

## Storage Mechanisms & control in carbohydrate metabolism

\* In Glycolysis 1 Glucose molecule enters Glycolysis & 1F all carbons continue  
 Glycolysis  $\rightarrow$  Pyruvate, 2ATP are produced  
 $2H_2O, 2H^+$ ,  $4e^-$  lost  
 From Glucose  
 Cytosol  $\rightarrow$  GTP  
 10 reaction  $\rightarrow$  10 enzymes

\* reverse of Glycolysis is Gluconeogenesis

\* Pentose phosphate path - important for synthesis of ribose sugar that is imp. for the structure of nucleotides & DNA

\* Pyruvate  $\rightarrow$  Could be further oxidized through citric acid cycle

- If the cell need energy the Glucose-6-phosphate will continue through Glycolysis through citric acid cycle

\* If the cell need to build nucleotide some of G6P will go into ribose-5-phosphate

\* Remember, G6P is produced after the first reaction of Glycolysis



- If there is a lot of Glucose in the body, some of that Glucose will convert to

Glycogen

It's in cells

Some of Glycogen will be broken down to produce Glucose & the Glucose will be used to make energy

↓ Glucose: Glyconeogenesis will allow syn. of Glucose from pyruvate, lactate, ...

- We have intermediate in Glycolysis that allows us to synthesize lipid / a.a

\* Citric acid cycle: we have some intermediate that allows us to syn. a.a

\* Which metabolic path would be followed depend on the need of the cell, these metabolic paths might be followed by the cell all at the same time but at different rates.

## \* Glycogen breakdown / synthesis

reversible to each other but they don't use the same enzyme

- Glycogen is a polymer of Glucose

- If the cell need Glucose → Glycogen will be broken down to produce G<sub>1</sub>P, Could continue through Glycolysis

- A lot of Glucose, more than we need, the Glucose is converted to Glucose-6-phosphate → G<sub>1</sub>P → UDPGlucose, then it's added to Glycogen

## \* Breakdown of Glycogen

store of energy  
→ source of energy -

Mainly stored in liver / muscle / kidney

\* When you eat a carbohydrate rich meal, some of the carbo. will be burn to produce energy but some of that carbo. will be stored as Glycogen for later use

\* When the cell need energy while fasting, Glycogen might be a source to provide our cells with Glucose

- Breakdown of Glycogen → 3 steps require 3 enzymes

① 1 Glucose molecule removed from Glucose polymer  $(\text{Glucose})_n - 1$  & this Glucose molecule reserve a phosphate group to become G1P

The enzyme catalyzing this reaction is called Glycogen phosphorylase enzyme

take 1 Glucose molecule at time, convert it to G1P → G6P & then it can continue through Glycolysis

Glyco. oligosaccharide \*

is branched

visible just few branch → so it's branched → 4 Glucose

\* Enzyme called debranching enzyme → removes branches, takes the 3 Glucose monomers from the branch & put it to the closest longer chain & the same enzyme will be able to remove the last Glucose molecule at branch

\* So basically all Glucose monomers removed from the Glycogen by debranching phosphotriesterase enzyme, will be converted into GIP & then G6P by enzyme phosphoglucomutase

- Now the G6P it continue through Glycolysis or through PPP

\* For synthesis 3 enzymes

- 1 UDP Glucose pyrophosphorylase
- 2 Glycogen synthase
- 3 Glycogen branching enzyme

- First step Glycogen syn. begin G6P → GIP by the same enzyme phosphoglucomutase, then GIP → UDP Glucose exchange phosphate with nucleotide

During this process 2 phosphate Group are removed - pyrophosphate - by the enzyme Pyrophosphatase

Then Glycogensynthase enzyme take Glucose From UDP (remove UDP) & add Glucose into Glycogen



\* When pyrophosphate is split into 2 PP<sub>i</sub>  
high energy will be released

it will drive the coupling reaction

\* UDP Glucose → Glucose molecule with  
a phosphate at carbon number 1 +  
nucleotide with 1 phosphate

4 phosphate → 3 UTP  
+ Glucose phosphate  
2 leaves as pyrophosphate remain

2

Then we have enzyme Glycogen

Synthase

- remove Glucose add it to  
chain of Glycogen & what is left  
is UDP

\* The Glycogen synthase can't  
start building Glycogen from nothing  
~~can't start Base 1 step~~

, make  
Glycosidic bond  
between Glucose  
molecule in the linear  
Chain

A protein called  
Glycogenin

\* In the middle of Glycogen  
Glycogenin is way

using Glycogen synthase. also d-  
Glucose molecule start to build  
Glycogen

& the branching enzyme start  
making branches

When Glycogen Synthase  
synthesizes a chain that is  
13 monosaccharides long, the branching enzyme  
removes the last 7 & adds them to the main  
chain to introduce a new branch

Glycogen  
ways  
ways

\* Glycogen synthase break down  
is regulated by phosphorylation  
& allosteric effectors

So the enzyme Glycogen phosphorylase  
which is imp. for breaking down  
Glycogen regulated by several  
allosteric effectors

Also its activity is regulated by hormones  
& these hormones will initiate Phosphorylation/dephosph.  
(Insulin) ---

- 2 state of enzymes T state  
R state

Phosphorylase

B

A

L

active state unphospho.

could be inhibited

by Glucose

\* AMP  $\rightarrow$  product of ADP which is  
product of ATP

$\uparrow$  AMP  $\downarrow$  ATP It's like  
a signe for cell to need more  
Glucose

- unphosphorylated could be inhibited by ATP (to break ATPase)  
جافی کیمی ATP می خورد

$\downarrow$  Glucose level in the blood, our body will produce Glucagon, epinephrine

$\uparrow$  Glucose level production of Insulin

Aslıpıllı

receptor on a surface of cell A that

that will allow the activation of phosphorelase at the end.

↓ Glucose : we need Glucose as one source is by activating enzymes that will breakdown Glycogen, one of them is phosphorylase, how do it activate? by phosphorylating it, at the same time we inhibit Glycogen synthase by phosphorylation

less active  $\xrightarrow{\text{no Gluc}}$   
active  $\xrightarrow{\text{yes Gluc}}$

\* cell will produce Glycogen when

↑ Glucose  $\leftarrow$  Insulin Dephos.

