GLYCOGEN METABOLISM,BLOOD GLUCOSE HOMEOSTASIS, DIABETES AND INSULIN

BY: RASAQ NURUDEEN OLAJIDE

LECTURE CONTENT

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- GLYCOGEN SYNTHESIS (Glycogenesis)
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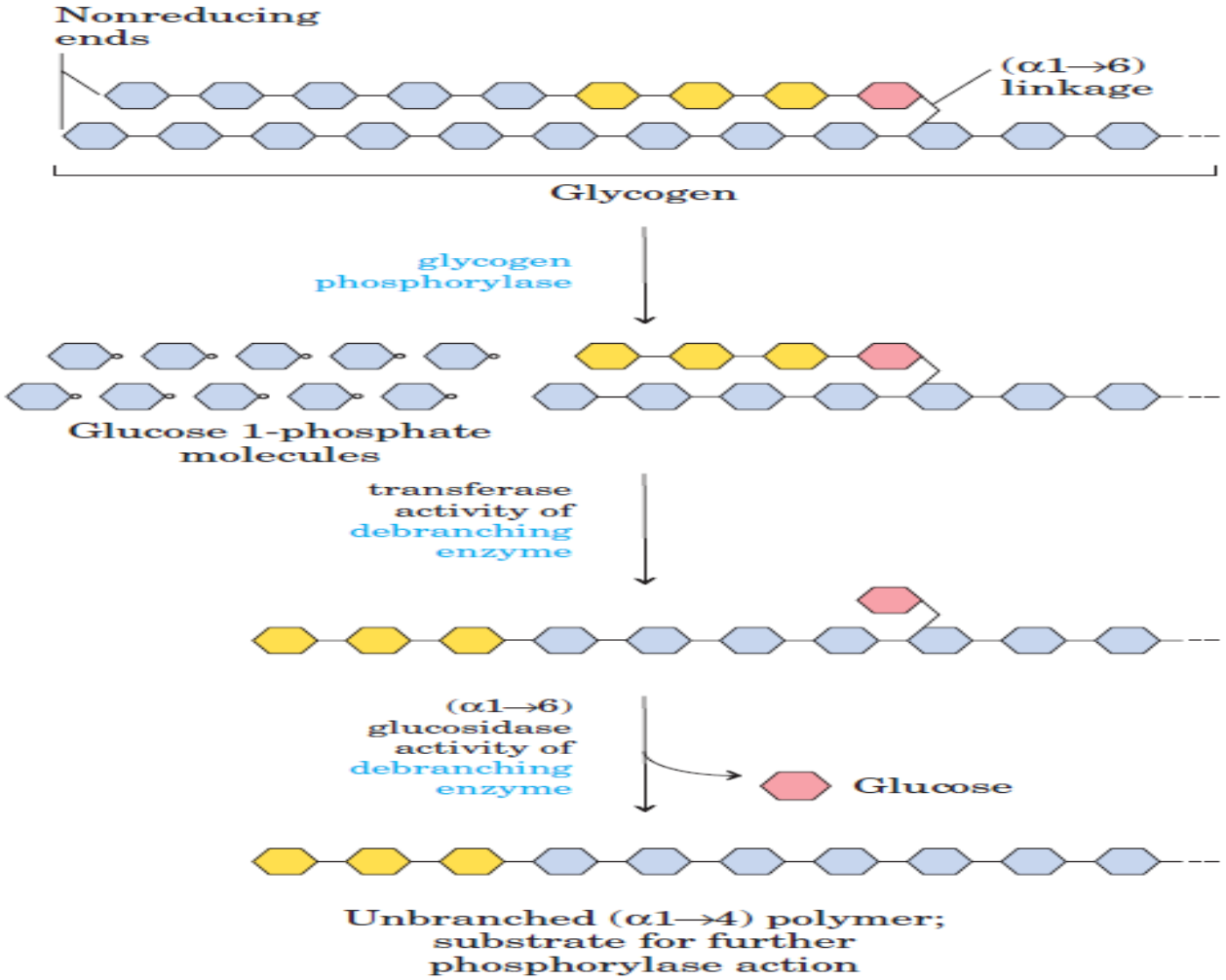
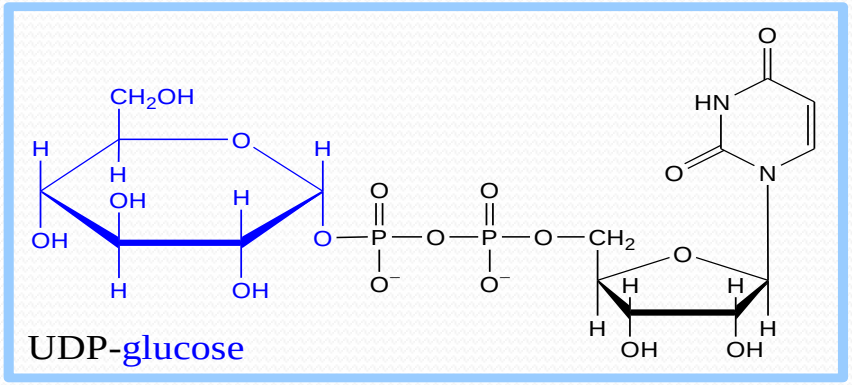
INTRODUCTION

