Biochemistry Team 435

جامعة الملك سعود
King Saud University

MAJOR METABOLIC PATHWAYS OF GLUCOSE

- **Color coding:**
  - Very important
  - Extra information

"STOP WISHING START DOING"

RECALL

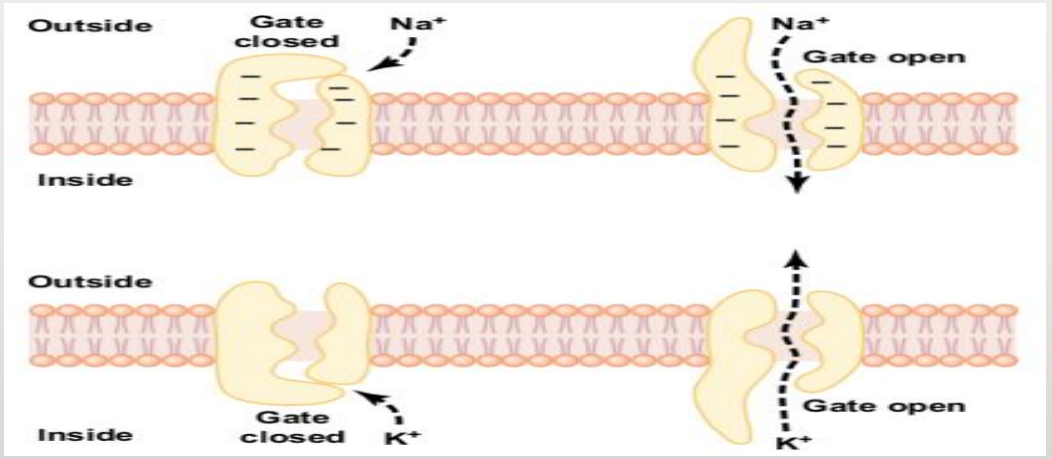
٣ سلايدات من تيم الفسيولوجي ستساعدكم في فهم بعض المفاهيم في المحاضرة وفي الربط ☺

435 Biochemistry Team

Transport Through The Cell Membrane

- **Cell membrane is selectively permeable .** (النفاذية الاختيارية)
- **Substances that pass through the protein** ⟶
  water – soluble substances (ions , glucose).
- **Directly through the lipid bilayer** ⟶
  fat – soluble substance (O_2 ,CO_2 , N_2 , alcohol).

All substances enter into the cell either by **proteins** or by **lipid bilayer**



an example of how protein works as a channel for ions

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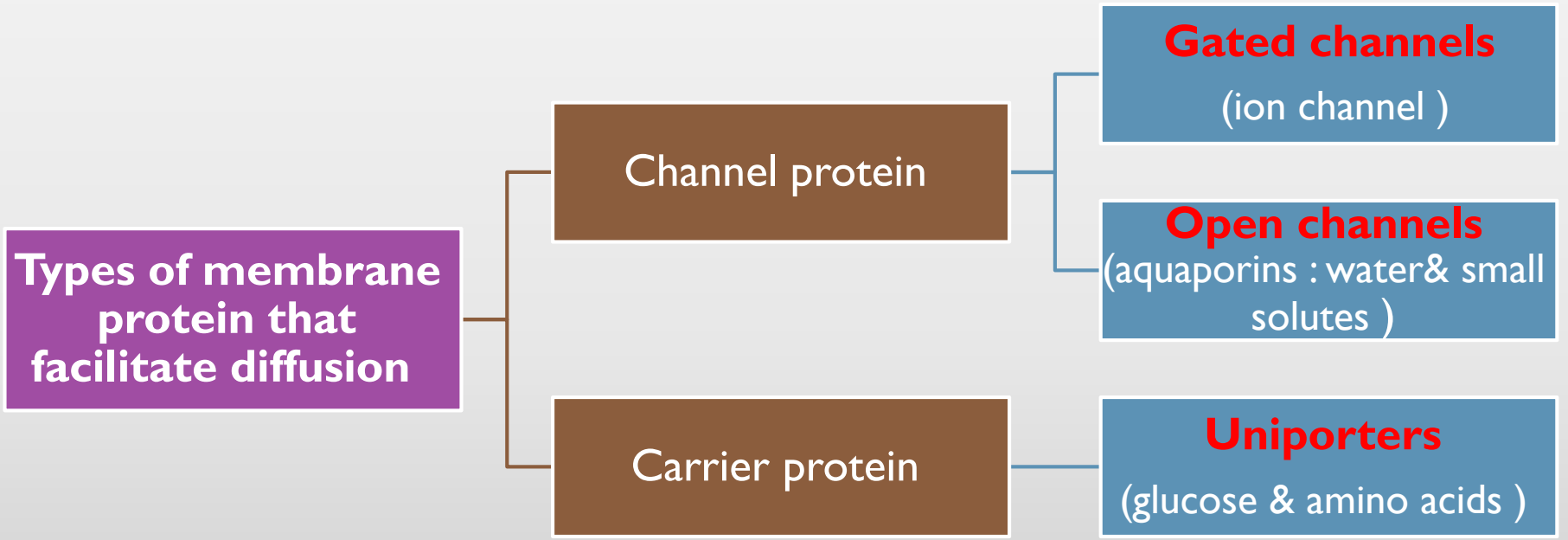
Passive Transport (Facilitated diffusion)

Facilitated diffusion :

- **Carrier mediated transport down an electrochemical gradient.**



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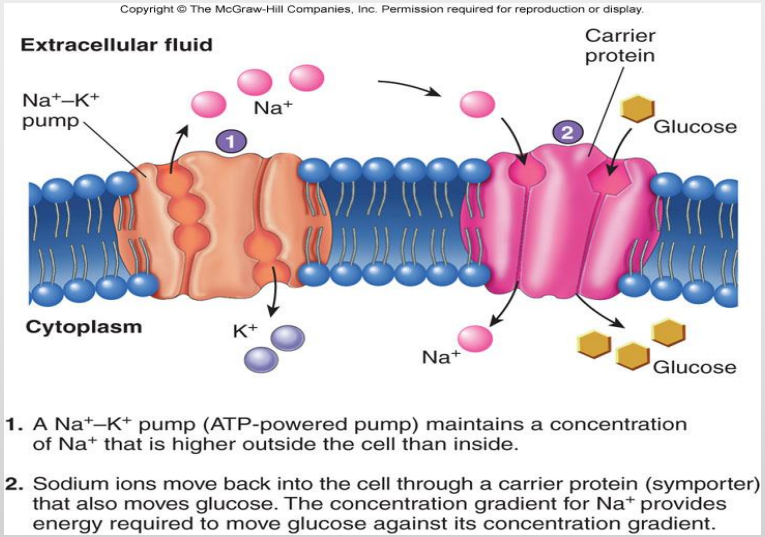
Active Transport

❖ Co-transport:

- All solutes move **in the same direction** " inside cell".
- Na+ - glucose Co-transport.
- Na + - amino acid Co-transport.

in the intestinal tract & kidney.



1. A Na^+–K^+ pump (ATP-powered pump) maintains a concentration of Na^+ that is higher outside the cell than inside.
2. Sodium ions move back into the cell through a carrier protein (symporter) that also moves glucose. The concentration gradient for Na^+ provides energy required to move glucose against its concentration gradient.

❖ Counter transport:

- Na+ is **moving to the interior causing other substance to move out.**
- Ca^{+2} / Na^+exchanger (present in many cell membranes)
- Na + / H + exchange in the kidney.