↓ Glucose Phospho.

\*\* If the phosphorylation system is activated an enzyme called protein kinase A will be activated & this enzyme will phosphorylate.

The enzyme phosphorylase A kinase will phosphorylate the Glycogen phosphorylase & now it's active, it will breakdown Glycogen releasing Glucose, at the same time an enzyme will phosphorylate Glycogen synthase & now it's not active

\* Insulin activate dephosphorylation system.  
this system activates an enzyme called phosphoprotein phosphatase inhibitor  
& this will activate a Phosphatase  
- enzyme → remove phosphate  
kinase → add

\* phosphatase enzyme acts as both Glycogen syn./break

- remove phosphate from Glycogen synthase & now it's active
- It will remove phosphate from Glycogen phosphorylase & now it's not active

\* Because there is a lot of Glucose, some of the Glucose must be used to synthesis Glycogen, that means we need to activate Glycogen synthase but at the same time inhibit enzyme that breaks the Glycogen

new formation

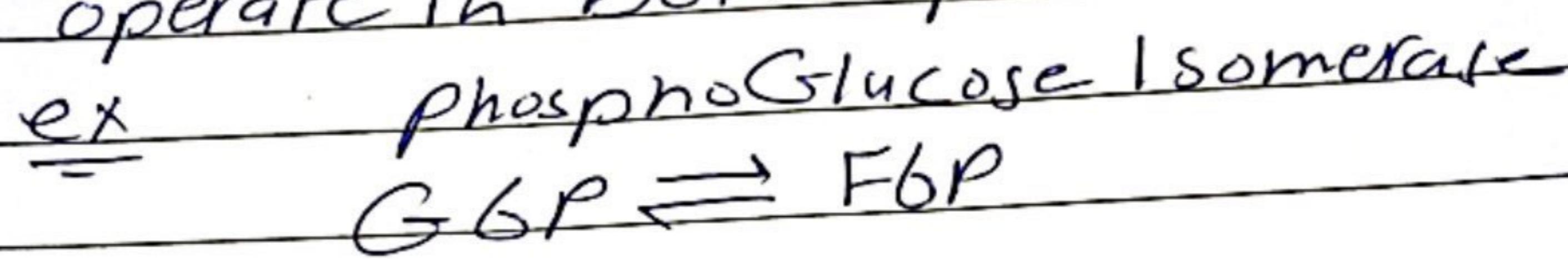
\* next path → Glyconeogenesis

Going from pyruvate → Glucose

1. ~~ATP~~ only addition, 2. 12

\* happen in liver to provide Glucose  
to the blood, the liver can do that by breaking Glycogen or by activating Glyconeogenesis

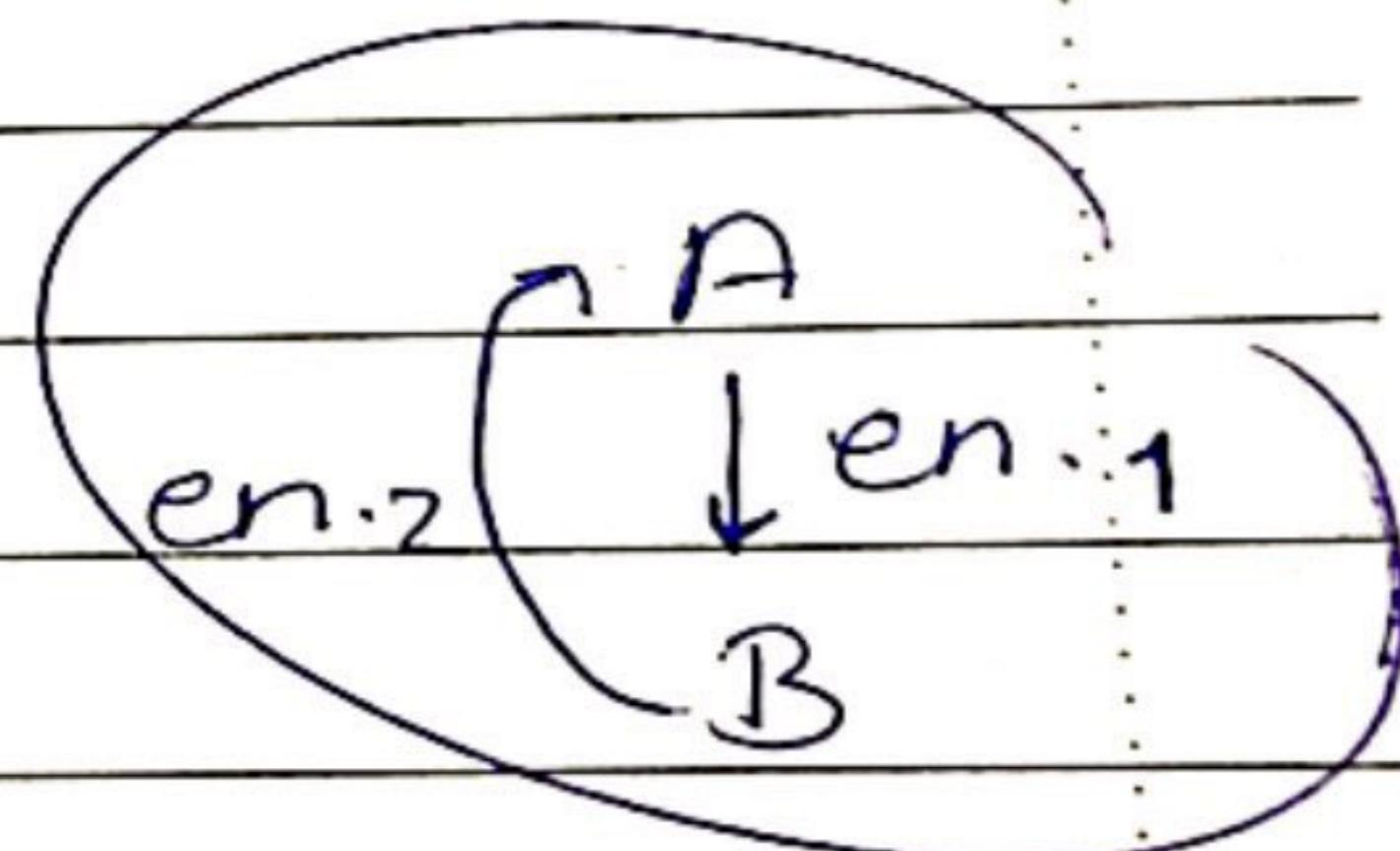
we \* we have 7 enzymes that can operate in both path.