- In many organisms, excess glucose is converted to polymeric forms for storage – glycogen
- In vertebrates, glycogen is found primarily in the liver and skeletal muscle
- Liver glycogen serves as a reservoir of glucose for other tissues when dietary glucose is not available (between meals or during a fast)
- In humans, the total amount of energy stored as glycogen is far less than the amount stored as fat (triacylglycerol)
- Glycogen granules are complex aggregates of glycogen and the enzymes that synthesize and degrade it as well as the machinery for regulating these enzymes

GLYCOGEN BREAKDOWN



GLYCOGEN SYNTHESIS

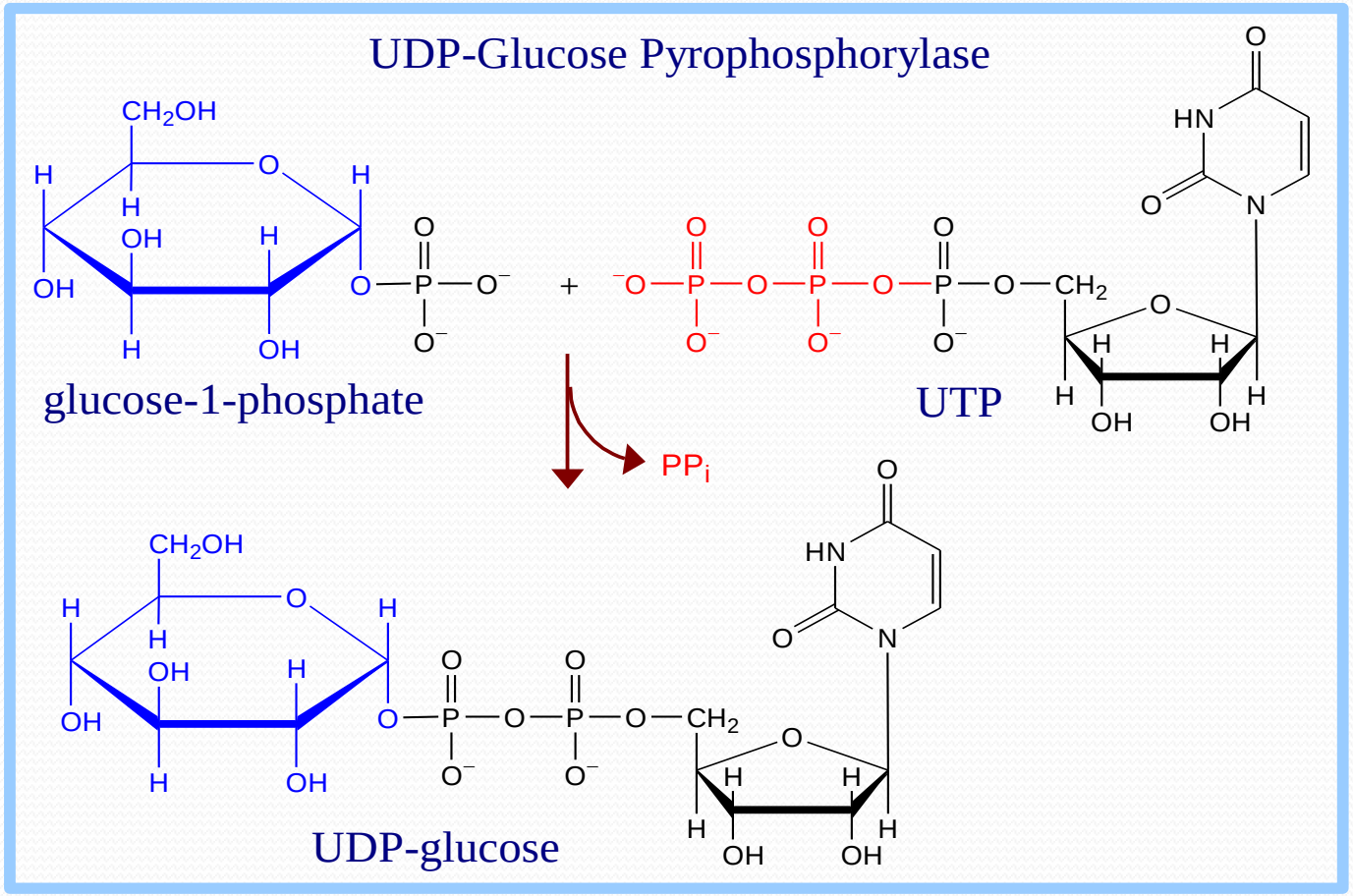


