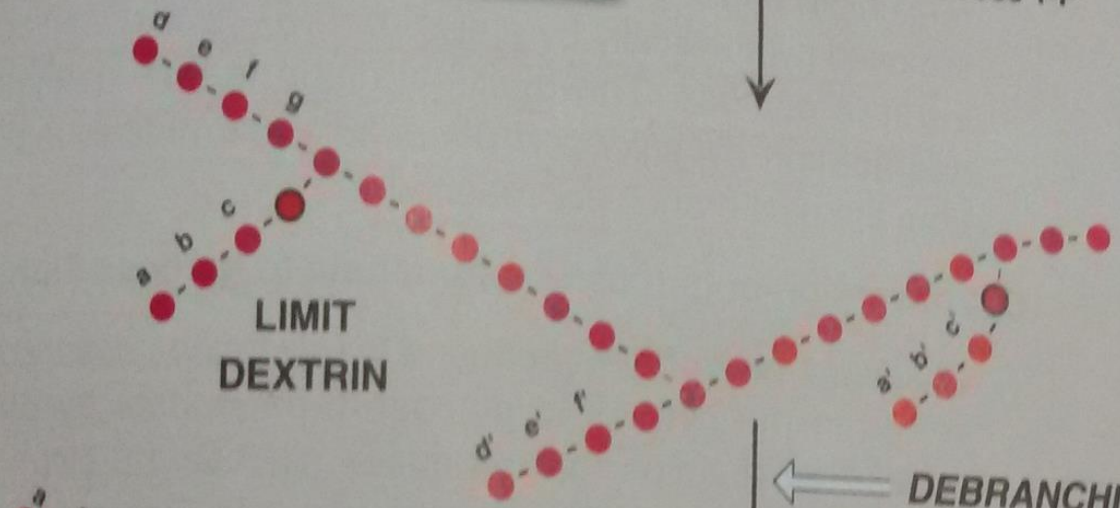


- Deficiency of the liver isozyme causes Type VI: Hers disease with mild fasting hypoglycemia.

Glucose 1-P

TYPE III: CORI DISEASE
(*4:4 TRANSFERASE* and/or *1:6 GLUCOSIDASE* DEFICIENCY)

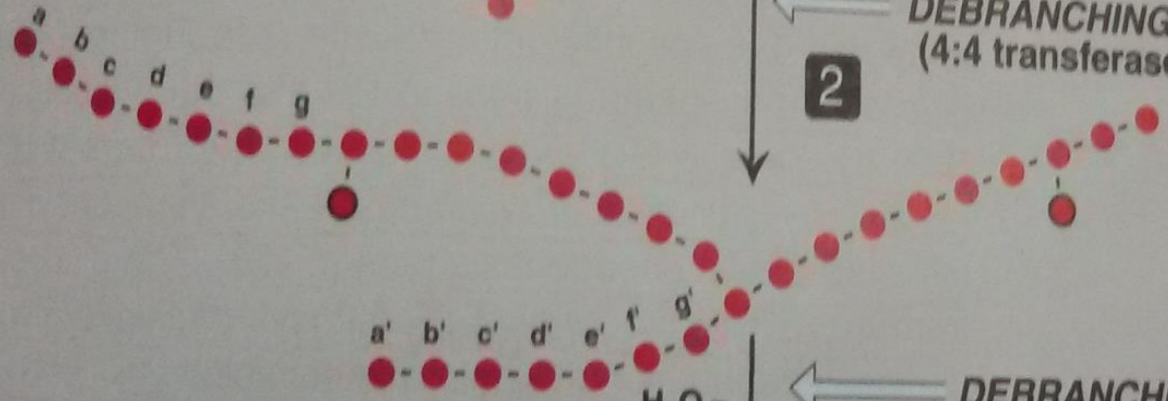
- Fasting hypoglycemia
- Glycogen has abnormal structure with four or one glucosyl residues at branch points



LIMIT DEXTRIN

DEBRANCHING ENZYME
(4:4 transferase activity)

2

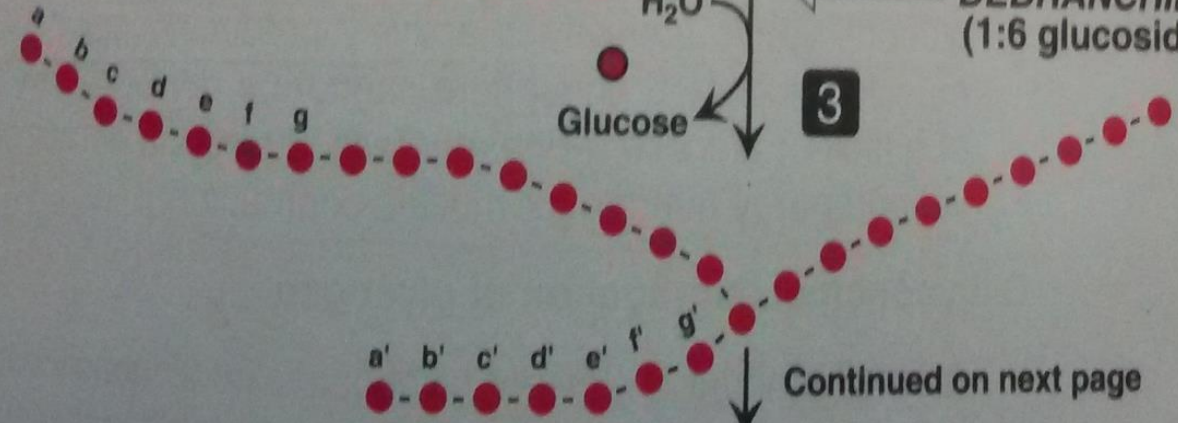


H_2O

DEBRANCHING ENZYME
(1:6 glucosidase activity)

Glucose

3



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Type	Affected tissue	Enzyme defect	Clinical features	Tissue needed for diagnosis*	Outcome
1 (Von Gierke's disease)	Liver, intestine, kidney	Glucose-6-phosphatase	Hepatomegaly, hypoglycaemia, stunted growth, obesity, hypotonia	Liver	If patients survive initial hypoglycaemia, prognosis is good; hyperuricaemia is a late complication
2 (Pompe's disease)	Liver, muscle, heart	Lysosomal α-glucosidase	Heart failure, cardiomyopathy	Leukocytes, liver, muscle	Death in first 6 months; juvenile and adult variants seen
3 (Forbes' disease)	Liver, muscle (abnormal glycogen structure)	Amylo-1, 6-glucosidase	Like Type I	Leukocytes, liver, muscle	Good prognosis
4 (Andersen disease)	Liver (abnormal glycogen structure)	1,4-α-glucan branching enzyme	Failure to thrive, hepatomegaly, cirrhosis and its complications	Leukocytosis, liver, muscle	Death in first 3 years

Disease	Deficient Enzyme	Organ Affected	Glycogen Structure	Clinical Features
Type V Mc Ardle's	Glycogen phosphorylase	Muscle	Normal (increased amount)	Muscle cramping, fatigue, myalgia and myoglobinuria with strenuous exercise
Type VI Her's	Glycogen phosphorylase	Liver	Normal (increased amount)	Fasting hypoglycemia, ketosis, hepatomegaly, hyperlipidemia (less severe than Von Gierke's)

References

- Chatterjea
- Lippincott’s


Thank
You