Glycolysis: 3 irreversible steps catalyzed by 3 enzyme (large -ΔG)

- 1 hexokinase
- 2 phospho Fructokinase
- 3 Pyruvate kinase

Substrate cycling → A  
B



5vi Side step

Glycolysis goes to Glyconeogenesis

1 G6 phosphatase

2 Pi Fructose bis phosphate

3 PEPCK

4 Pyruvate

\* Pyruvate carboxylase is an enzyme that will convert pyruvate into oxaloacetate

- the pyruvate will receive an extra carbon from  $\text{CO}_2$  (this reaction requires ATP)

Remember Glycolysis happens in the cytosol & typically the pyruvate will go into inside the mitochondria to continue through the citric acid cycle

- now the pyruvate once it's converted to oxaloacetate

must go outside the mitochondria  
↳ Glycogen

Oxaloacetate → imp. intermediate of citric acid cycle or TCA cycle

↓  
convert into malate

↳ specific malate transporter allows malate to go outside the mitochondria, then malate will be converted back to oxaloacetate, then oxaloacetate continues through Glyconeogenesis

\* Oxaloacetate  $\rightarrow$  phosphoenolpyruvate  
by an enzyme called  
phosphoenol pyruvate  
carboxy kinase

Could continue through  
Glycolysis until we have  
the step where we have  
Fructose 1, 6 biphosphate

Glucose  $\xleftarrow[\text{G6phosphatase}]{\text{enzyme F6P}}$

\* we have an enzyme phosphofructokinase  
PFK

catalyses 3 - steps of Glycolysis,  
most imp. enzyme, highly controlled

- 2 similar to it

PFK<sub>1</sub> / PFK<sub>2</sub>

↓  
bifunctional enzyme  
kinase / phosphatase

which activity will dominate?

These 2 activities are controlled by phosphorylation,  
So if the enzyme is phosphorylated, the phosphates

→ activity will dominate & kinase activity  
will not be functional

If the phosphate group is removed, kinase activity will be on, phosphatase activity will be off

F6P ~~no just one is off \*~~

Some of it will be converted to F<sub>1</sub>, 2-6 phosphate by PFK<sub>2</sub> (this molecule can activate the PFK but at the same time it will inhibit the activity of this enzyme, because it makes more of F6P & G6P)

- Remember → Epinefrin, Glucagon produced when Glucose (both hormones activate phosphorylation system)

↓ Glucose → Glucagon/epinefrin → phospho.  
↑ Glucose → Insulin → Dephos.

\* metabolic path could be activated / inhibited by allosteric effectors. Some allosteric effectors are activators (activate some enzymes)

Note → PFK activated by AMP

\* Some enzymes become activated by phosphorylation like Glycogen-Phosphorelases

- we have Genetic control like lac operon

If a cell need Glycolysis to be activated the cell can make more enzymes from Glycolysis to increase it, but also we have substrate cycles

The point is we can control 2 different paths going in opposite directions by having some steps in both path that are catalyzed by different enzymes

We could have molecule X & if it's allosteric effector maybe it bind to E<sub>1</sub> & activate it but at the same time bind to E<sub>2</sub> & inhibit it & maybe there is other molecule Y does the opposite

\* Metabolic co-operation of organs

↳ Metabolic activity of different organs can cooperate with each other

\* Glycogen syn- / breakdown happen mainly in the liver, Glyconeogenesis in liver, so the enzymes required for them are

→ found in liver cells but also we have a collaboration between muscle cells & liver cells

لذا ينبع انتشار الجلوكوز من الكبد

Muscle cell will rely more on Glycolysis for ATP production

لأنها تزود ATP إلى العضلات

~~less oxygen will be delivered to your muscle which means muscles must rely on Glycolysis because it doesn't require O<sub>2</sub>~~

\* Glycolysis require NAD<sup>+</sup> to produce NADH. When the Glycolysis is the only source of ATP, all the NAD<sup>+</sup> will be gone/consumed, so Glycolysis will stop, which mean no more ATP will be produced inside muscle cell

→ To make NAD<sup>+</sup> the cell will start oxidizing NADH to make NAD<sup>+</sup> so that Glycolysis continue

ويتم ذلك من خلال

lactate acid fermentation

## \* Pyruvate $\rightarrow$ lactate

- by Enzyme lactate dehydrogenase & require NADH to be oxidized

\* What happens is lactate concentration will rises

- Lactate travel through blood into the liver & it will be convert to Pyruvate by enzyme lactate dehydrogenase & then pyruvate will be converted into Glucose through Glyconeogenesis & this Glucose will travel through blood from liver cell to muscle cells to allow Glycolysis to continue

## \* Regulation of Pyruvate kinase



- It catalyzes conversion of phosphoenolpyruvate into Pyruvate
- Catalyze irreversible step with a large  $- \Delta G$
- Control point

→ Could be controlled by allosteric effectors

→ de cou. modification

- This enzyme is inhibited by phosphorylation  
activated by dephosphorylation

Glycolysis requires ATP more than  
Pyruvate kinase requires more than \*

ATP → Some of ATP will be converted to cyclic AMP & it will activate phosphorylation & the Glycogenesis will be activated