Uridine diphosphate glucose (UDP-glucose) is the immediate precursor for glycogen synthesis.

As glucose residues are added to glycogen, UDP-glucose is the substrate and UDP is released as a reaction product.

Nucleotide diphosphate sugars are precursors also for synthesis of other complex carbohydrates, including oligosaccharide chains of glycoproteins, etc.

GLYCOGEN SYNTHESIS



UDP-glucose is formed from glucose-1-phosphate:

- **glucose-1-phosphate + UTP → UDP-glucose + PP_i**
- **PP_i + H_2O → 2 P_i**

Overall:

- **glucose-1-phosphate + UTP → UDP-glucose + 2 P_i**

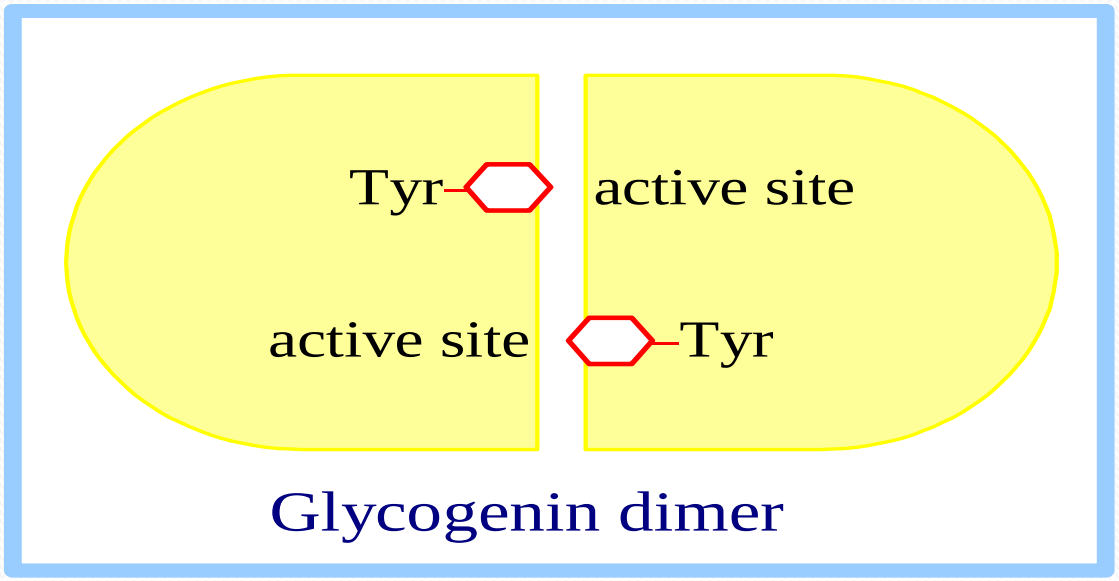
Spontaneous hydrolysis of the ~P bond in PP_i (P~P) drives the overall reaction.

