Chapter 18

- Gluconeogenesis — صناعة الجلوكوز
- Control Steps in Glycolysis — 1, 3, 10
- Glycogen
  - Degradation — تكسير
  - Synthesis — صناعة

Gluconeogenesis — صناعة جلوكوز

↳ In Liver Cells Only

CH17 : Glycolysis Glucose ⟶ 2 pyruvate

* Gluconeogenesis Reverse of Glycolysis 2 pyruvate ⟶ Glucose

NOT Exactly reversible

Because we have 3 irreversible Steps — غير عكسية

1, 3, 10

Reversible Step

A to B
or B to A
using the same enzyme

$$A \underset{\text{نفس الانزيم}}{\overset{E}{\rightleftharpoons}} B$$

Irreversible Step

$$A \xrightarrow{E} B$$

$$A \xleftarrow{\text{Other } E} B$$

Step 1

Glucose —(Hexokinase; ATP → ADP)→ Glucose-6-P

Step 3

Fructose 6-P —(PFK; ATP → ADP)→ Fructose 1, 6 Bisphosphate

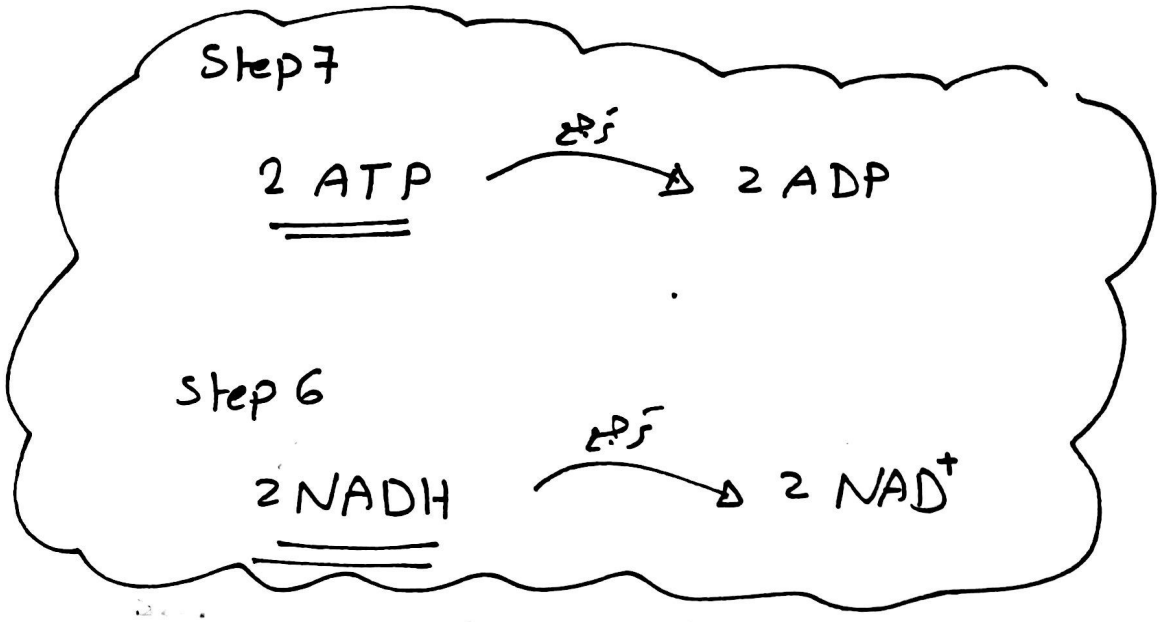
Step 10

Phosphoenol pyruvate —(pyruvate kinase; ADP → ATP)→ pyruvate

Remember: in Glycolysis

Step 1 & 3: 2 ATP → 2 ADP	
Step 6: 2 NAD+ → 2 NADH	Reversible
Step 7: 2 ADP → 2 ATP	Reversible.
Step 10: 2 ADP → 2 ATP	

واذاً مبدئياً في Gluconeogenesis



(4)

Pyruvate (3C) $\xrightarrow{CO_2,\ 2ATP}$ Oxaloacetate (4C) $\xrightarrow{CO_2,\ 2GTP}$ PEP (3C)