another path → pentose phosphate path

- imp. production of NADPH-1
- produces Ribose sugar

Reducing agent  
for anabolism specially  
Lipid metabolism / fatty acid

G6P → could be converted to ribulose 5 phosphate

I convert to  
ribose 6 phosphate

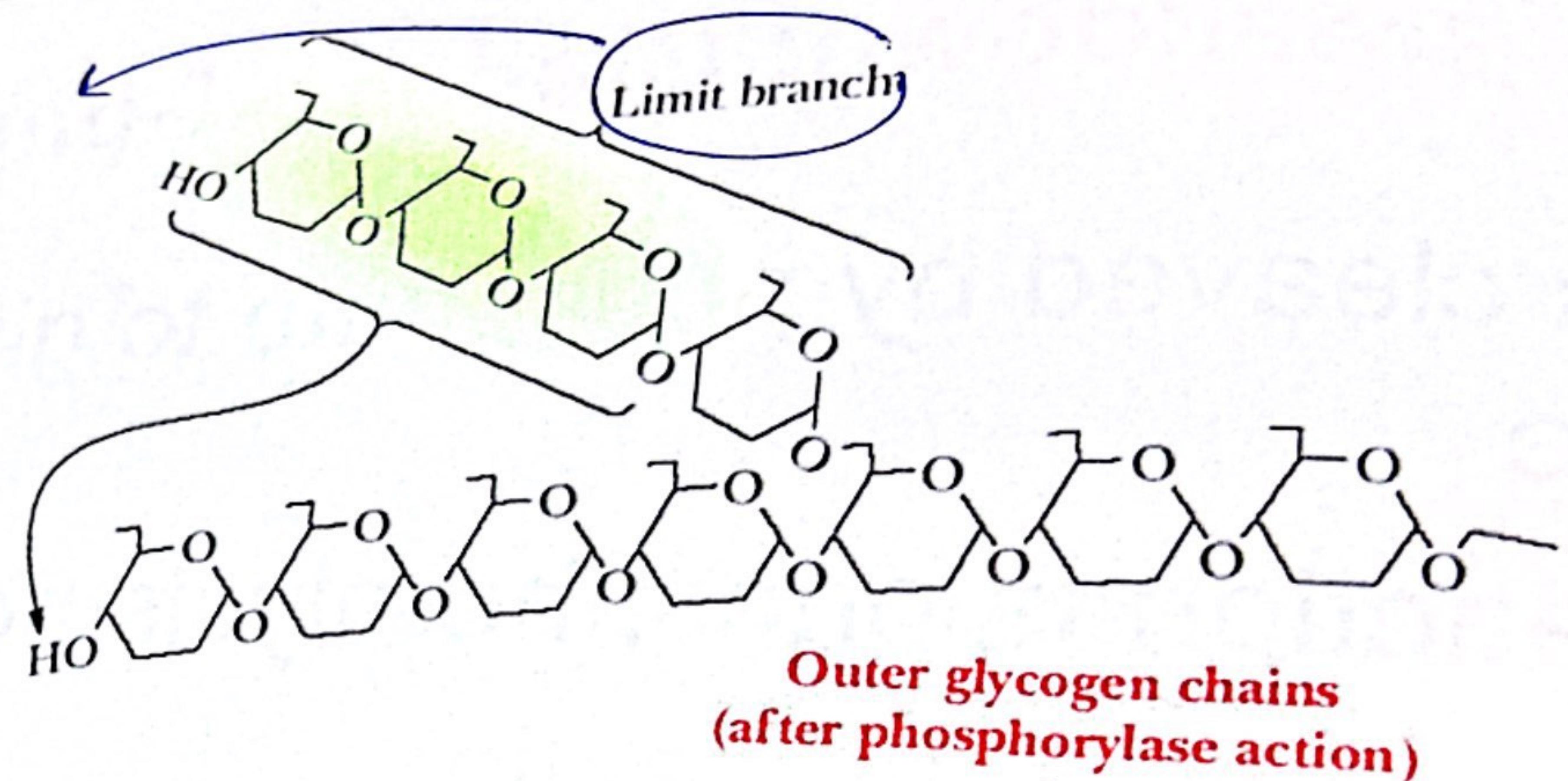
— So if the cell need to replicate it's DNA, which need to mate nucleotide. It will take some of G6P because it to mate ribose sugar

But at the same time there will be some carbons that could be feedback into Glycolysis

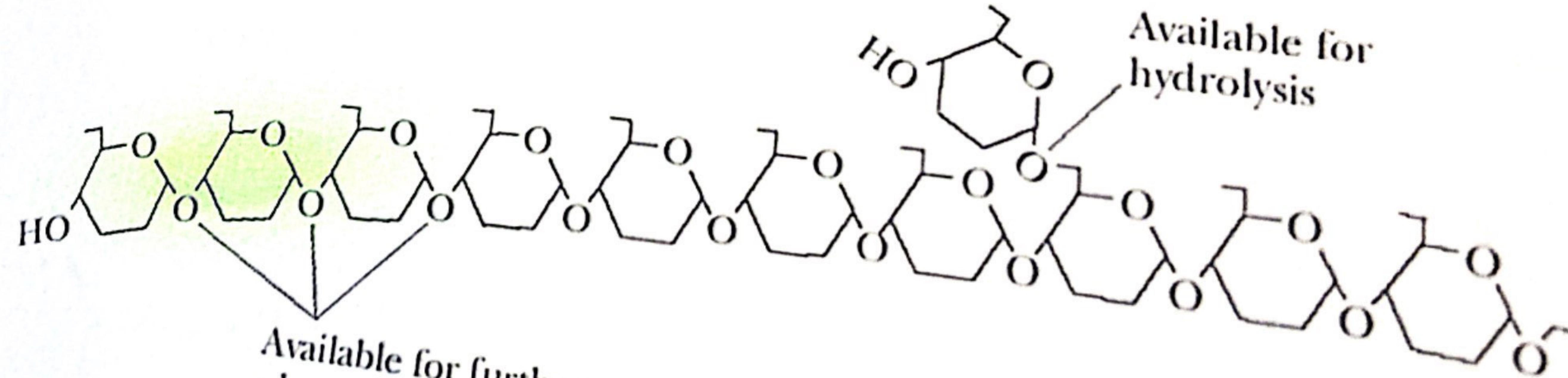
\* liver, due to hexokinase enzyme

\* Galactose could enter the Glycolysis but first it must be converted to G6P by the enzyme Galactokinase then to G1P

