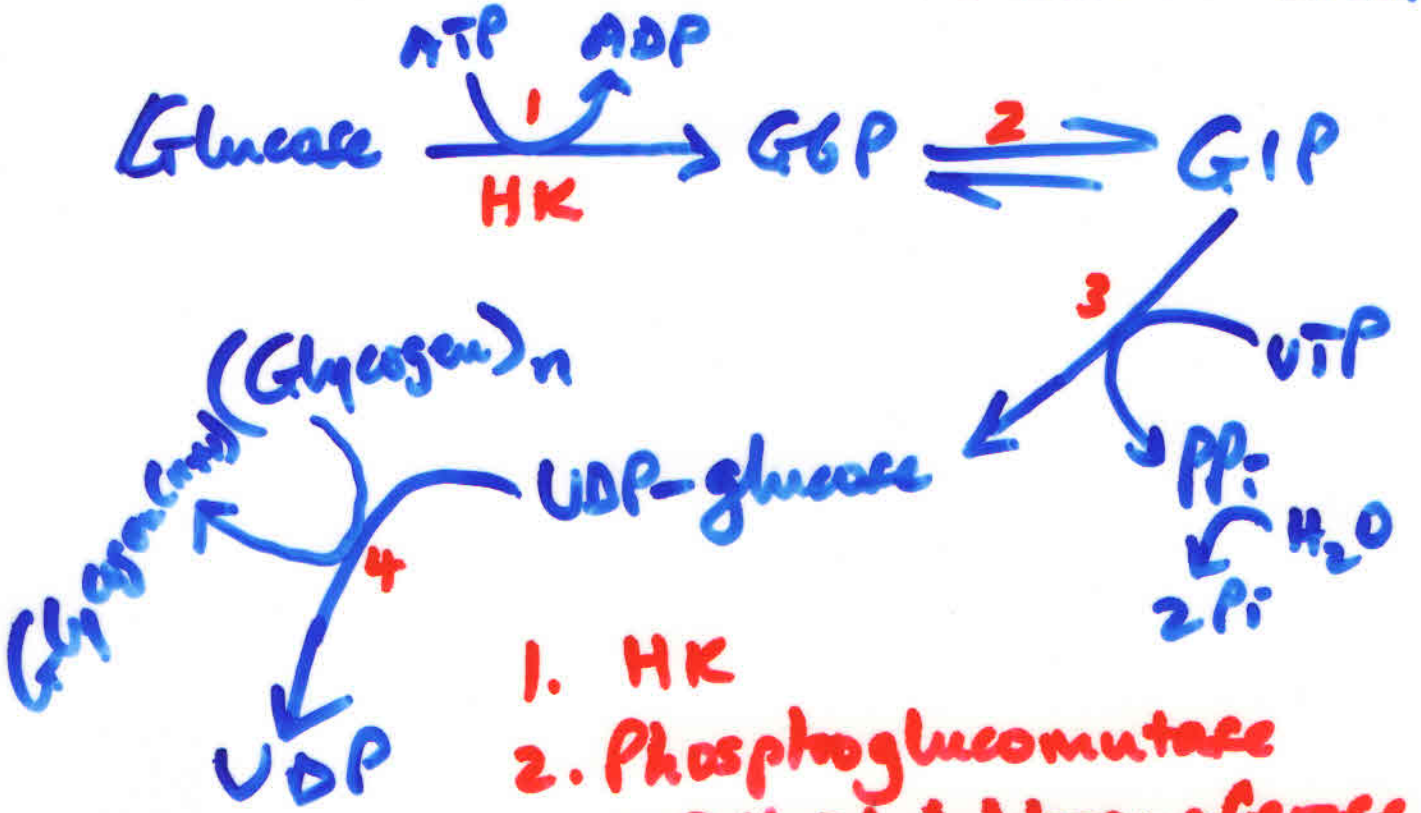
GLYCOGEN METABOLISM

1. GLYCOGEN SYNTHESIS = GLYCOGENESIS

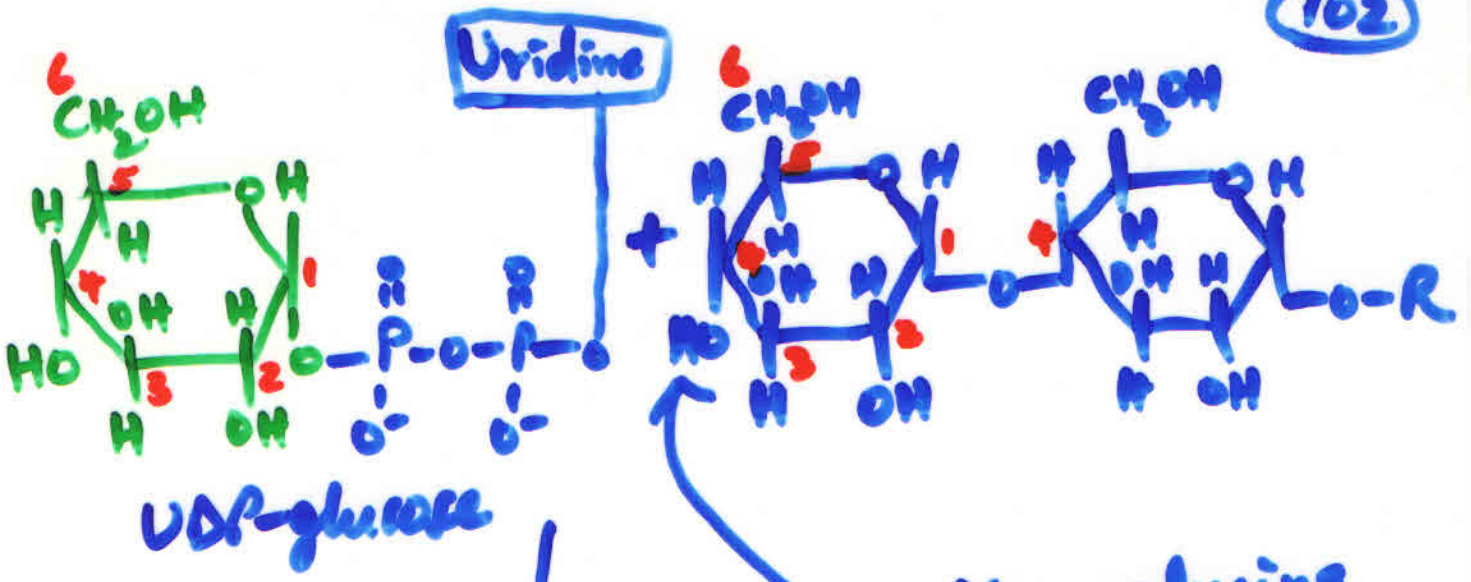
Occur in all tissues (cytosol) but very active in liver and skeletal muscles.