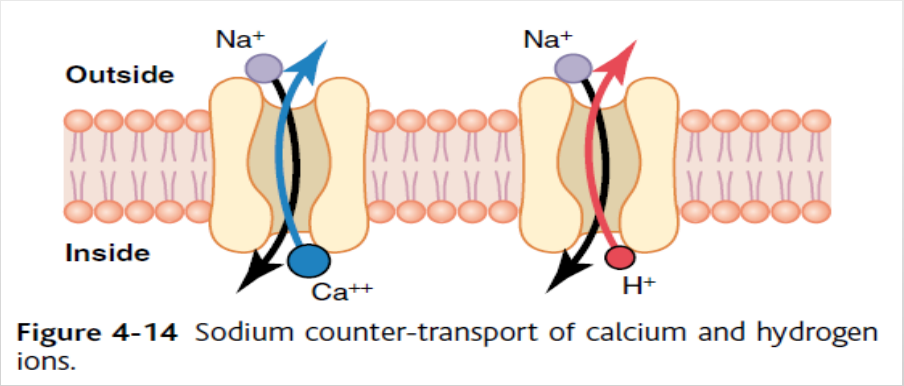


Figure 4-14 Sodium counter-transport of calcium and hydrogen ions.

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OBJECTIVES:

By the end of the first half of the lecture, students are expected to:

- Define a metabolic pathway.
- Define reactions, and rate limiting steps in a pathway
- Determine different regulatory mechanisms for
- metabolic pathways
- Describe the general metabolic pathways for glucose
- (production and utilization)
- briefly describe the glycogen metabolic pathway and
- HMP
- Recognize the mechanisms of glucose transport

Metabolic pathways

Definition

A series steps found in biochemical reactions that help convert molecules and substrates into different and more readily usable materials.

Site:

- Cellular (tissue)
-Subcellular

Regulatory mechanism(s) of metabolic pathways including:

1- Rapid short-term
-Covalent modification
-Allosteric

2- Slow long-term
-Induction\repression

Metabolic Pathways of Glucose

Production

Glycogenolysis
Catabloic

- Degradation of glycogen into glucose
- Mainly liver and muscle, Cytosol

Gluconeogenesis
Anabolic

Note : Producing of glucose from non-carbohydrates sources
e.g. : amino acids, glycerol & lactate

Hexose interconversion

Note : converting of other hexoses into glucose

Utilization

HMP/PPP
Catabolic

1- Important source for NADPH
Which is used in reductive syntheses.

2- Source for metabolically active ribose
Which is used for production of nucleotides:

- For nucleic acids.
- For co-enzymes.

Hexose interconversion

Note : Converting glucose into other hexoses

Glycolysis
catabolic

Krebs cycle

Glycogenesis
Anabolic

- Synthesis of glycogen from glucose
- Mainly liver and muscle, Cytosol

Catabolic cycles	Anabolic cycles
Glycolysis (Mainly) Krebs (Mainly) Glycogenolysis HMP	Gluconeogenesis Glycogenesis

Glucose ⟵ Glycogenolysis
Glycogen ⟵ Glycogenesis

Hexose Monophosphate Pathway (HMP) or Pentose Phosphate Pathway (PPP)

1- Important source for **NADPH** Which is used in reductive syntheses.

2- Source for metabolically active ribose
Which is used for production of nucleotides:

- For nucleic acids.
- For co-enzymes.

Glucose Transport

Na+-Monosaccharide Cotransporter

- Against concentration gradient
- Energy dependent
- Carrier-mediated
- Coupled to Na+ transport
- Small intestine, renal tubules & choroid plexus

Na+-Independent Facilitated Diffusion

- Down the concentration gradient
- Energy Independent
- Glucose Transporters (GLUT 1-14)

- الجلوكوز لا يستطيع أن ينتشر خلال الخلية , لأنه مركب هايدروفيلك \ محب للماء .
- لذلك فهو يحتاج إلى طريقة أخرى , فإما أن يدخل مع الصوديوم عن طريق الكو ترانسبورت الذي سبق أن تعرفنا عليه بالفسيولوجي وموجود في بدايه العرض ☺
- أو أنه يدخل عن كارير بروتينز خاصة به بطريقة الفاسيليتد دفيوجن والتي أيضا سبق التعرف عليها بالفسيولوجي وموجود في بدايه العرض ☺

Note : GLUT-4 is insulin sensitive, because it needs insulin to work.

Glucose transporters (Tissue-specific expression pattern)		
GLUT-1	Glucose uptake from blood	RBCs and brain
GLUT-2	Blood & cells (either direction)	Liver, kidney & pancreas
GLUT-3	Glucose uptake from blood	Neurons
GLUT-4	Glucose uptake from blood	Adipose tissue & skeletal muscle
GLUT-5	Fructose transport (it prefers fructose more than glucose)	Small intestine & testes
GLUT-7	-	Liver (ER-membrane)

phosphorylation

Phosphorylation:

(metabolic reaction that adds phosphate group to organic molecule)

you basically add one phosphate group and that's all.

Phosphorylation	
Oxidative	Substrate-level
Only in mitochondria	In mitochondria or cytosol
The formation of high-energy phosphate bonds by phosphorylation of ADP to ATP, coupled to the transfer of electrons from the reduced coenzymes to molecular oxygen via the electronic transport chain.	The formation of high-energy phosphate bonds by phosphorylation of ADP to ATP, coupled to the cleavage of high-energy metabolic intermediate.

Notes:

#In phosphorylation we change ADP →ATP.

#In oxidative phosphorylation we add phosphate group and transfer electrons(from reduced coenzymes to oxygen) in ETC.

#In substrate level phosphorylation you can change ADP→ATP or GDP→GTP).

Overview of glycolysis

Glycolysis

(**major pathway for glucose oxidation**=تكسير الجلوكوز)

Aerobically

Oxygen, mitochondria

Produces 8 ATP

E.g. Skeletal muscles

Anaerobically

No oxygen ,or no mitochondria

Produces 2 ATP

E.g. Red Blood Cells(RBC)

Skeletal muscles

Notes:

#RBCs always use Anaerobic glycolysis because it doesn't have mitochondria.

#Aerobic glycolysis always need oxygen and intact mitochondria(functioning ,not damaged)

#glycolysis is mainly catabolic but has some anabolic so it's called amphibolic

Regulation of glycolysis

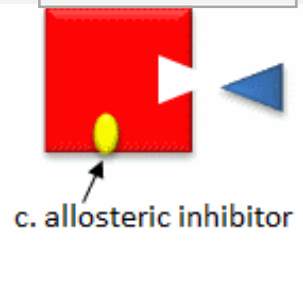
Enzymes that regulate glycolysis (enzymes of irreversible steps)	
Glucokinase/Hexokinase	Step 1
PFK-1 (phospho-fructo kinase-1)	Step 3 *most important
Pyruvate kinase	Step 10 *Deficiency of it causes hemolytic anemia

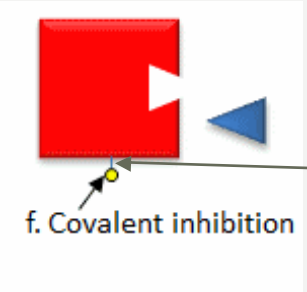
Notes:
#In the exam if they ask about the regulatory enzyme(or rate limiting enzyme) it is **PFK-1**(doctor's note).
#rate limiting step = irreversible step = regulatory step.
#Glucokinase only in hepatocyte(liver).Hexokinase in the rest of the body.
#PFK-1 is activated by AMP and inhibited by ATP.

Regulation of glycolysis

Mechanisms regulate glycolysis

- Fast (short-term)
  - Allosteric
  - Covalent modification
- Slow(long-term) Induction/Repression By hormones.