Can't be  
attack by  
Glycogen  
phosphorylase

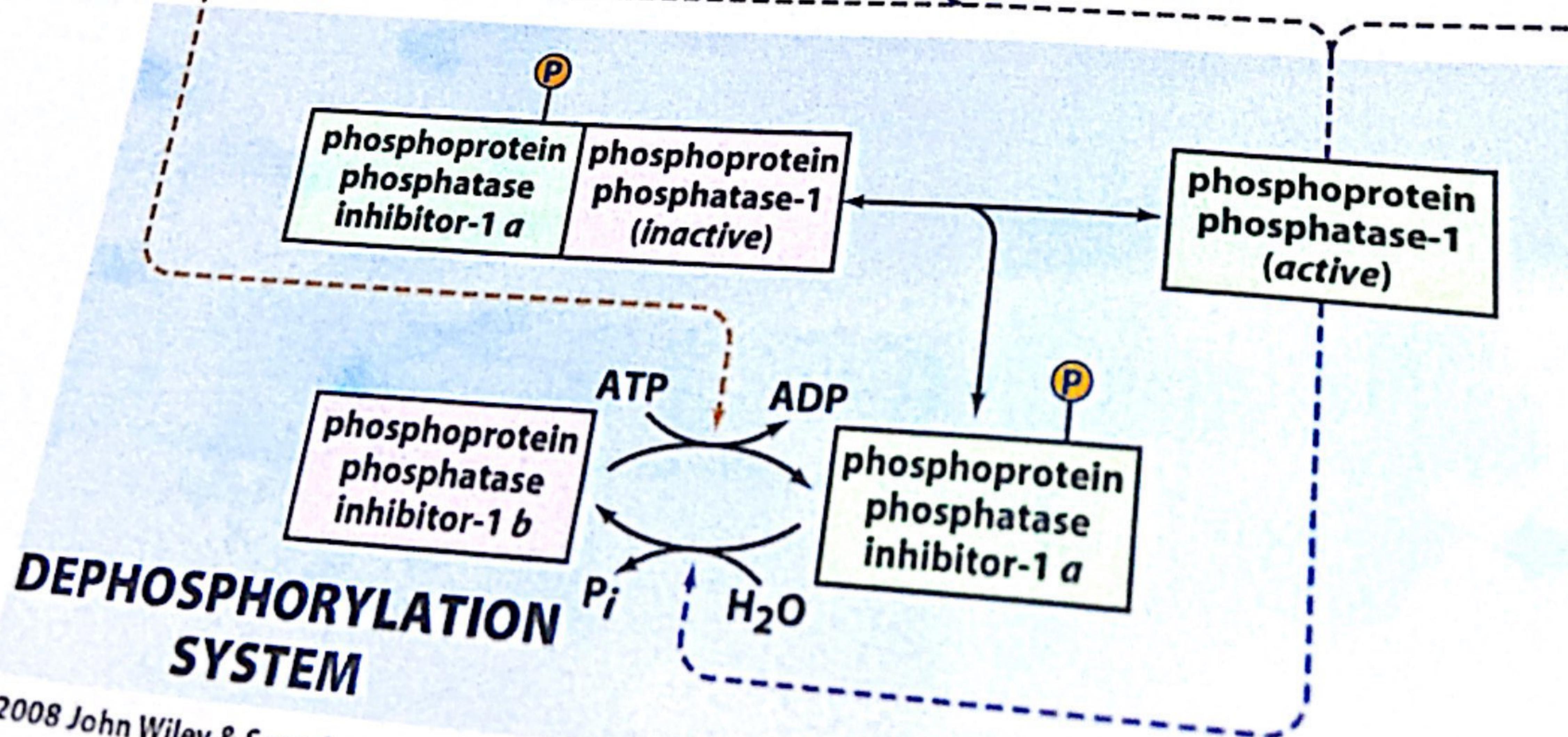
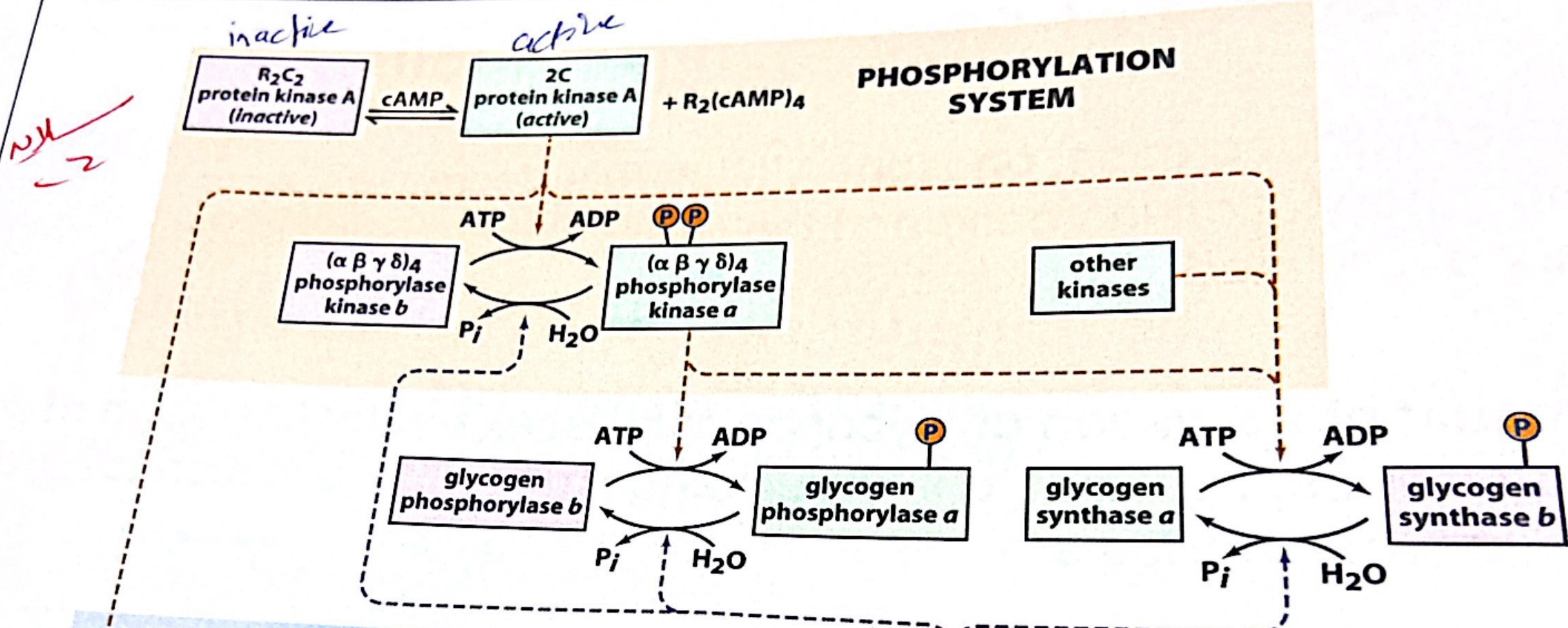


(N)



- The mode of action of the debranching enzyme in glycogen breakdown end of another branch. The same enzyme also transfers three  $\alpha(1 \rightarrow 4)$ -linked glucose residues at the branch.
- The enzyme transfers three  $\alpha(1 \rightarrow 4)$ -linked glucose residues at the branch.