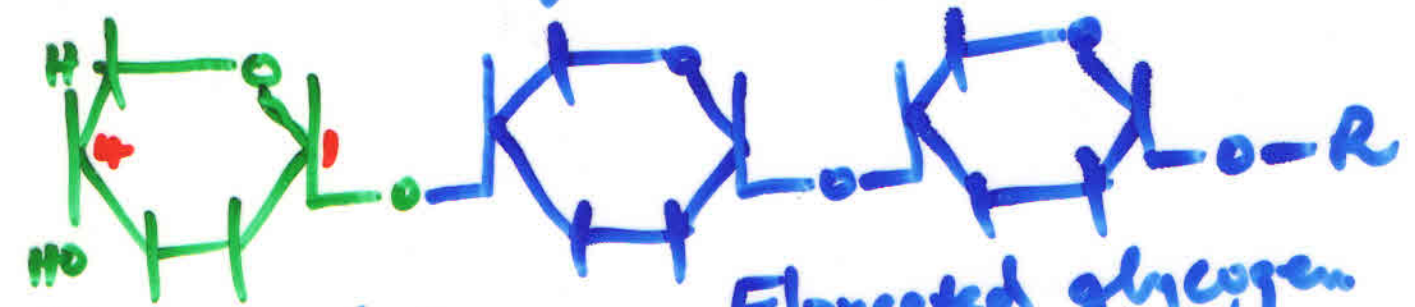


1. HK
2. Phosphoglucomutase
3. G1P Uridylyltransferase
4. Glycogen synthase (GS)

UDP-Glucose

1. It is an intermediate in the conversion of Gal to Glc.
2. It serves as a donor of glucose units in the synthesis of glycogen in the GS reaction. Promotes transfer of a glucosyl residue to a non-reducing end of glycogen.





NEW non-reducing terminus

Elongated glycogen with n+1 glucose residues

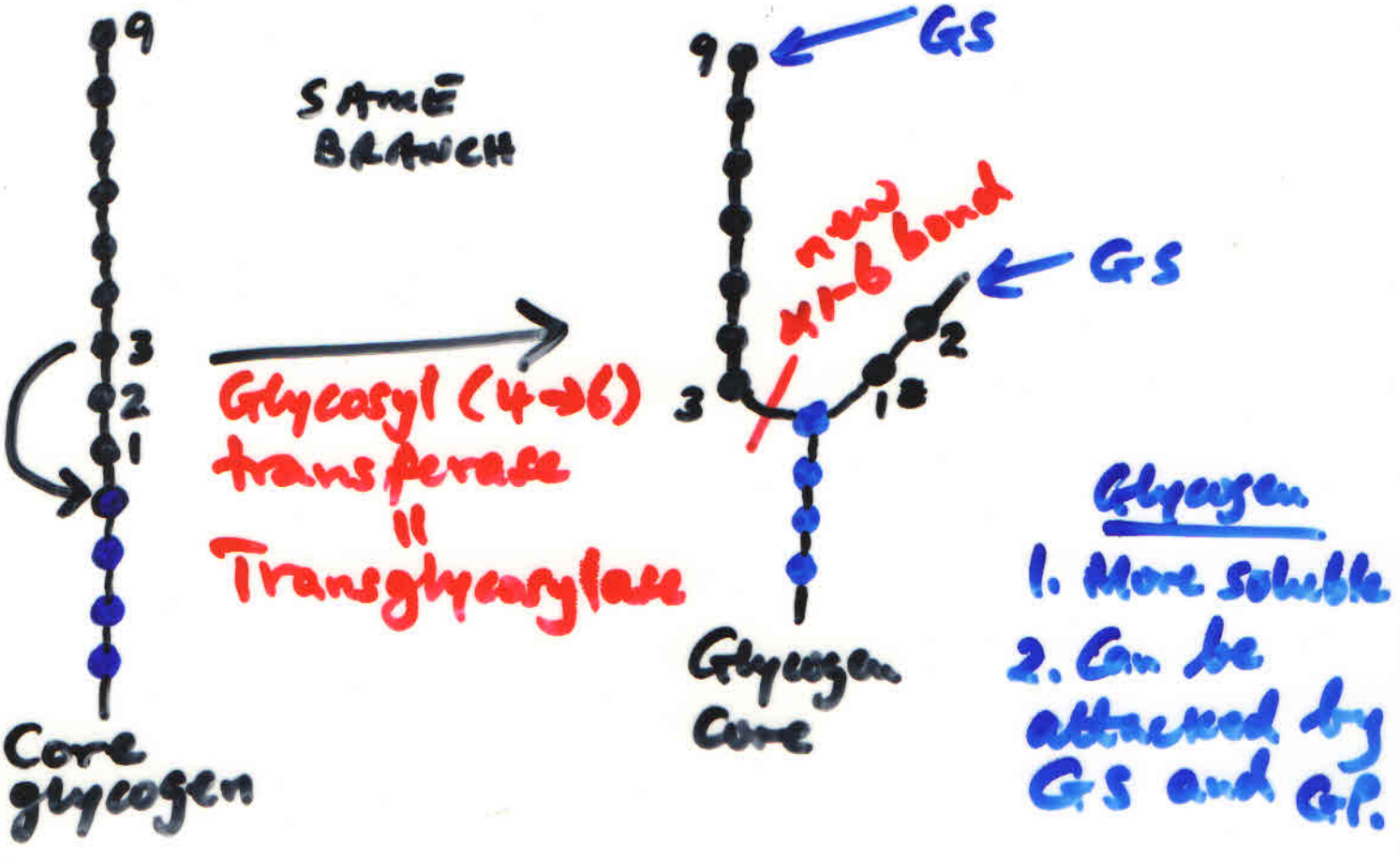
GS reaction

1. A new α1-4 glycosidic linkage is formed between carbon atom 1 of the incoming glucose and carbon atom 4 of the terminal glucose residue of a glycogen molecule (chain).

Q. What about the α1-6 linkage found in glycogen? How is it made?

GS cannot make α1-6 bonds found at the branch points of glycogen.

∴ A branching-enzyme Glycosyl (4→6) transferase catalyzes the transfer of a terminal Oligosaccharide fragment of 7 glucosyl residues from the non-reducing end of a glycogen chain to the 6-hydroxyl group of a glucose residue of the same or another glycogen chain - creating a new branch. Further glucosyl residues are then added by the GS.