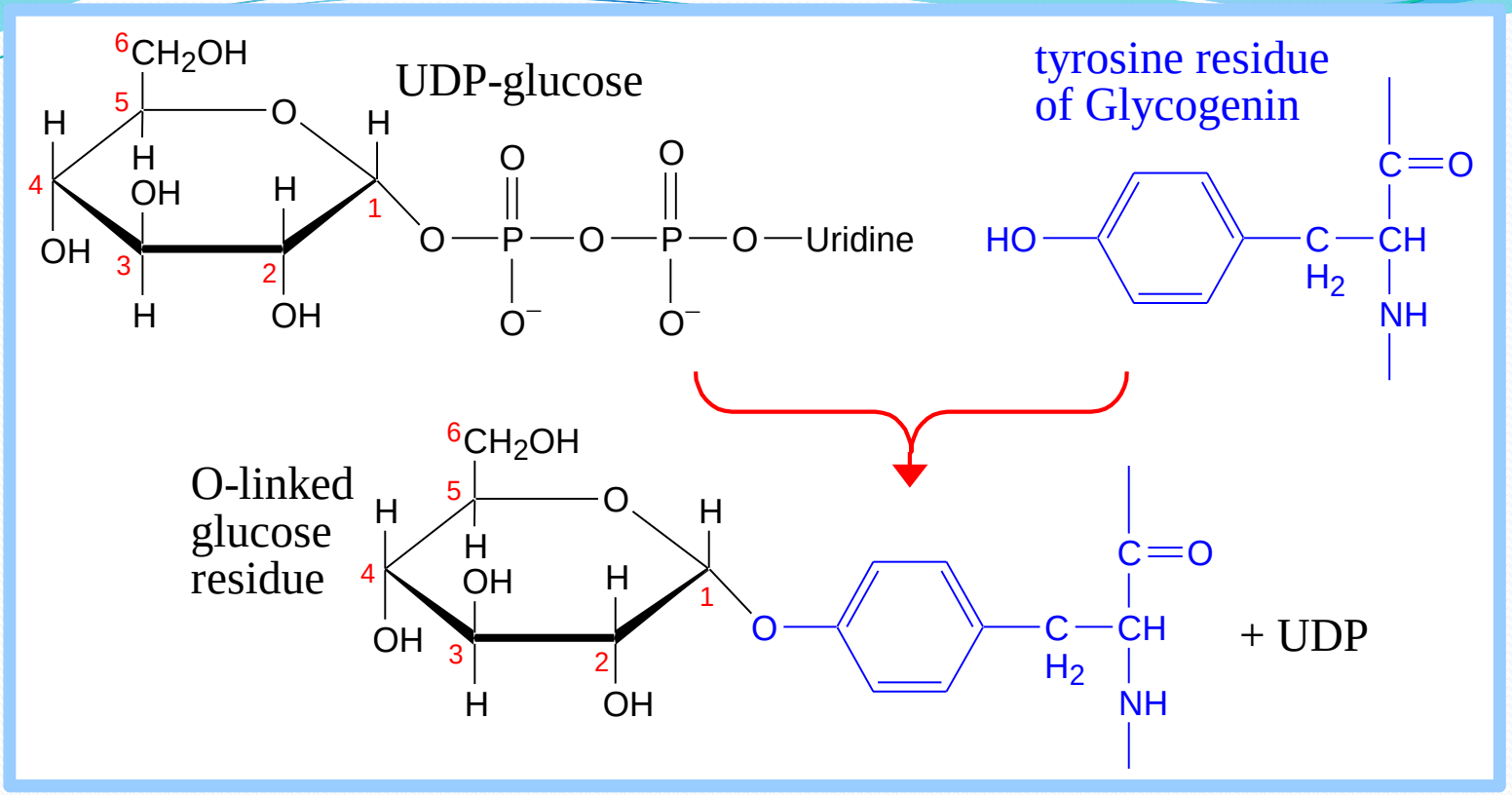
Cleavage of PP_i is the only energy cost for glycogen synthesis (<u>one</u> ~P bond per glucose residue).

Glycogenin initiates glycogen synthesis.

Glycogenin is an enzyme that catalyzes attachment of a **glucose** molecule to one of its own **tyrosine** residues.