## PHOSPHORYLATION SYSTEM

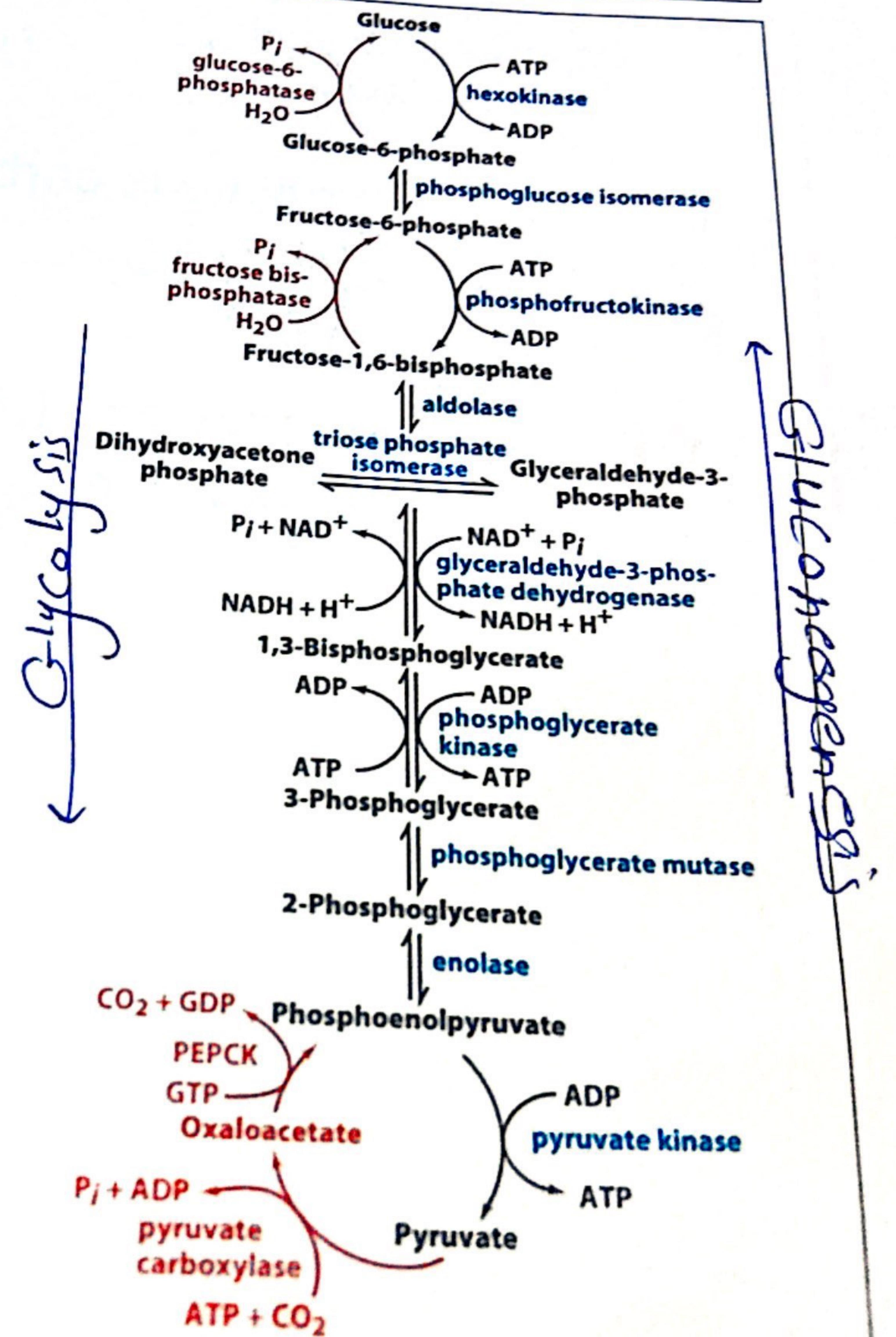


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- Net result of gluconeogenesis is reversal of these three steps, but by different pathways and using different enzymes