Glycogen

1. More soluble
2. Can be attacked by GS and GP.

ATP cost

2 ATPs are required to store each glucose as glycogen.

1. Glucose + ATP → G6P + ADP
2. G6P ⇌ G1P
3. G1P + UTP + H_2O → UDP-glucose + 2Pi
4. UDP-glucose + $(Glycogen)_n$ → UDP + $(Glycogen)_{n+1}$
5. UDP + ATP → UTP + ADP (Regeneration of UTP)

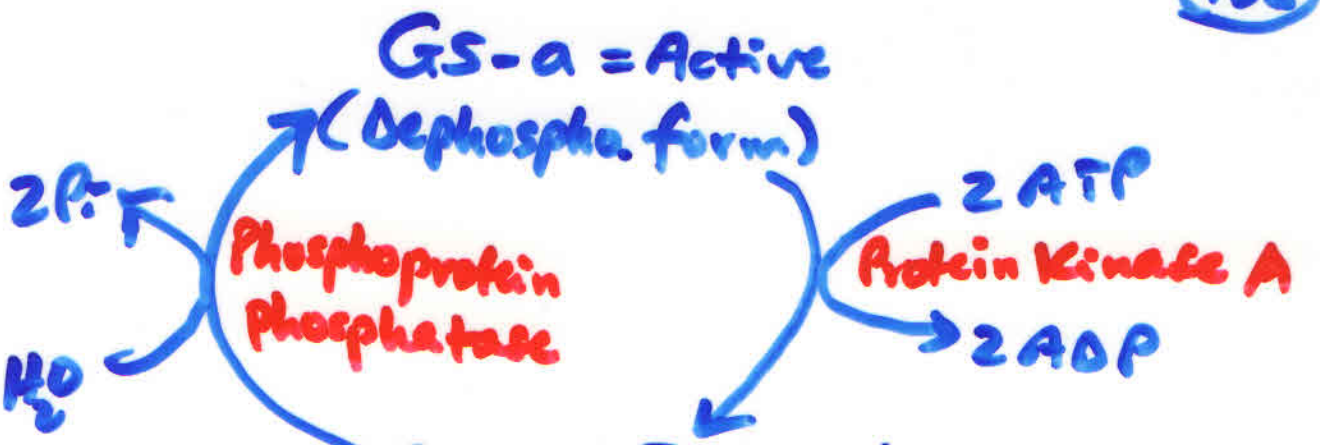
NET

$(Glycogen)_n$ + Glucose + 2ATP + H_2O → $(Glycogen)_{n+1}$ + 2ADP + 2Pi

Regulation of glycogen synthesis

1. Insulin promotes synthesis.
2. Glucagon / Epinephrine inhibits.
3. Phosphorylation of GS inhibits.
4. G6P activates.

* GS is the main enzyme — It is regulated covalently & allosterically.



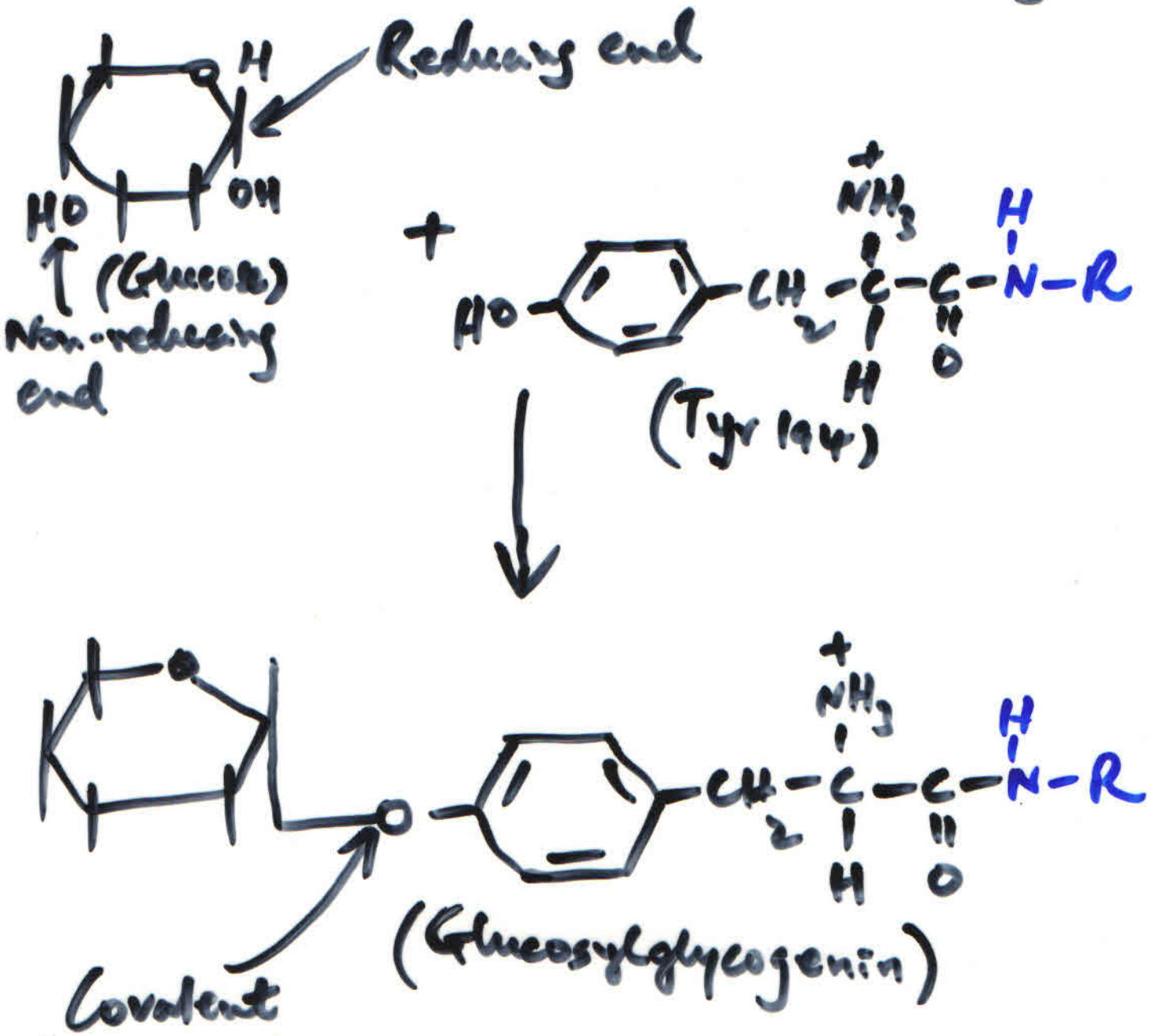
Protein Kinase – regulated by hormones
- Insulin inactivates
- Glucagon / epinephrine activates.