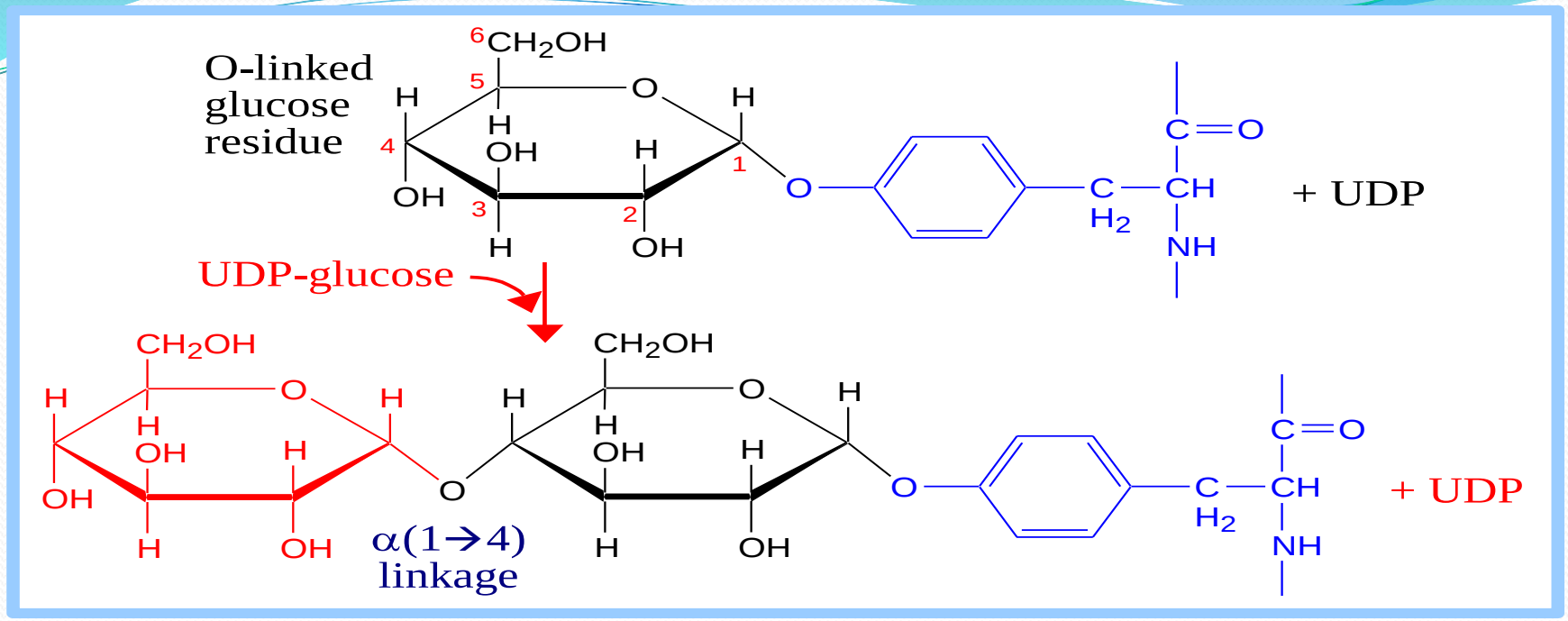
Glycogenin is a **dimer**, and evidence indicates that the 2 copies of the enzyme glucosylate one another.





A **glycosidic bond** is formed between the anomeric C1 of the glucose moiety derived from UDP-glucose and the hydroxyl oxygen of a **tyrosine** side-chain of **Glycogenin**.

UDP is released as a product.



Glycogenin then catalyzes glucosylation at C_4 of the attached glucose (UDP-glucose again the donor), to yield an O-linked disaccharide with a(1-4) glycosidic linkage.
This is repeated until a short linear glucose polymer with a(1-4) glycosidic linkages is built up on Glycogenin

Glycogen Synthase catalyzes transfer of the glucose moiety of UDP-glucose to the hydroxyl at C_4 of the terminal residue of a glycogen chain to form an $\alpha(1\rightarrow 4)$ glycosidic linkage:

$$\text{glycogen}_{(n\ \text{residues})} + \text{UDP-glucose} \rightarrow \text{glycogen}_{(n+1\ \text{residues})} + \text{UDP}$$

A branching enzyme transfers a segment from the end of a glycogen chain to the C6 hydroxyl of a glucose residue of glycogen to yield a branch with an a(1-6) linkage.