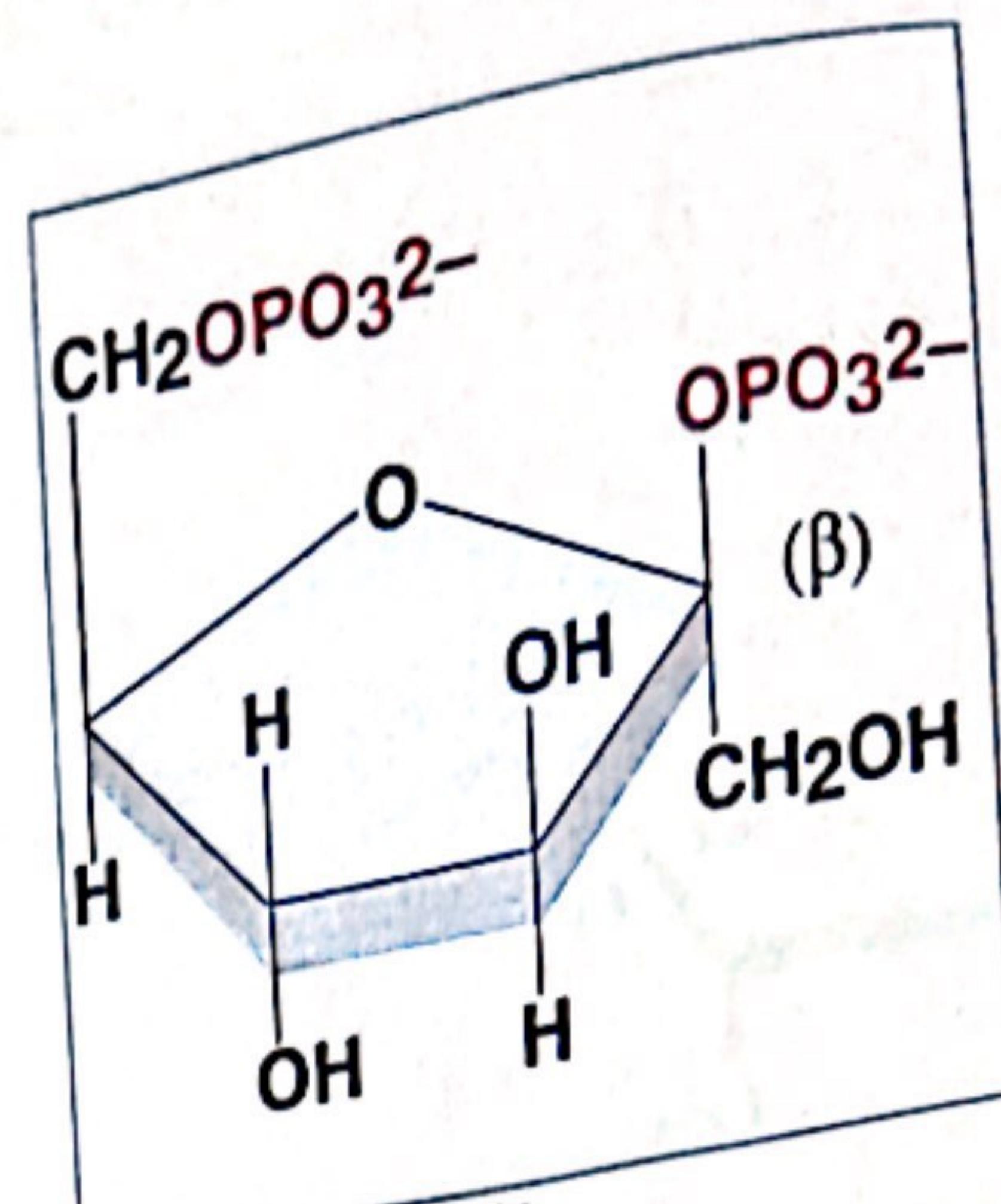
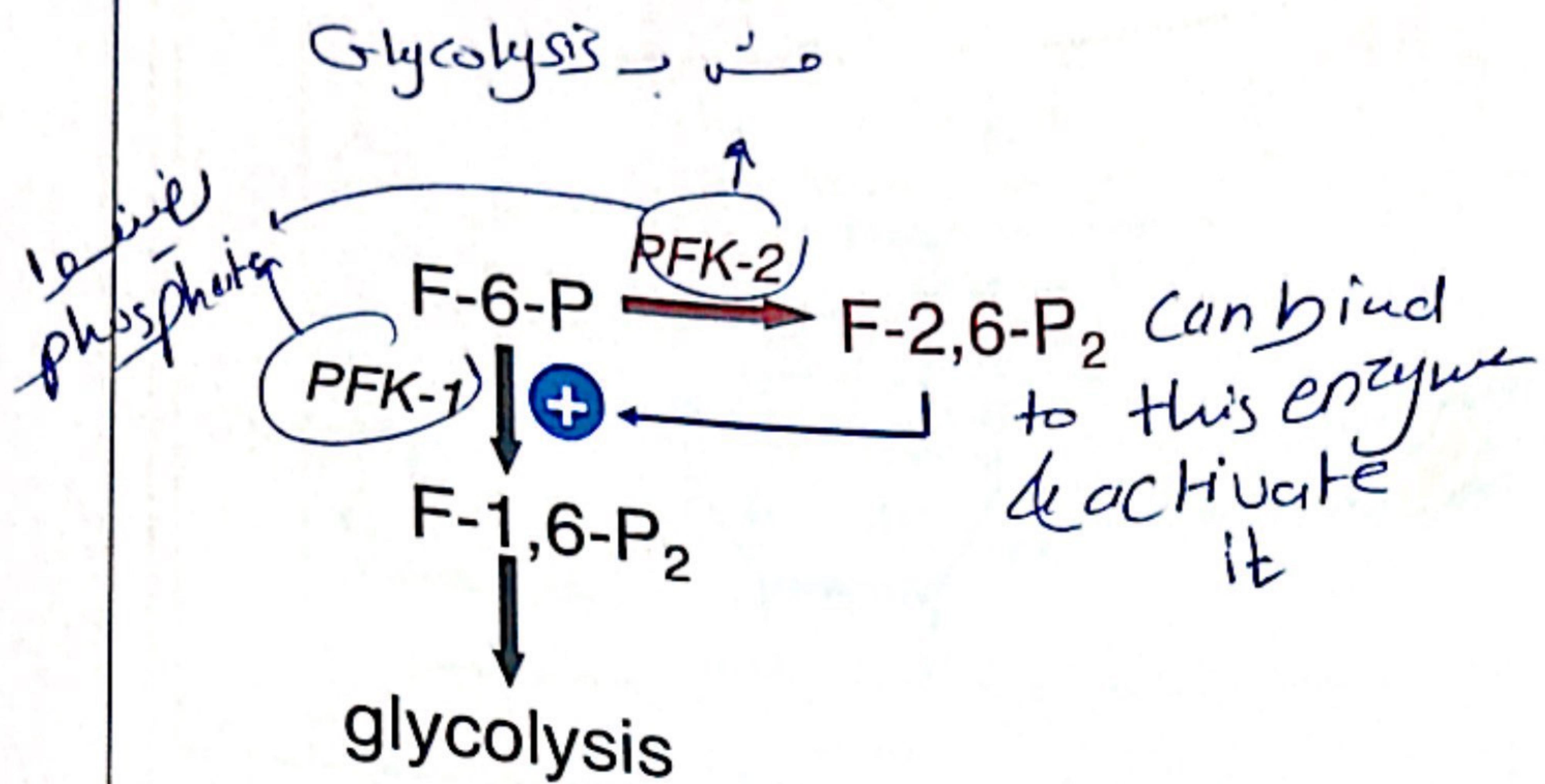
## Gluconeogenesis