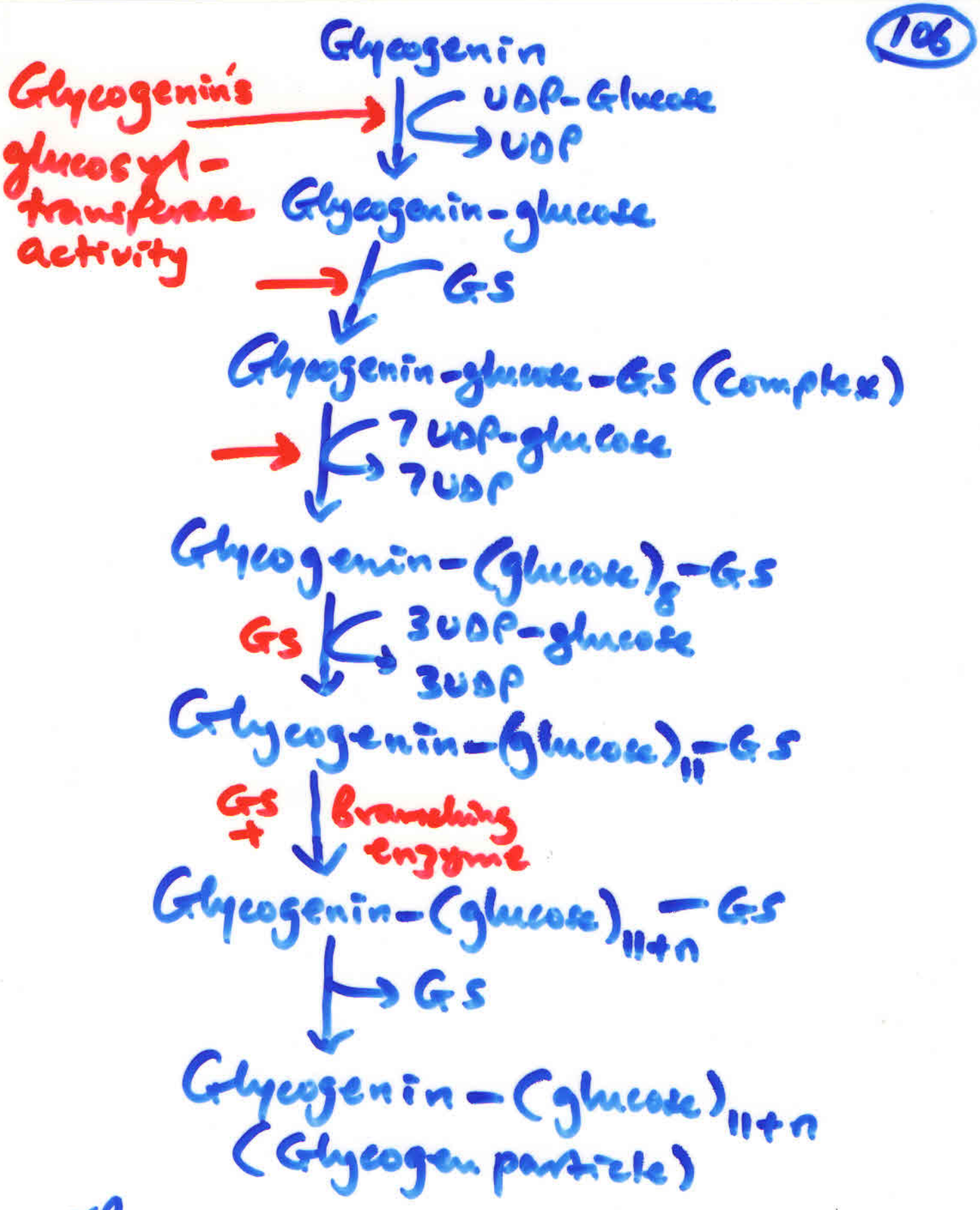
Initiation of a glycogen particle by glycogenin;

Glycogenin – a protein (37,000 mwt) with an essential Tyrosine residue at position 194.
- It acts as an original primer in glycogen synthesis.
- It also has a catalytic function = Glucosyl-transferase.
- It remains buried with the glycogen particle attached to the single reducing end of the glycogen core.

Glycogenin = An enzyme!

- A homodimer 37 kDa.
- Has an essential amino acid residue (Tyr 194).
- Has an intrinsic glucosyltransferase activity - promotes autocatalysis.





NB

GS requires as a primer an α1-4 polyglucose chain or branch having at least 8 glucose residues.

2. GLYCOGEN BREAKDOWN / GLYCOGENOLYSIS

- Most active in Liver and skeletal muscle.
- Comes into play when there is CHO lack- resulting in the falling of glucose levels.
- Under hormonal regulation.
  - Insulin inhibits.
  - Glucagon / Epinephrine promotes.
  - Phosphorylation of GP activates.
  - Ca^{2+} – Calmodulin activates.
- The main enzyme is Glycogen phosphorylase (GP).
- The breakdown is via an amplified cascade involving hormones and enzymes.

* Critical factor is the level of cAMP. ↑[cAMP] = glycogenolysis.

ATP $\xrightarrow{AC}$ cAMP + PPi $\xrightarrow{H_2O}$ 2Pi

Hormone → Excited receptor → G-protein – Activated A.C → ATP → cAMP (2nd messenger)