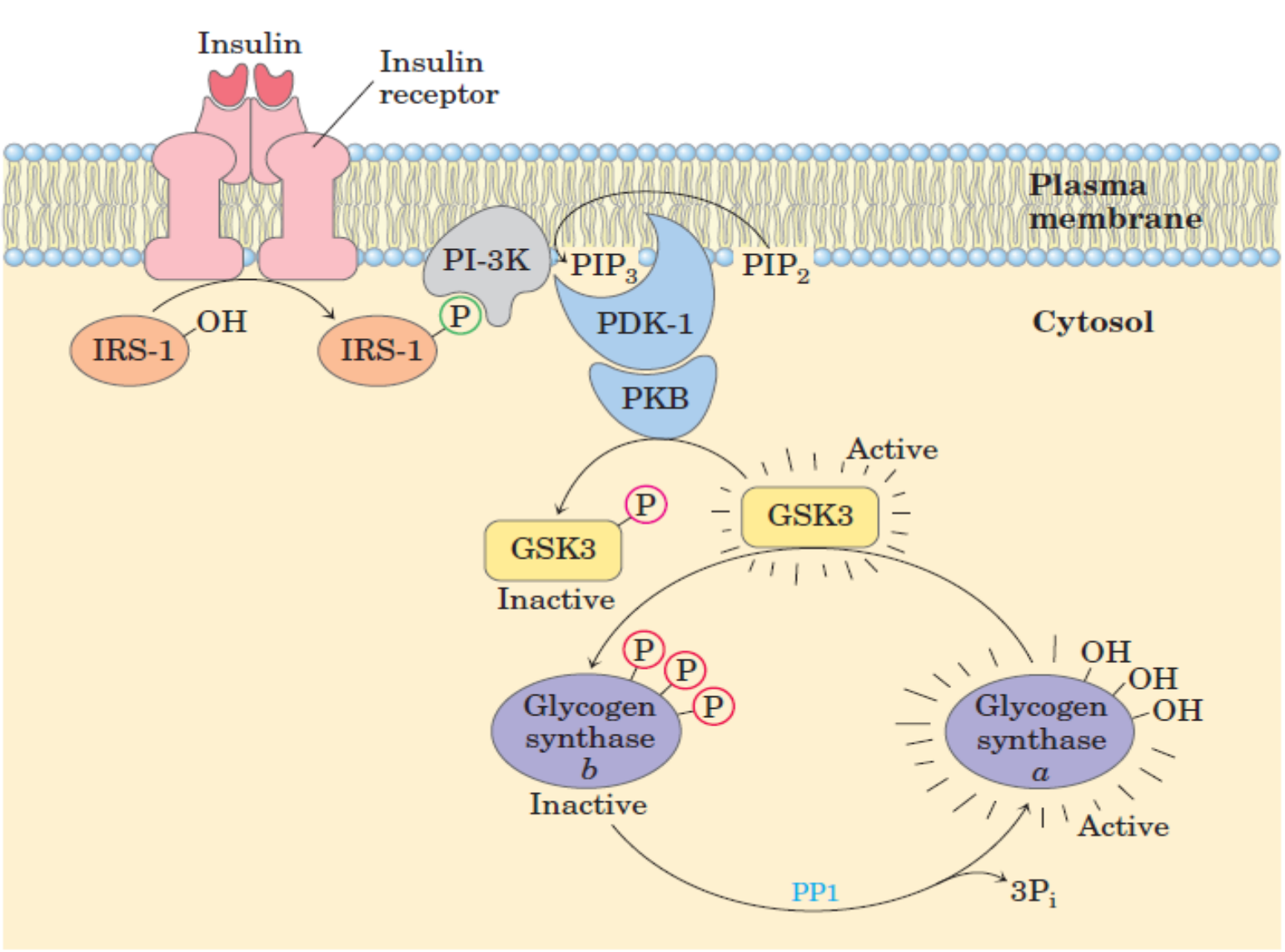
REGULATION OF GLYCOGEN METABOLISM