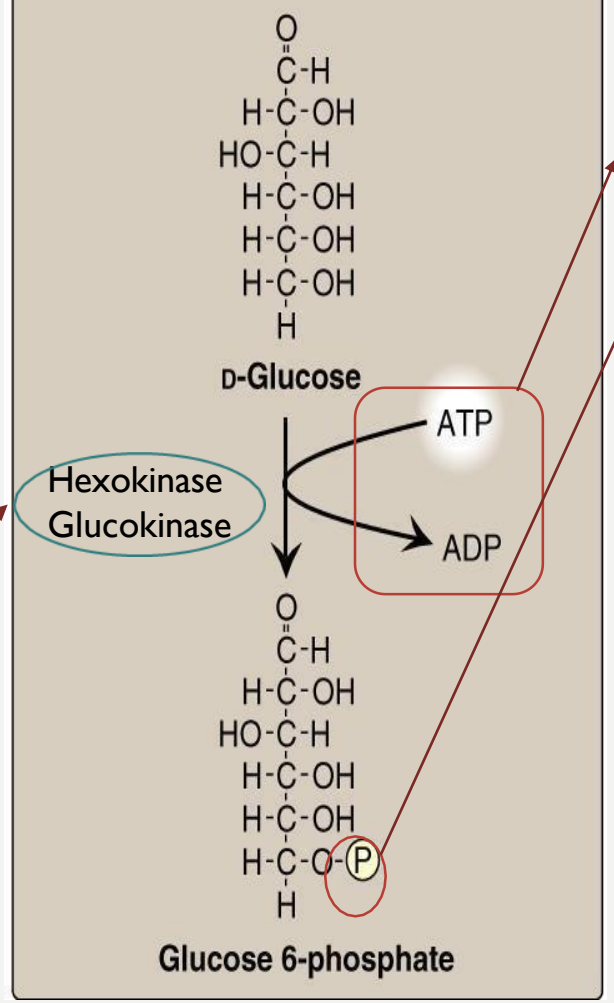
E.g. of allosteric enzymes:
PFK-1,
Hexokinase,
pyruvate kinase.

E.g.
- **Insulin** induce(**activate**) PFK-1,glucokinase/hexokinase ,pyruvate kinase.
- **Glucagon** repress(**reduce**) PFK-1,glucokinase/hexokinase ,pyruvate kinase.

Recall:
#allosteric regulation: when the molecule bind to the enzyme in the allosteric site(inactive site) and inhibit substrate to bind to active site of that enzyme.

Aerobic Glycolysis 1&2

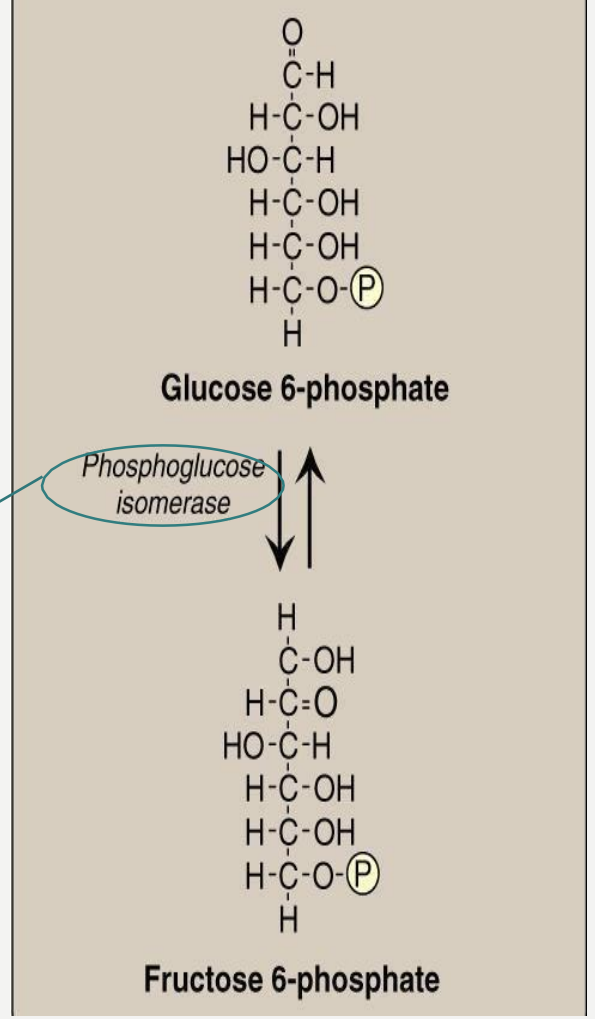
Step 1



- **Hexokinase** → most tissues
- **Glucokinase** → hepatocytes (liver)

Phosphorylation of glucose is the process of adding a (p) group derived from ATP to the molecule **(1st ATP consumed)**

Step 2



This enzyme isomerize or (transform) glucose 6-phosphate to fructose 6-phosphate

Recall:

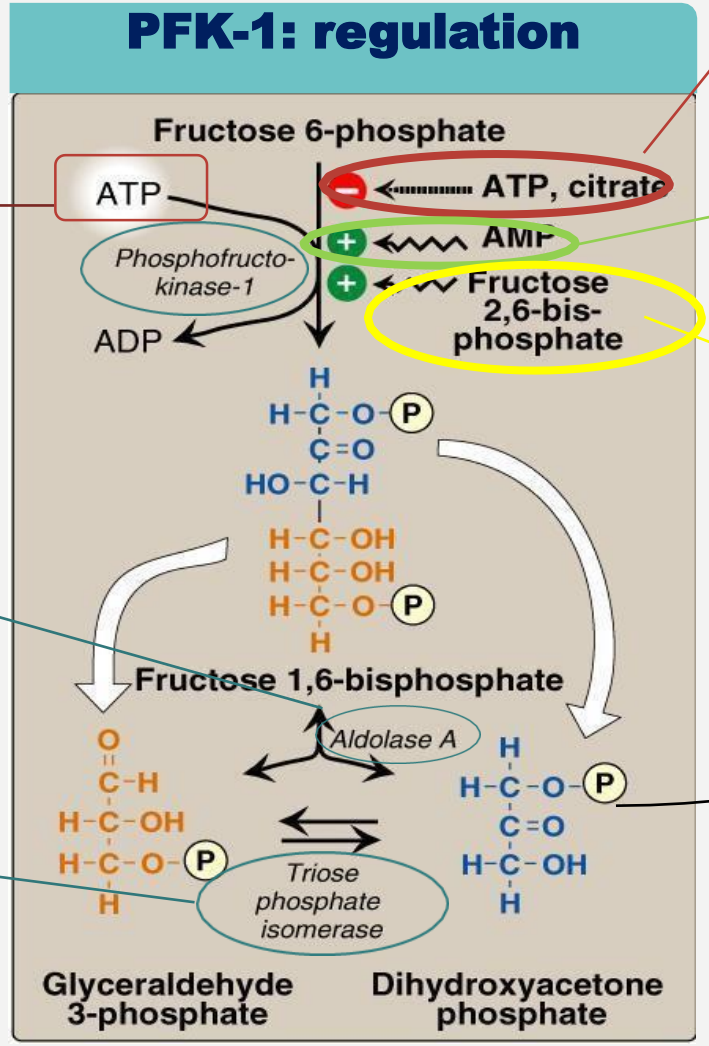
- في محاضرة الكاربوهيدرايتس قلنا أن الفركتوز هو أيزومر للجلوكوز , وكانو يختلفون بالمجموعه الوظيفية .
- الجلوكوز كان يحتوي على مجموعة الدهيد و الفركتوز كان يحتوي على مجموعة كيتون .
- ماهو نوع الايزمرزيشن هنا ياشاطرين؟

↓ irreversible ↓↑ revesible

Aerobic Glycolysis 3-5

PFK-1: is the rate-limiting regulatory enzyme

2nd ATP is consumed
And the (p) group is added to F6P molecule t



Pfk-1 is inhibited allosterically by high levels of ATP & citrate

Pfk-1 is activated allosterically by high levels of AMP

Dihydroxyaceton phosphate is used for synthesis of lipid. So this is the anabolic feature of glycolysis

A) Most potent activator of PFK-1
B) Is an inhibitor of fructose 1,6-biphosphatase, an enzyme of gluconeogenesis!