1st messenger e.g. Epinephrine / Glucagon

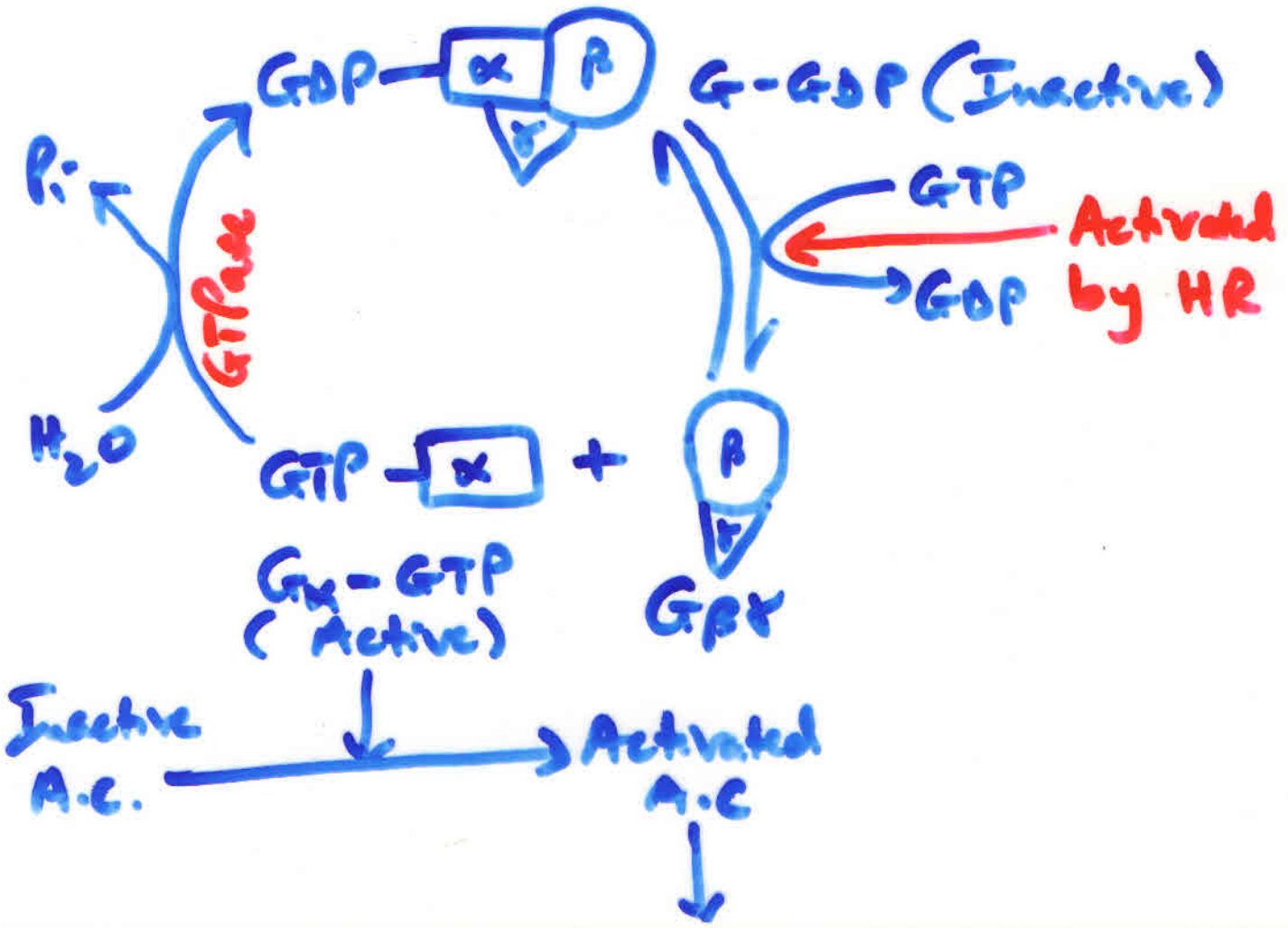
G-Protein

- It is a guanyl-nucleotide binding protein.
- It couples hormone receptors to Adenylate Cyclase (A.C).

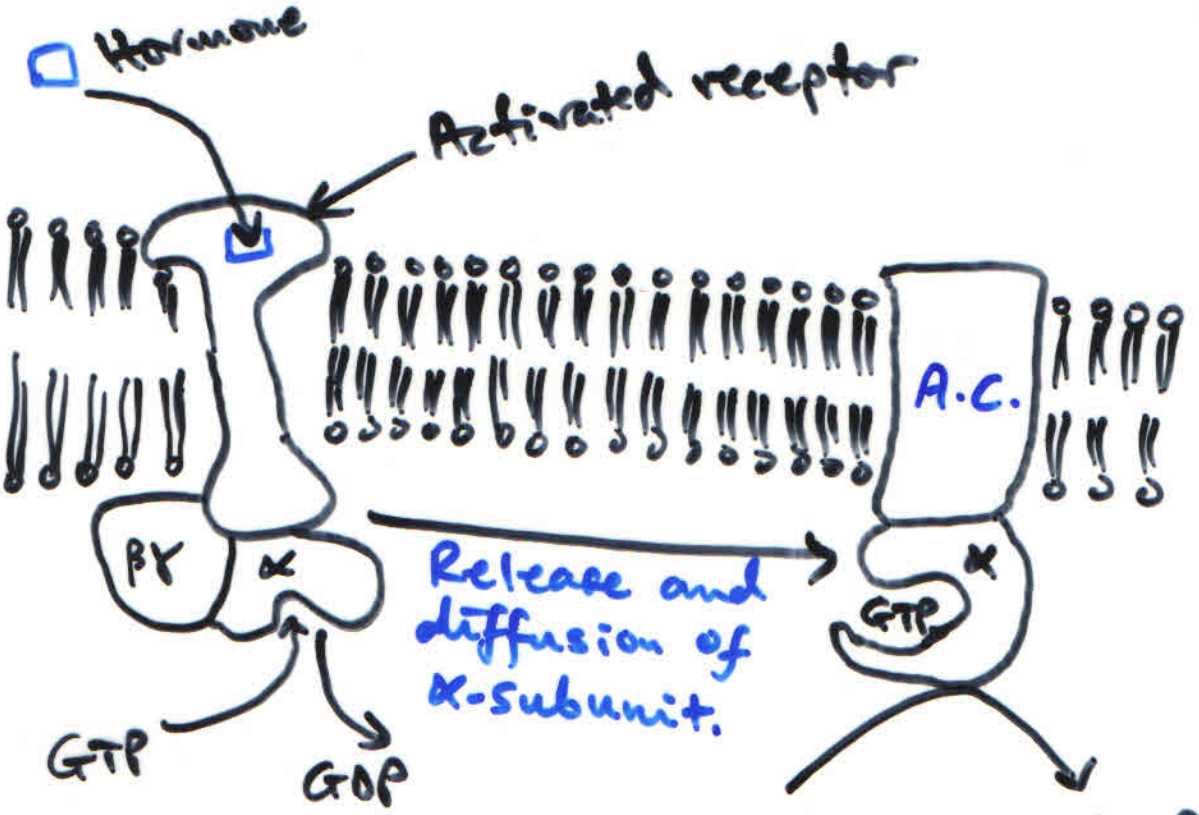
Q. How does the binding of a hormone such as epinephrine to a specific receptor lead to the activation of A.C?

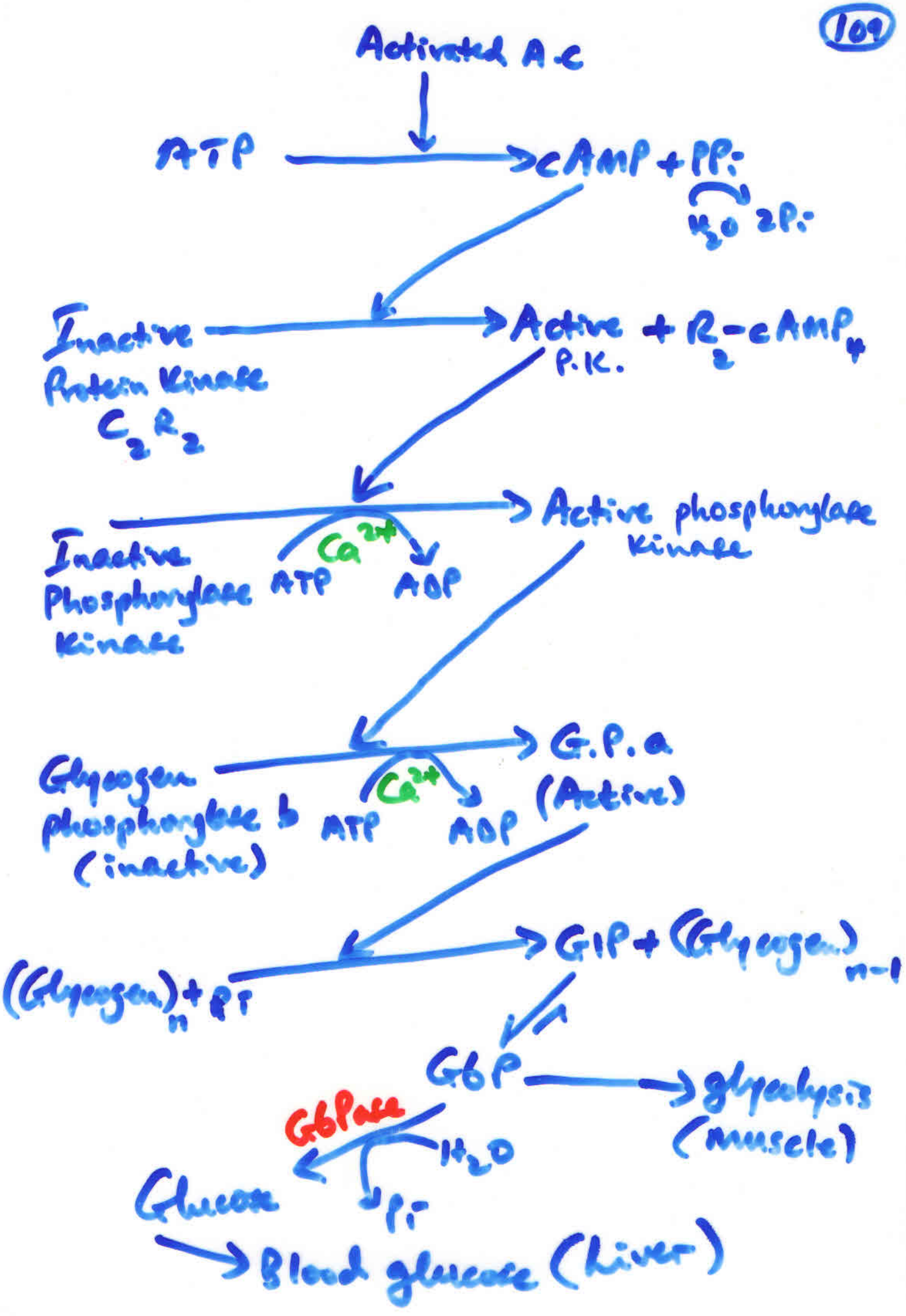
HR Complex ⟶ G-Protein ⟶ A.C.
(excited receptor)