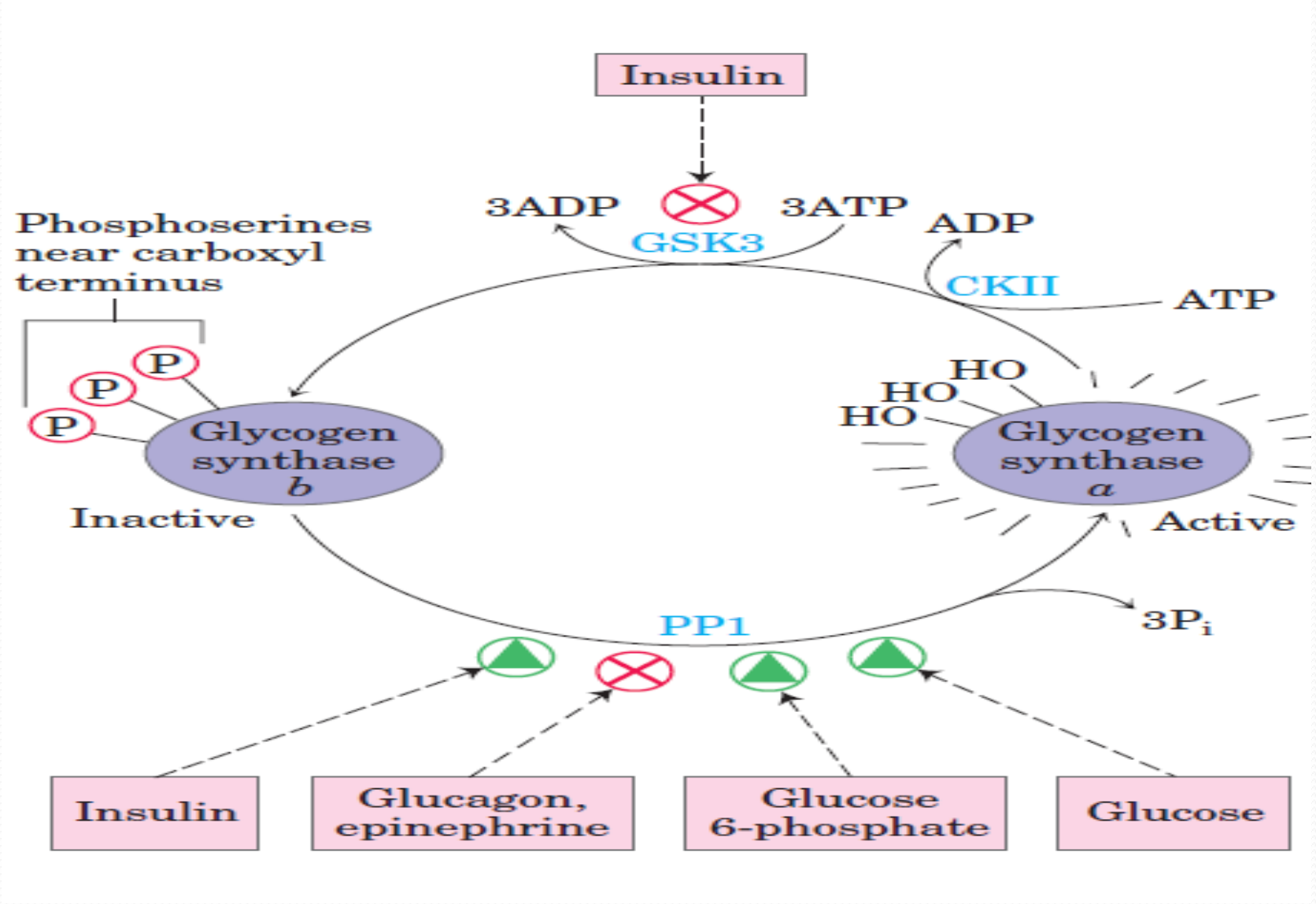
- **Both synthesis & breakdown of glycogen are spontaneous.**