- This enzyme cleaves fructose 1,6-biphosphate to :
- glyceraldehyde 3-phosphate (GAP) & dihydroxyacetone phosphate (DHAP) (3 C each)

- GAP is the only molecule that continues in the glycolytic pathway.
- The enzyme triose phosphate isomerase (TIM) recognize DHAP to GAP so it can continue in the glycolytic pathway

#Note :
the first 5 reactions of glycolysis correspond to an energy investment phase in which the phosphorylated forms of intermediates are synthesized at the expense of 2 ATP

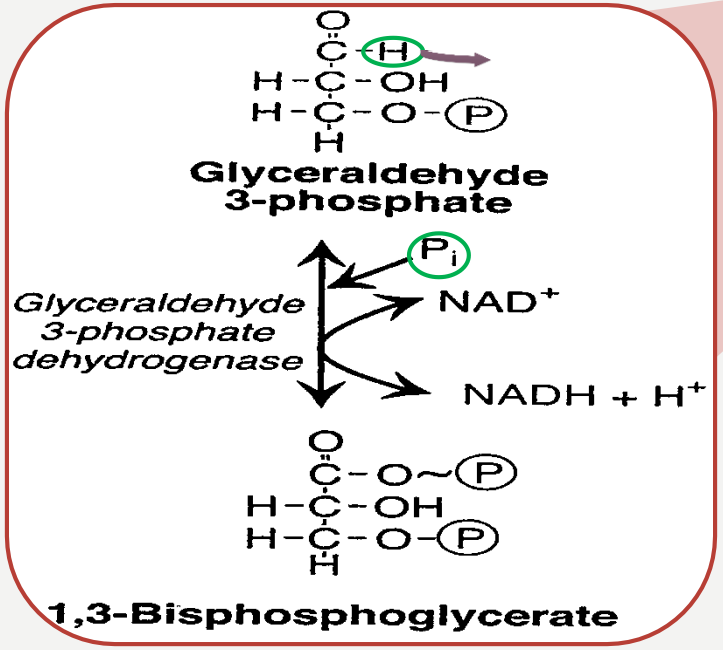
Aerobic glycolysis 6-10

6th step

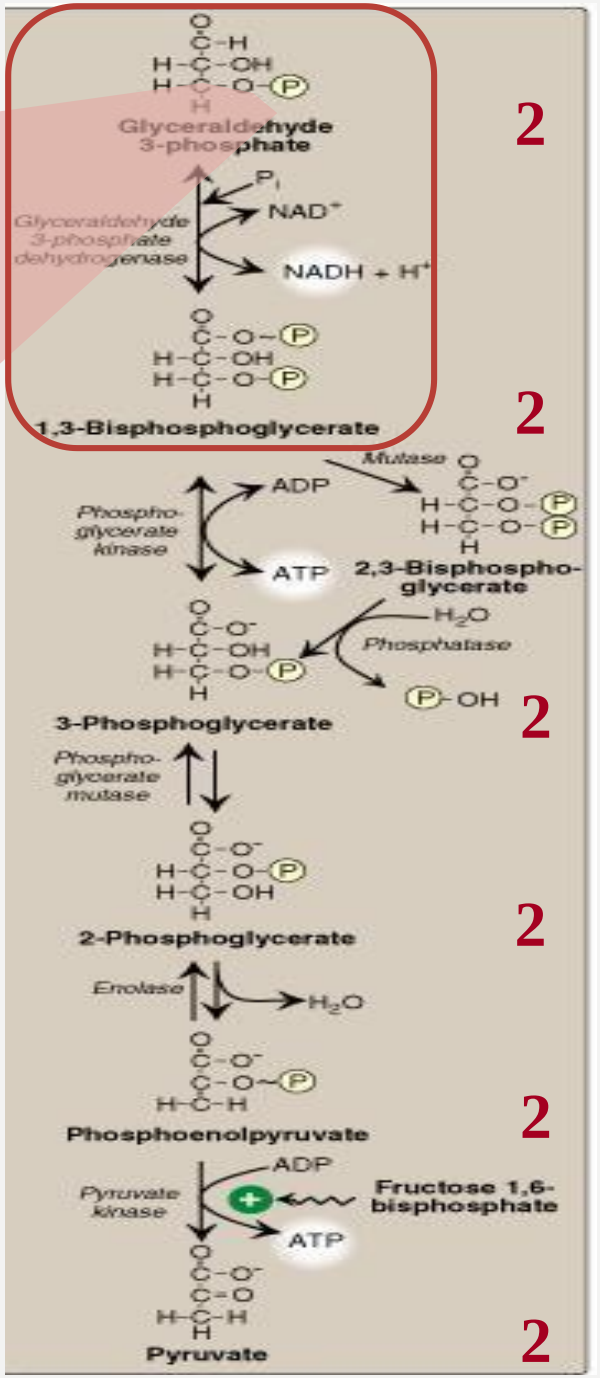
- Glyceraldehyde 3-phosphate is converted to 1,3-Bisphosphoglycerate (1,3 BPG) by enzyme called Glyceraldehyde 3-phosphate dehydrogenase .
- The enzyme detaches a H from Glyceraldehyde 3- phosphate (oxidising it).
- NAD+ is reduced to NADH. High-energy phosphate group attaches to carbon 1 of 1,3 BPG by the same enzyme , conserving much of energy produced by the oxidation of aldehyde group .

NOTE !

For each NADH, 3 ATP will be produced by ETC in the mitochondria i.e., 6 ATP areproduced



glyceraldehyde 3-hosphate يتحول إلى 1,3 –bisphosphoglycerate بواسطة الإنزيم glyceraldehyde 3-hosphate dehydrogenase
ينزع هذا الانزيم هيدروجين من مجموعة الألدهيد الموجودة في جلسرألدهيد ثلاثي الفوسفات (أكسدة) .
NAD+يُختزل إلى NADH عند اكتسابه الهيدروجين. كما يربط الإنزيم مجموعة الفوسفات ذات الطاقة العالية بذرة الكربون الأولى لمركب 1,3 –bisphosphoglycerate باستخدام الطاقة الناتجة عن الأكسدة ويحفظ ارتباط الفوسفات بالمركب المتبقي من الطاقة.



7th step

the enzyme Phosphoglycerate Kinase uses the energy of high-energy phosphate group to convert **ADP** into **ATP** .

Phosphoglycerate Kinase يحول الإنزيم ADP إلى ATP باستخدام طاقة مجموعة الفوسفات ذات الطاقة العالية. نحصل على جزيئين ATP نضرب في ٢ .