- Most of Gluconeogenesis is Glycolysis in reverse.
- Only irreversible steps must be different
- Oxaloacetate is the required molecule to start gluconeogenesis



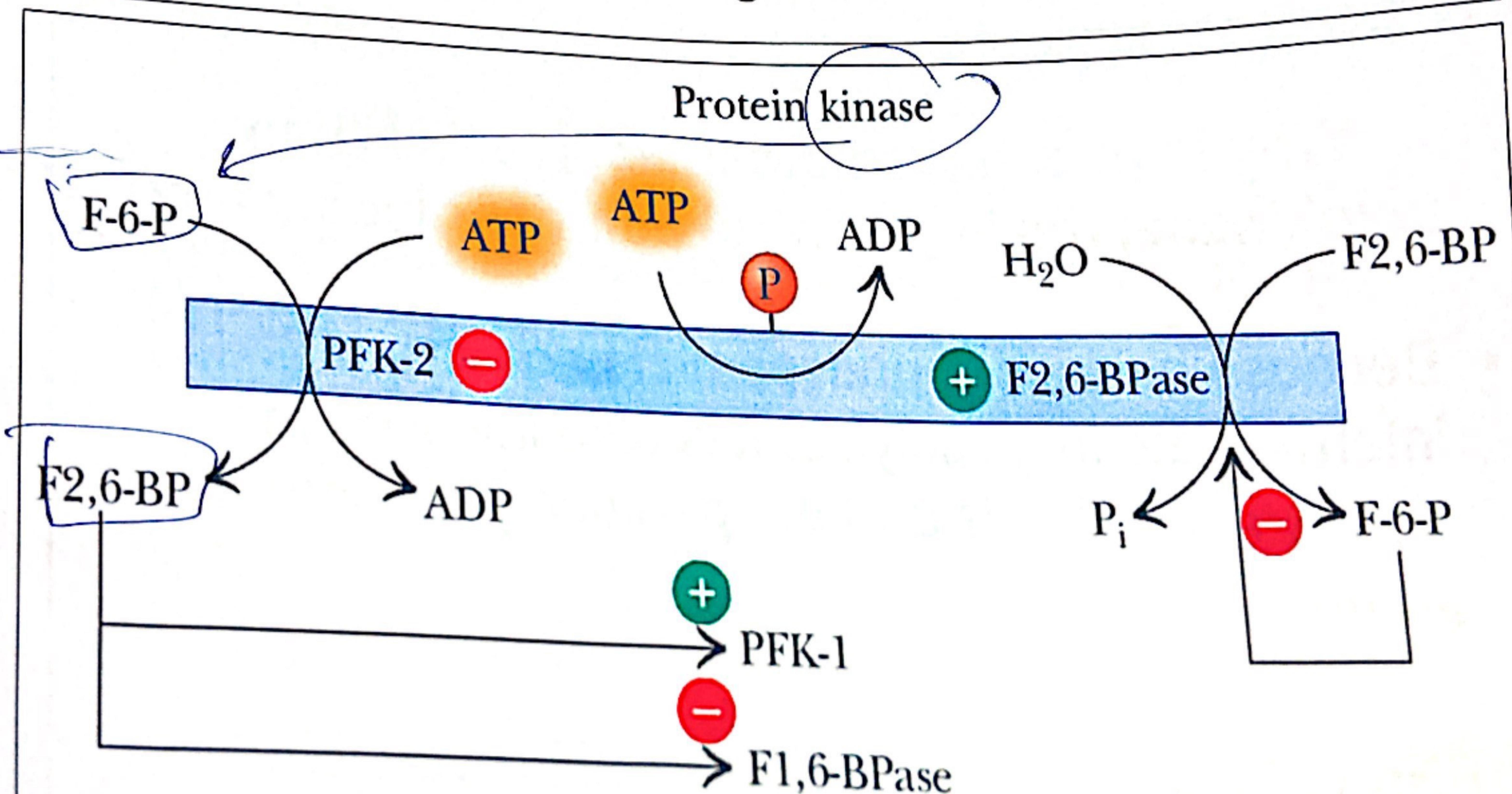
# Phosphofructokinase (PFK) in glycolysis

- PFK-1 activated by:
- Fructose-2,6-bisphosphate (F-2,6-P<sub>2</sub>)



F-2,6-P<sub>2</sub>

- Activates PFK-1 by increasing its affinity for fructose-6-phosphate and **diminishing the inhibitory effect of ATP**.



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- The formation and breakdown of fructose-2,6-bisphosphate (F2,6P) are catalyzed by two enzyme activities on the same protein:
- These two enzyme activities are controlled by a phosphorylation/ dephosphorylation mechanism. Phosphorylation activates the \_\_\_\_\_

## Group Transfer Reactions

**Table 18.2**

**Group-Transfer Reactions in the Pentose Phosphate Pathway**

	Reactant	Enzyme	Products
Two-carbon shift	$C_5 + C_5$	Transketolase ↔ Transaldolase	$C_7 + C_3$
Three-carbon shift	$C_7 + C_3$	↔ Transketolase	$C_6 + C_4$
Four-carbon shift reaction	$C_5 + C_4$ $3C_5$	↔ ↔	$C_6 + C_3$ $2C_6 + C_3$

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\* Once ribulose 5 phosphate is produced the remaining carbon, with the shuffling of carbons between sugars having 7C, 6C, 5C, 3C, 4C

F6P, G3P give  $\approx 40\%$

## Control of the Pentose Phosphate Pathway

Non-shuffling reactions are catalyzed by:

**Transketolase** for the transfer of two-carbon units

**Transaldolase** for the transfer of three-carbon units

The PPP is maintained by:

G6-phosphate (G6P) can be channeled into either the pentose phosphate pathway or the glycolysis, if ATP is needed

Channelling into the pentose phosphate pathway, if

Ribose 5 phosphate are needed