- It is a peripheral protein located on the cytosolic side of the plasma membrane.



The activation of adenylate cyclase




Activated A.c
ATP
cAMP + PPi
H2O
2Pi
Inactive Protein Kinase
C2R2
Active P.K.
+ R2-cAMP4
Inactive Phosphorylase Kinase
ATP
Ca2+
ADP
Active phosphorylase Kinase
Glycogen phosphorylase b (inactive)
ATP
Ca2+
ADP
G.P.a (Active)
(Glycogen)n + Pi
G1P + (Glycogen)n-1
G6P
glycolysis (muscle)
G6Pase
H2O
Pi
Glucose
Blood glucose (liver)

Amplification Cascade (Liver / Muscle)

External Stimulus e.g. Danger

↓

CNS

↓

Adrenal Medulla

↓

Epinephrine

↓

Receptor on membrane

↓

G- Protein

↓

Adenylate cyclase

↓

ATP → cAMP

↓

Protein kinase

↓

Phosphorylase kinase

↓

Glycogen phosphorylase

↓

$(Glycogen)_n + P_i \rightarrow Glycogen_{(n-1)} + G1P$

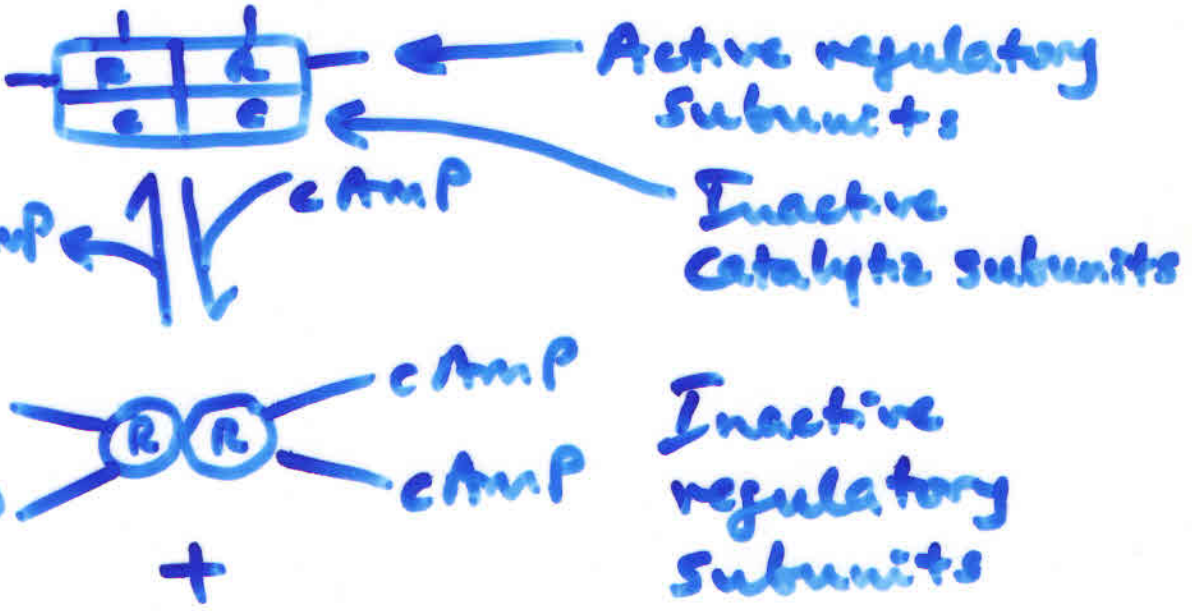
G1P ⇌ G6P

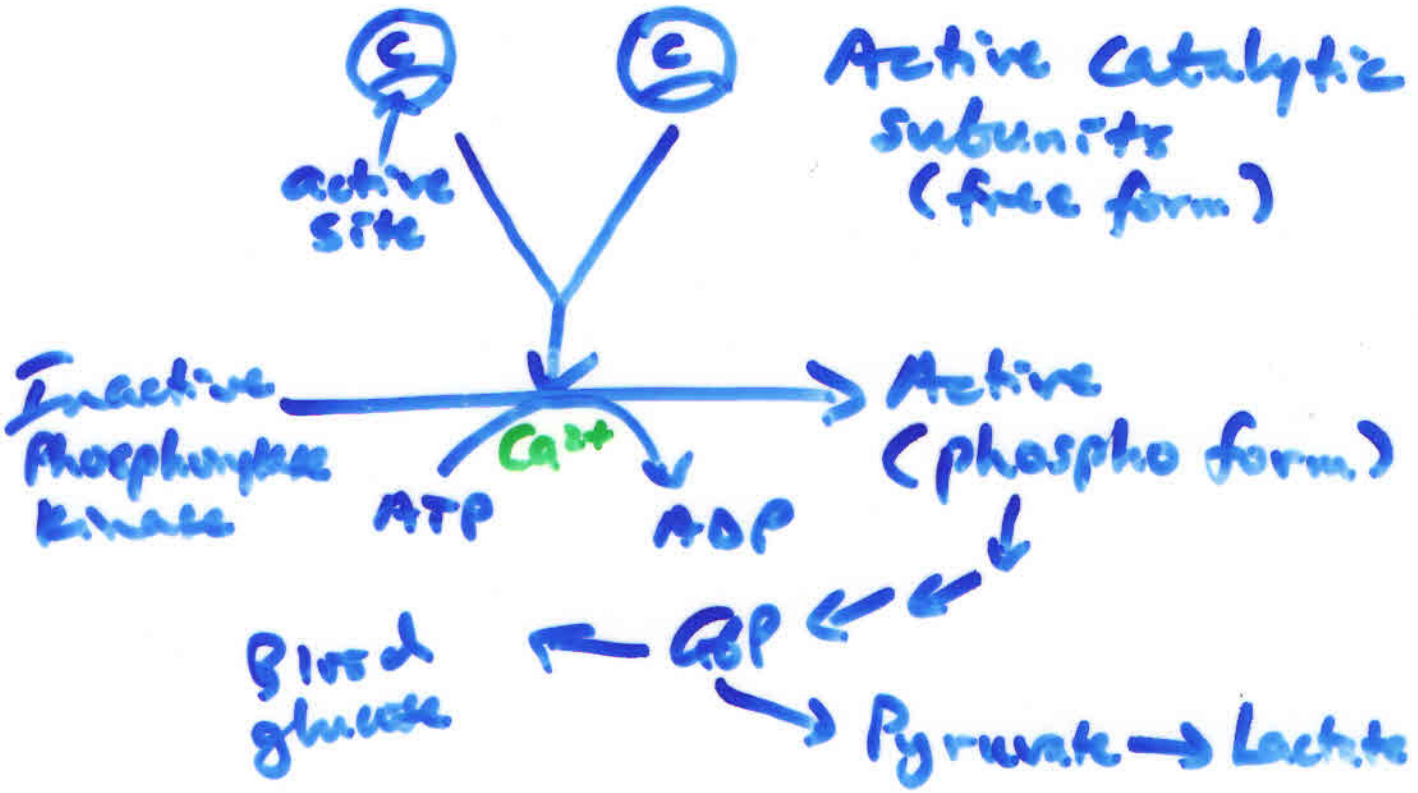
G6P → Lactate (Muscle)