الفسفرة نوعان

1-Oxidative level phosphorylation

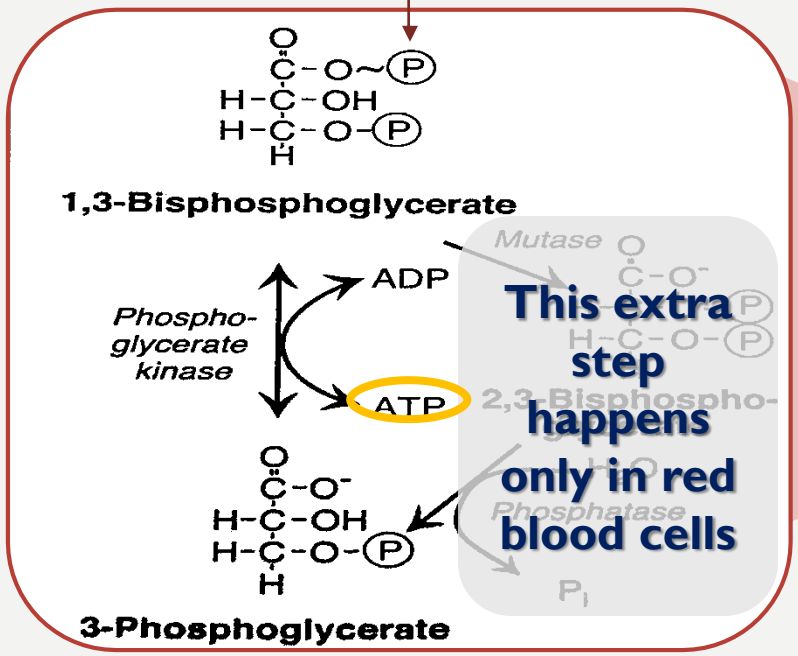
2- substrate level phosphorylation

النوع الأول يتطلب حدوثه وجود ميتوكندريا

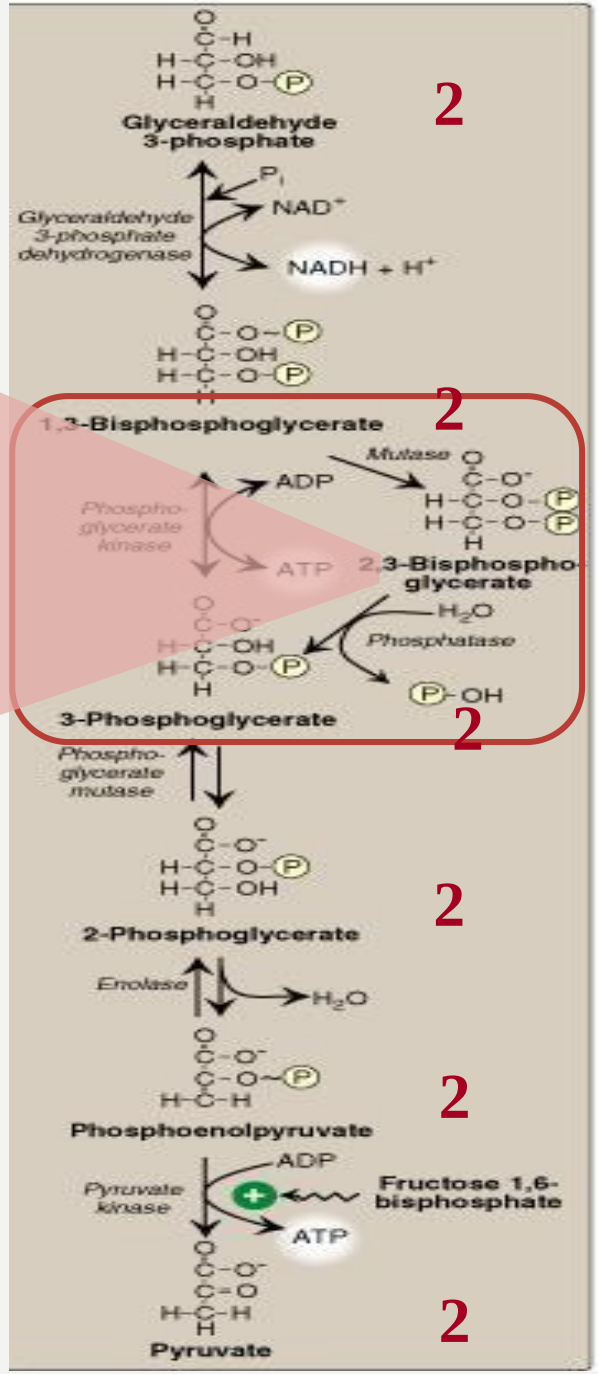
النوع الثاني يحدث في السيتوسول

(السيتوبلازم) أو الميتوكندريا ، ويتطلب فقط أن تحتوي المادة(substrate) على مجموعة فوسفات ذات طاقة عالية .

الفوسفات اختفت وراحت مع الاي دي بي علشان تكون أي تي بي

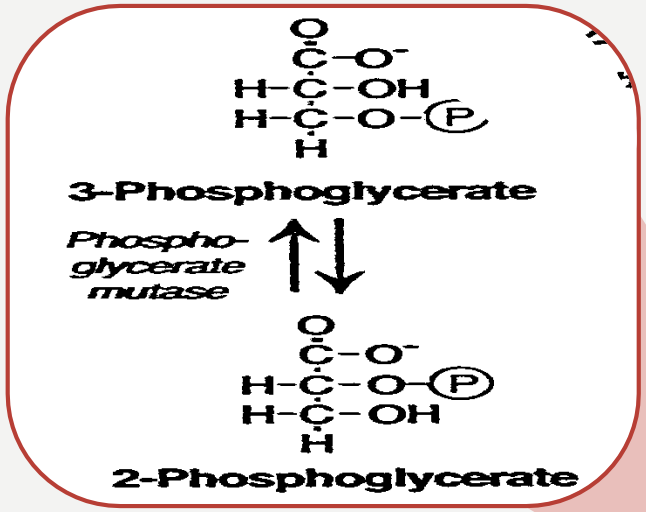


Substrate level phosphorylation



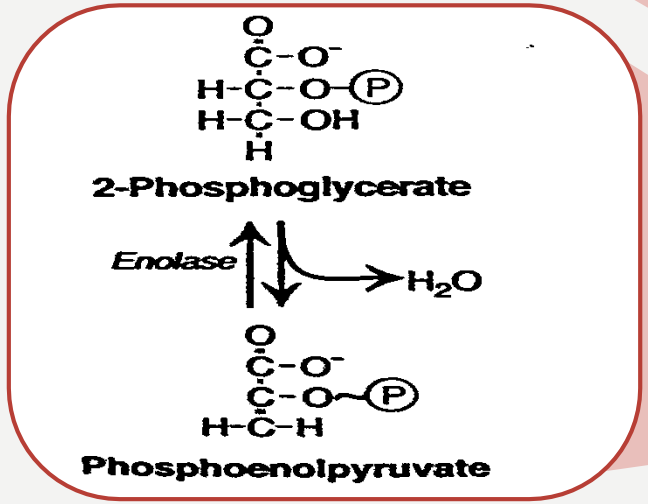
8th step

يتحول 3-phosphoglycerate
إلى 2-phosphoglycerate
بنزع مجموعة الفوسفات عالية الطاقة . كما تنتقل مجموعة الفوسفات إلى ذرة الكربون رقم ٢ هذا التفاعل يحدث بمساعدة إنزيم يسمى
Phosphoglycerate mutase