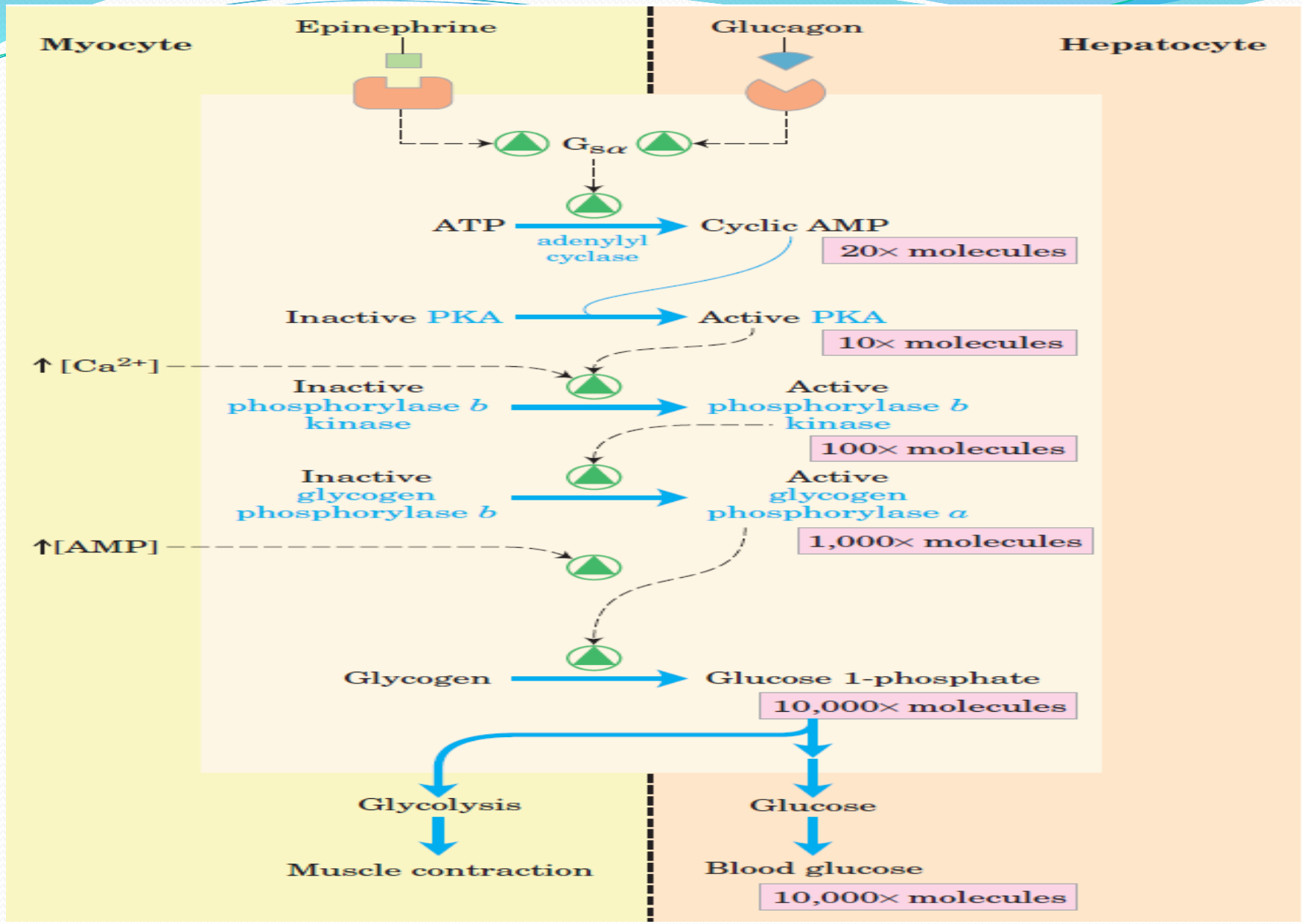
If both pathways were active simultaneously in a cell, there would be a "futile cycle" with cleavage of one ~P bond per cycle (in forming UDP-glucose).

To prevent such a futile cycle, Glycogen Synthase and Glycogen Phosphorylase are reciprocally regulated

- **Regulation of glycogen metabolism is achieved through (1)Covalent modification of key enzymes (2)Allosteric mechanisms and (3) Regulations by hormones (glucagon, epinephrine and insulin)**


Insulin
Insulin receptor
Plasma membrane
PI-3K
PIP3
PIP2
PDK-1
PKB
Cytosol
IRS-1
OH
P
IRS-1
Active
GSK3
P
GSK3
Inactive
P
P
P
Glycogen synthase b
Inactive
OH
OH
OH
Glycogen synthase a
Active
PP1
3Pi


Insulin
3ADP
GSK3
3ATP
ADP
CKII
ATP
Phosphoserines near carboxyl terminus
P
P
P
Glycogen synthase b
Inactive
HO
HO
HO
Glycogen synthase a
Active
3Pi
PP1
Insulin
Glucagon, epinephrine
Glucose 6-phosphate
Glucose


Myocyte
Epinephrine
Glucagon
Hepatocyte
$G_{s\alpha}$
ATP
adenylyl cyclase
Cyclic AMP
20× molecules
Inactive PKA
Active PKA
10× molecules
↑ [Ca^{2+}]
Inactive phosphorylase b kinase
Active phosphorylase b kinase
100× molecules
Inactive glycogen phosphorylase b
Active glycogen phosphorylase a
↑[AMP]
1,000× molecules
Glycogen
Glucose 1-phosphate
10,000× molecules
Glycolysis
Muscle contraction
Glucose
Blood glucose
10,000× molecules