G6P —(G6Pase, H_2O)→ Glucose (Blood) (Liver) + P_i

Protein kinase

- Allosteric enzyme with cAMP as its + stimulator.
- Has 4 subunits < 2C, 2R





* [cAMP] important for glycogen breakdown.

Degradation of cAMP ?

- After hormone levels fall → ↓[A.C] ↓ falls

↓[cAMP]

↓

cAMP on Protein kinase is released

The regulatory subunits of Protein Kinase combines with the Catalytic subunits → Inactive Protein kinase

- Degradation of cAMP is by the action of Phosphodiesterase.

$$cAMP + H_2O \xrightarrow[\text{Phosphodiesterase}]{Ca^{2+}\text{-Calmodulin}} AMP$$

- The enzyme is inhibited by Caffeine and Theophylline = found in coffee and tea. They prolong the activity of the hormone by decreasing the rate of breakdown of cAMP.

Caffeine = 1, 3, 7-Trimethylxanthine

Theophylline = 1, 3-Dimethylxanthine

Q. What is the role of Calmodulin ?

- Calmodulin is a Ca^{2+}-binding protein.
- Acts as a mediator in many Ca^{2+}-stimulated enzymatic reactions and membrane transport systems.

Ca^{2+}
- Muscle contraction
- Neuromuscular transmitter release.
- Endocytosis/Exocytosis
- Glycogen metabolism
- Cell motility

Calmodulin — Primary receptor of Ca^{2+}

Ca^{2+} ↓

Calmodulin – Ca^{2+}

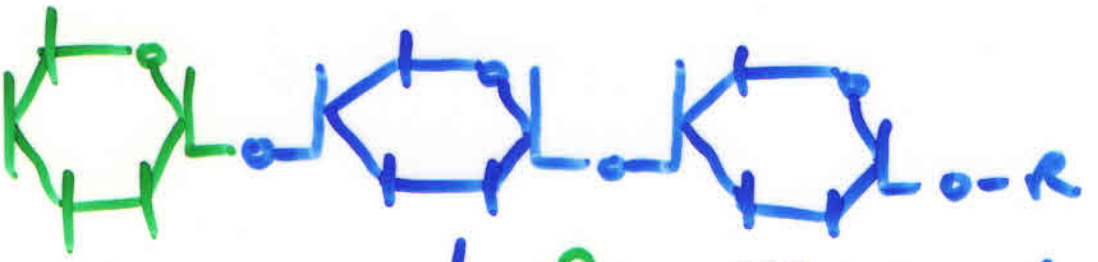
↓ Inactive Enzyme

Enzyme – Calmodulin – Ca^{2+}
(Active) e.g. Phosphorylase Kinase

Glycogen phosphorylase (G-P) is the key enzyme in glycogen breakdown.

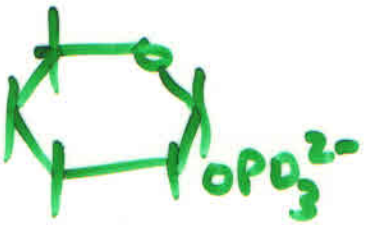
$$(Glycogen)_n + P_i \xrightarrow[PLP]{GP} (Glycogen)_{n-1} + G1P$$

- It removes the glucose residue that is on the nonreducing end by phosphorolysis = A phosphate is used to break an α1-4 glycosidic bond – releasing the terminal glucose as G1P.



GP (Repetitive reaction) | Pi PLP

Glycogen chain (Glucose)$_n$



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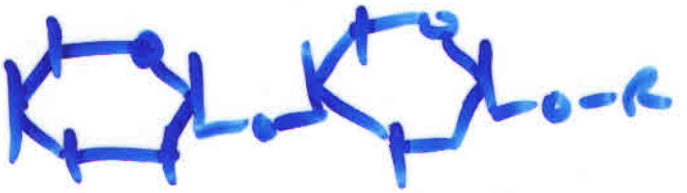


G1P

Glycogen chain shortened by one residue (Glucose)$_{n-1}$

GP is unable to act on an α1-6 bond.

A de-branching enzyme: (α1-6) glucosidase comes in. Also called Amylo-1,6-glucosidase/4-glucanotransferase.