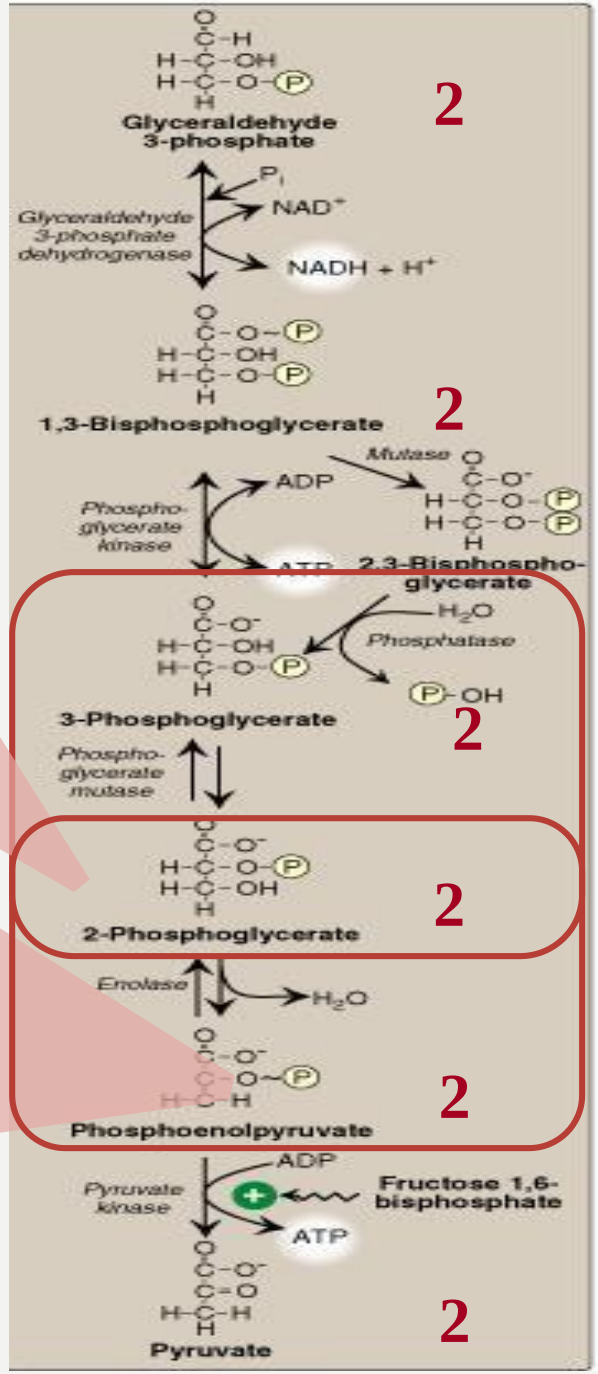


9th step

يتحول 2-phosphoglycerate
إلى(PEP) Phosphoenolpyruvate
يحدث ذلك عندما ينزع الإنزيم Enolase
جزيء ماء فتتحول مجموعة الفوسفات إلى مجموعة فوسفات ذات طاقة عالية.



* معلومات إضافية :
الاعوجاج في رابطة مجموعة الفوسفات دليل على أن مجموعة الفوسفات ذات طاقة عالية.



10th step

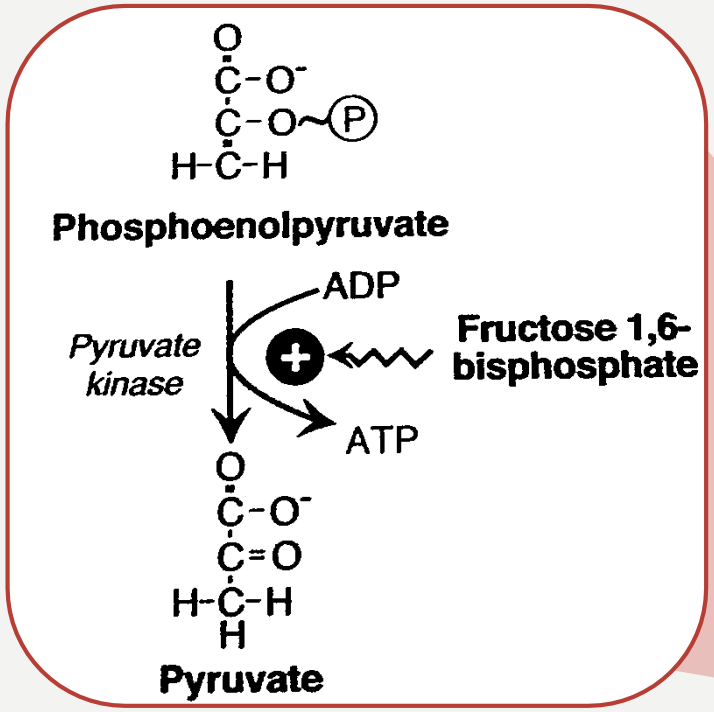
Substrate level phosphorylation

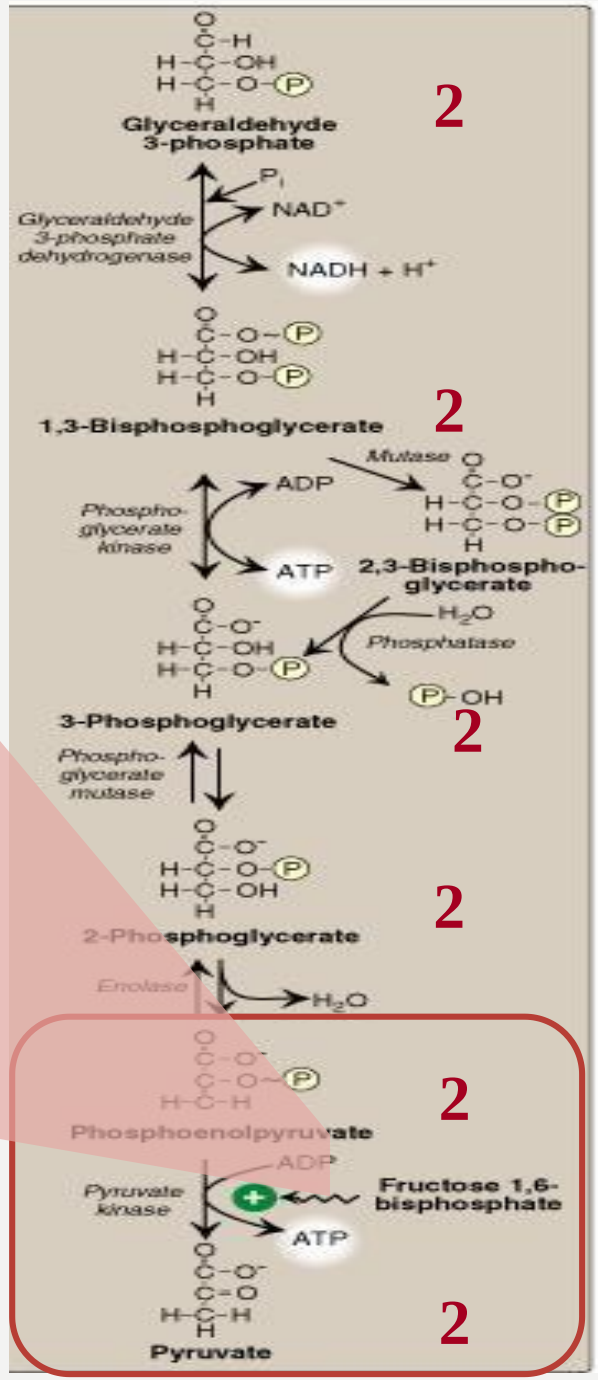
يتحول Phosphoenolpyruvate(**PEP**) إلى pyruvate
يقوم إنزيم pyruvate kinase بتكسير مجموعة الفوسفات ذات الطاقة العالية وتحويل ADP إلى ATP.

Fructose 1,6-bisphosphate **activates** the enzyme pyruvate kinase (**PK**).

Regulatory step

Irreversible reaction





Pyruvate Kinase Covalent Modification

Since the conversion of Phosphoenolpyruvate (PEP) to pyruvate is catalyzed by pyruvate kinase (PK) There's a specific mechanism that regulates this process known as [pyruvate kinase covalent modification]

What happens in this process?

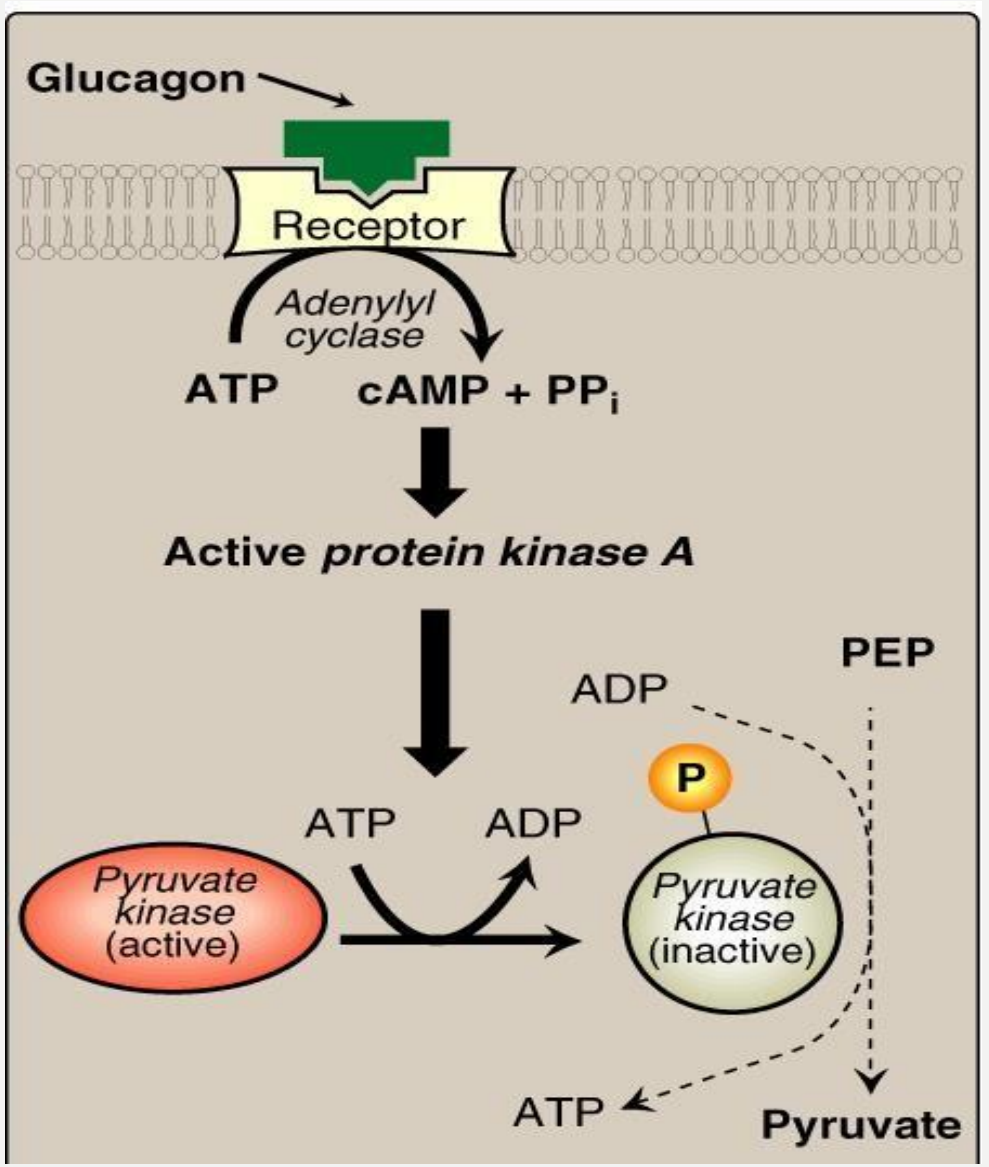
Glucagon binds to the receptor, then activates "adenylyl cyclase" which will forms "cAMP" this will activate "Active protein kinase A"

"Active protein kinase A" phosphorylate (adds a phosphate group) to "pyruvate kinase" which results in inactivating it!

so we will not get neither pyruvate nor the ATP coming with it.

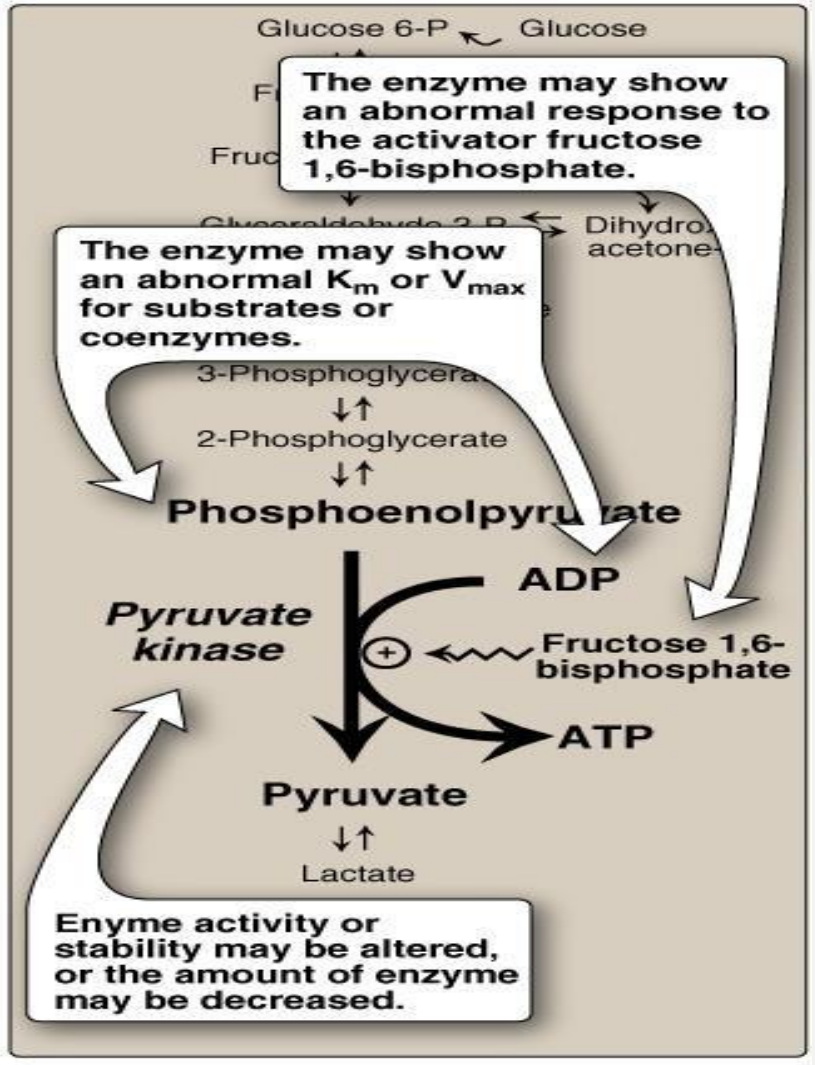
Now why glucagon inhibits glycolysis?