Q. What is the reaction mechanism of the de-branching enzyme?

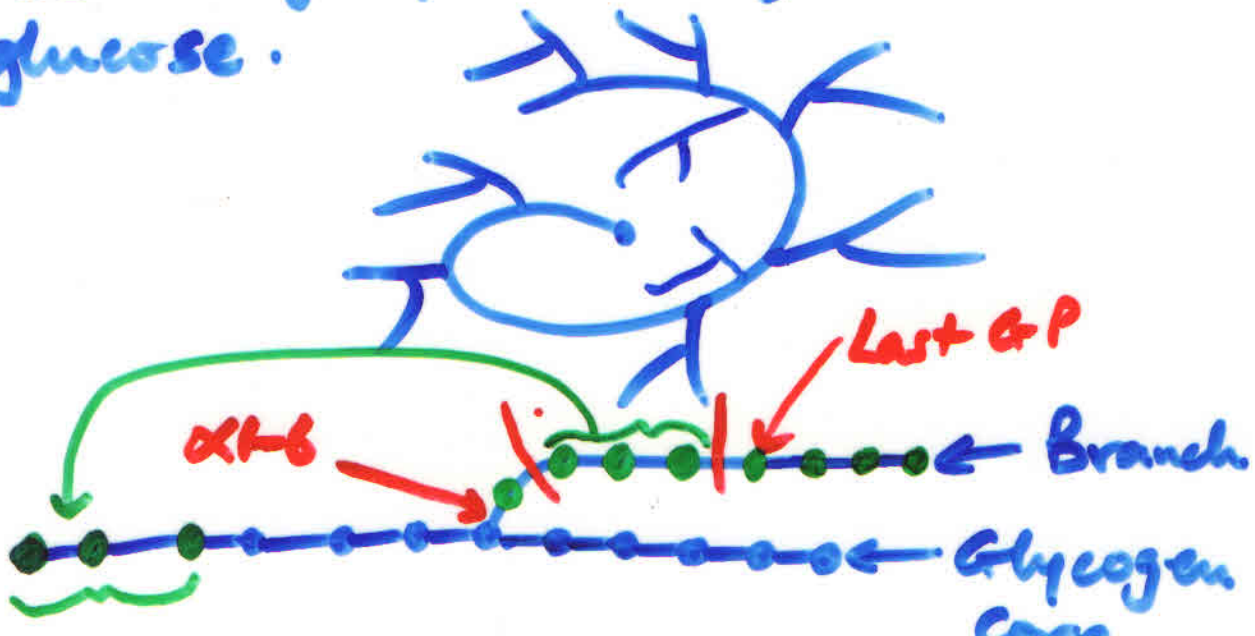
A. – It has both transferase and glucosidase activities.

i.e. – It catalyzes 2 reactions;

a) Removes 3 of the 4 glucose and transfers them to the end of another branch = transferase activity.

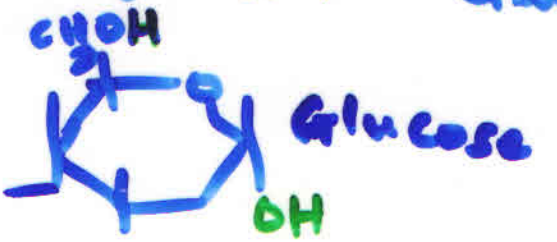
+ Glucosidase

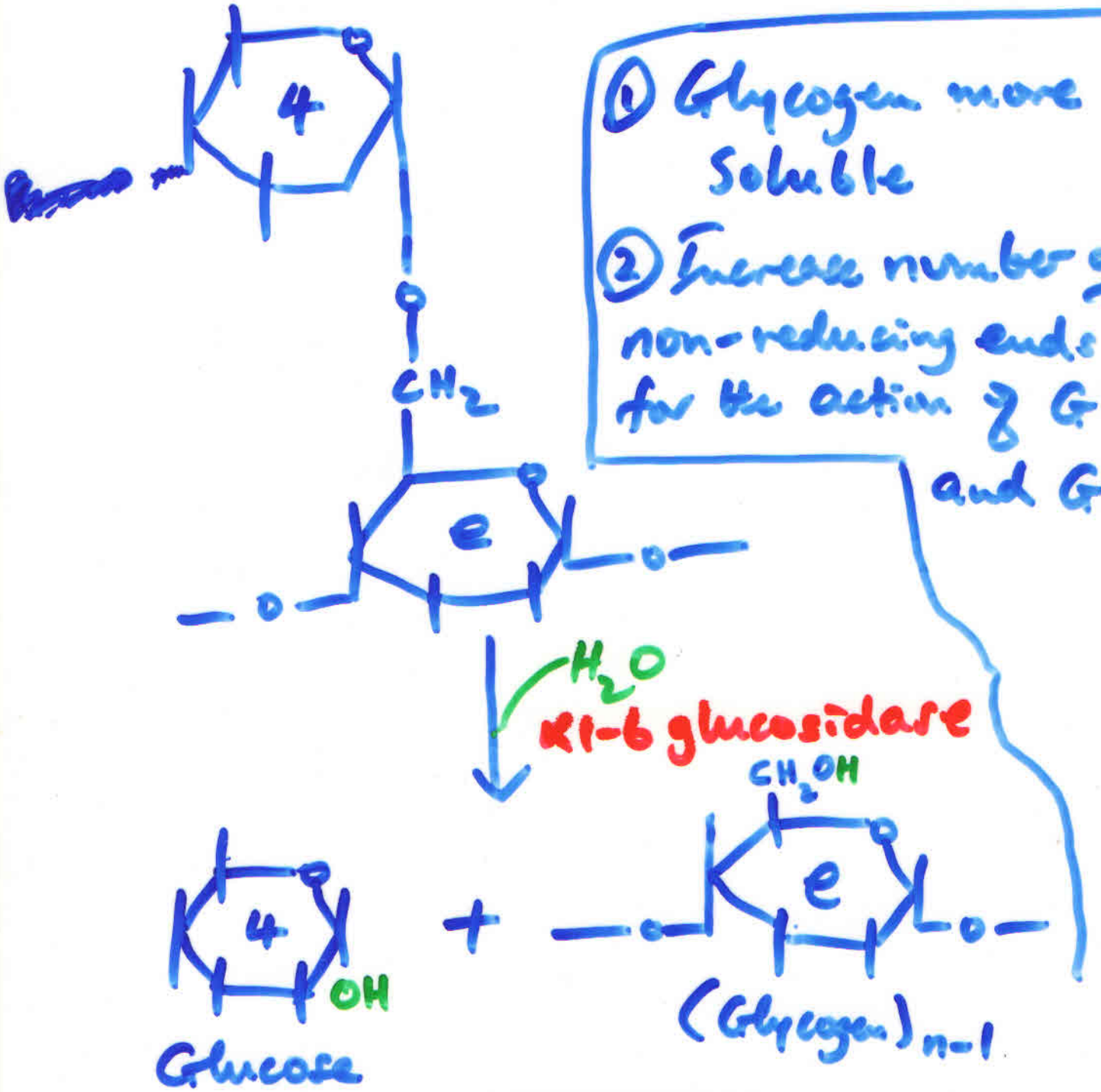
b) The remaining one glucose which is attached by α1-6 bond is removed by the glucosidase activity of the enzyme. This action makes available another length of glycogen to the action of GP. This glucose is removed by H_2O but not P_i. H_2O provides the -OH group at C1 of the removed glucose.



STEPS

$(Glycogen)_n \xrightarrow{H_2O} (Glycogen)_{n-1} + Glucose$





① Glycogen more Soluble

② Increase number of non-reducing ends for the action of GP and GS.

Regulation of Glycogen metabolism

Synthesis Versus Breakdown

GS Vs GP

Both GS and GP are regulated covalently and noncovalently.

GP
- a - covalently by ATP
- b - noncovalently by AMP = Muscle
  - " " Glucose = Liver

GS
- a - Covalently by ATP (GS-I)
- b - Noncovalently by G6P (GS-D)

GP and GS activities are regulated in a reciprocal manner.