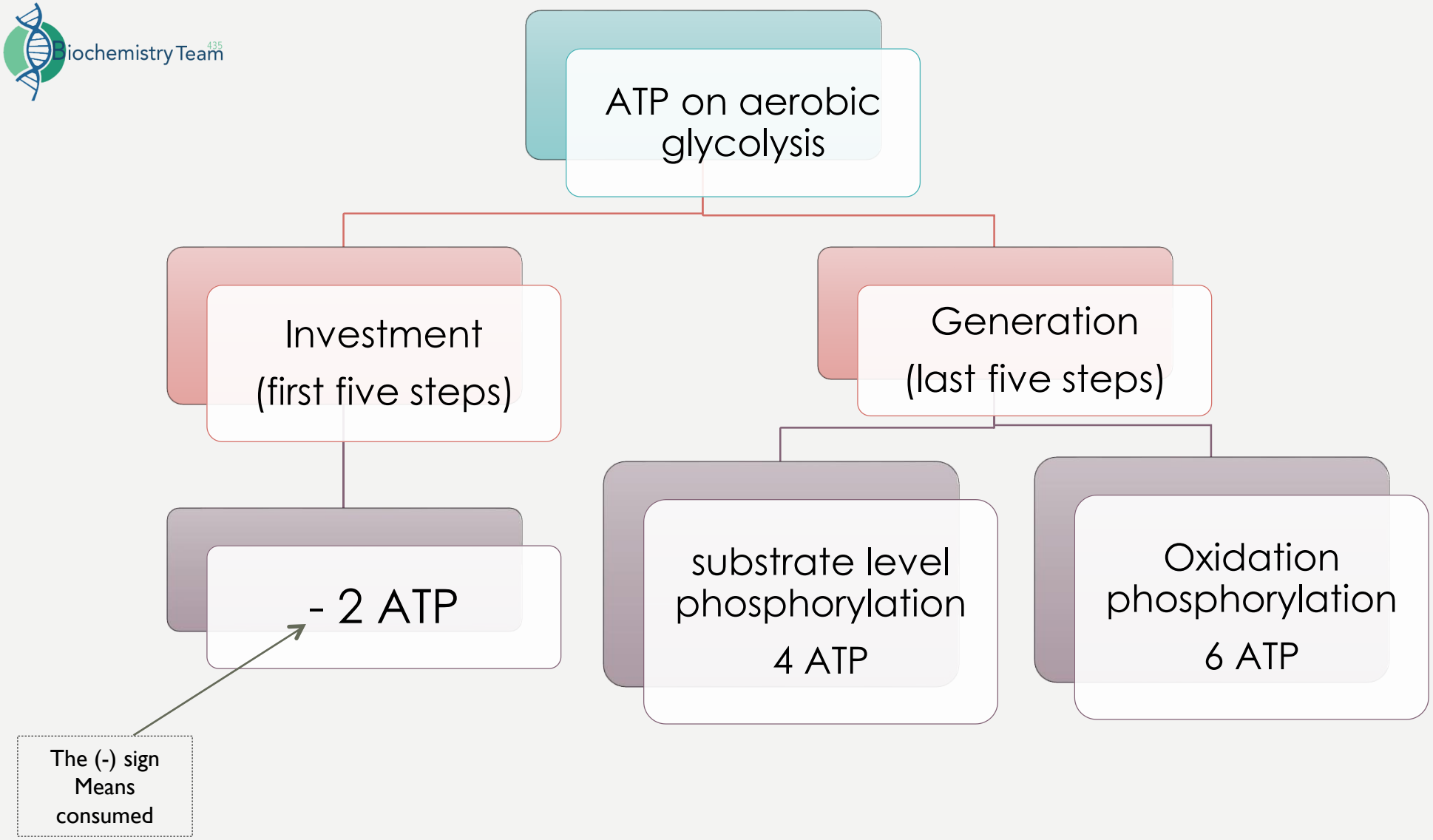
Because glycolysis is the process of breaking sugar And when pancreas releases glycogen it means blood sugar is low, so why break sugar when you need it?



Pyruvate Kinase Deficiency Hemolytic Anemia

- Mature RBCs lack mitochondria and are, therefore,
completely dependent on glycolysis for ATP production.
- ATP is required to meet the metabolic needs of RBCs and to fuel the ion pumps necessary for the maintenance of the flexible, biconcave shape that allows them to squeeze through narrow capillaries.
- The anemia observed in glycolytic enzyme deficiencies is a consequence
of the reduced rate of glycolysis, leading to decreased ATP production.
-The resulting alterations in the RBC membrane lead to changes in cell shape and, ultimately , to Phagocytosis, this hemolytic anemia caused by deficiency of pyruvate kinase can be seen in three different scenarios illustrated in the diagram →





Net = 4 ATP – 2 ATP + 6 ATP = 8 ATP

Videos

- ✓ Glycolysis in general: http://highered.mheducation.com/sites/0072507470/student_view0/chapter25/animation__how_glycolysis_works.html
- ✓ Glycolysis reactions: https://www.youtube.com/watch?v=hDq1rhUkV-g
- ✓ Pyruvate Kinase Deficiency: https://www.youtube.com/watch?v=sEoRtGtT-tU

MCQ

1-Glycolysis occurs in :
A. Mitochondria
B. Ribosomes
C. Cytosol

2-Breakdown of glucose to pyruvate and lactate is known as:
A. Glycogenosis
B. Lipolysis
C. Glycolysis

3- The net gain of ATP in conversion of glucose to pyruvate is:
A. 6
B. 8
C. 12

4-End product of aerobic glycolysis is :
A. Acetyl co A
B. Pyruvate
C. Lactate

5-Major oxidative pathway of glucose is:
A. Gluconeogenesis
B. Glycolysis
C. Krebs Cycle

6-During aerobic glycolysis, energy yield from each molecule of glucose is:
A. 2 ATP
B. 30 ATP
C. 8 ATP

7-The reaction catalyzed by the following enzyme is freely reversible:
A. Hexokinase
B. Phosphohexose isomerase
C. PFK-1

1-C
2-C
3-B
4-B
5-B
6-B
7-B

MCQ

8-Glycolysis is always anaerobic in :
A. Erythrocytes
B. Kidney
C. Liver

9-Phosphofructokinase is allosterically inhibited by:
A. fructose1,6 bisphosphate
B. Lactate
C. Citrate

10-What is the name of the enzyme that catalyzes the phosphorylation of a glucose molecule in the first step of glycolysis?
a) Phosphoglucose isomerase.
b) Phosphoglycerate mutase.
c) Pyruvate kinase.
d) Hexokinase & glucokinase.

11- In glycolytic steps 1&3 what is the source of the phosphate groups that are added to glucose & fructose 6-phosphate respectively ?
a) ATP, AMP.
b) GTP, GDP .
c) In both cases the source is ATP.
d) In both cases the source is GTP

12-In step 4 of glycolysis, why is dihydroxyacetone phosphate (DHAP) immediately converted into glyceraldehyde 3-phosphate (GAP) by the enzyme triosphophate isomerase (TIM)?
a) To prevent DHAP inhibition to glycolysis.
b) Only GAP continues in glycolytic pathway so DHAP is converted into GAP.
c) DHAP fully convert glucose into pyruvate.
d) DHAP is toxic to the cell.

8-A
9-C
10-D
11-C
12-B

MCQ

13-Active protein kinase A is activated by:

A. GTP
B. GDP
C. cATP
D. cAMP

14-Hemolytic anemia is caused by:

A. Phagocytosis of RBC
B. Alternation in RBC shape
C. Decreased ATP production
D. All above

15-A substrate linked phosphorylation is catalyzed by:

A.Hexokinase
B.Phosphofructokinase-1
C.Phosphoglycerate kinase

16-One of these pathways (produces) glucose:

A. Krebs cycle
B. Glycogenesis
C. Glycogenolysis
D. HMP/PPP

17-Synthesis of glycogen from glucose is:

A. HMP/PPP
B. Glycogenesis
C. Krebs cycle
D. Gluconeogenesis

18-Glucose transporter present in the adipose tissue and skeletal muscle:

A. GLUT-3
B. GLUT-4
C. GLUT-5
D. GLUT-7

13-D
14-D
15-C
16-C
17-B
18-B

Boys Team:

- عبدالعزيز المالكي.
- مهند الزهراني.
- أحمد الرويلي .
- محمد الصهيل .
- خالد النعيم .
- إبراهيم الشايع.
- عبد الله الشنيفي.

Girls Team:

- شهد العنزي.
- نوره الرميح .
- جواهر الحربي.
- منيره الحسن.
- ساره العنزي.
- دلال الحزيمي.
- نوره القحطاني.
- بدور جليدان.
- علا النهير.
- أفنان المالكي.
- فاطمه الدين.
- جوهره المالكي.
- خوله العريني.
- لجين السواط.
- منيال باوزير.
- رزان السبتي .
- رهف العباد .
- وضحى العتيبي.
- ساره الحسين .

شكر خاص لتيم الفسيولجي ☺

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