Pyruvate Carboxylase

Need 2 ATP, Mg^{+2}, Biotin

because it is 2 pyruvate

activation / control

↑ Acetyl-CoA

Cofactors

GTP → ATP

Phospho Enol Pyruvate Carboxy-Kinase

PEPCK

found in Mitochodria & Cytosole

* GTP: Guanosine-Tri-phosphate

* these reactions have small ΔG°

⇒ close to Equilibrium التوازن

⇒ Consider Law of Mass action

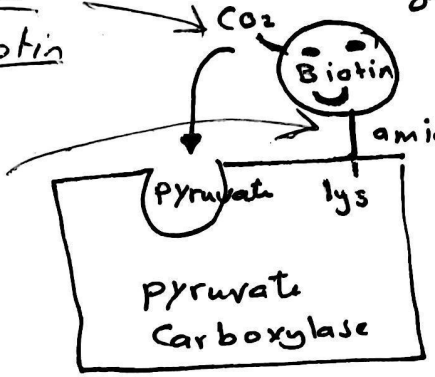
* if Oxaloacetate ↑ → to right

* if PEP ↑ → to left

* ATP used in this step to add CO_2 to biotin

Biotin is CO_2 Carrier حامل

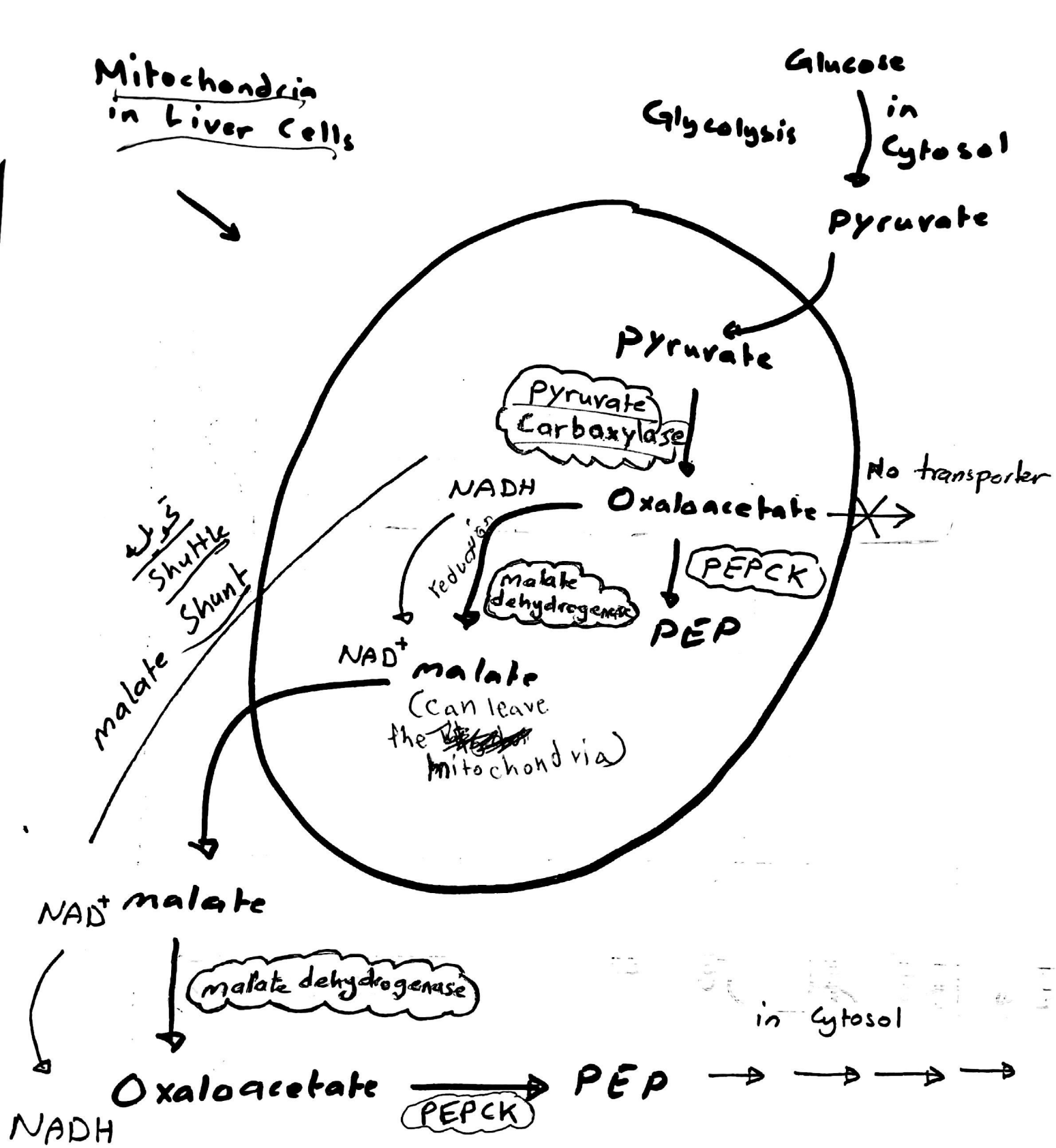
* CO_2 bind covelently to biotin by amide Bond



this step occur in Mitochodria

Because pyruvate Carboxylase found Only in Mitochondria

PEP ↑ Pyruvate



what is the aim of malate Shunt?

as you know for gluconeogenesis we need NADH in Step 6, and the Cytosol has low Concentration of NADH (low $\frac{NADH}{NAD^+}$ ratio), so we get it from Mitochodria in this way

ops 9 → 3 all are reversible
occur in Cytosol

Step 7 2 ATP ↘ 2 ADP

Step 6 2 NADH ↘ 2 NAD+

Step 3

Fructose 1,6 Bisphosphate → Fructose - 6 - P

Fructose 1,6 Bisphosphatase

↑ ATP — activation

inhibition — - AMP, - Fructose 2,6 Bisphosphate

- Site: Cytosol
- ΔG -ve — -4 Kcal/mole
غير مباشرة لصناعة ATP

- Phosphatase removes a phosphate but doesn't use it
- Kinase removes a phosphate and use it in ATP

Step 1

Glucose 6 - P → Glucose

Glucose.6.phosphatase → found only in Endoplasmic Reticulum
الشبكة الإندوبلازمية

- ΔG -ve — -3.3 Kcal/mole
غير مباشرة لصناعة ATP

General notes:-

* Gluconeogenesis take place in Mitochondria, Cytosol and ~~Endoplasmic~~ Reticulum

* Entary points الخطوة الأخيرة في الصناعة
  1. Lactate → Can be oxidized to pyruvate
  2. Amino acids → Can be converted to pyruvate or Oxaloacetate
  3. Glycerol → Can be Converted to Dihydroxyacetone

The Overall reaction of Gluconeogenesis

2 pyruvate ⟶ Glucose

2 ATP ⟶ 2 ADP

2 GTP ⟶ 2 GDP

2 ATP ⟶ 2 ADP

2 NADH ⟶ 2 NAD+

2 pyruvate + 4 ATP + 2 GTP + 2 NADH ⟶ Glucose + 4 ADP + 2 GD + 2 NAD+

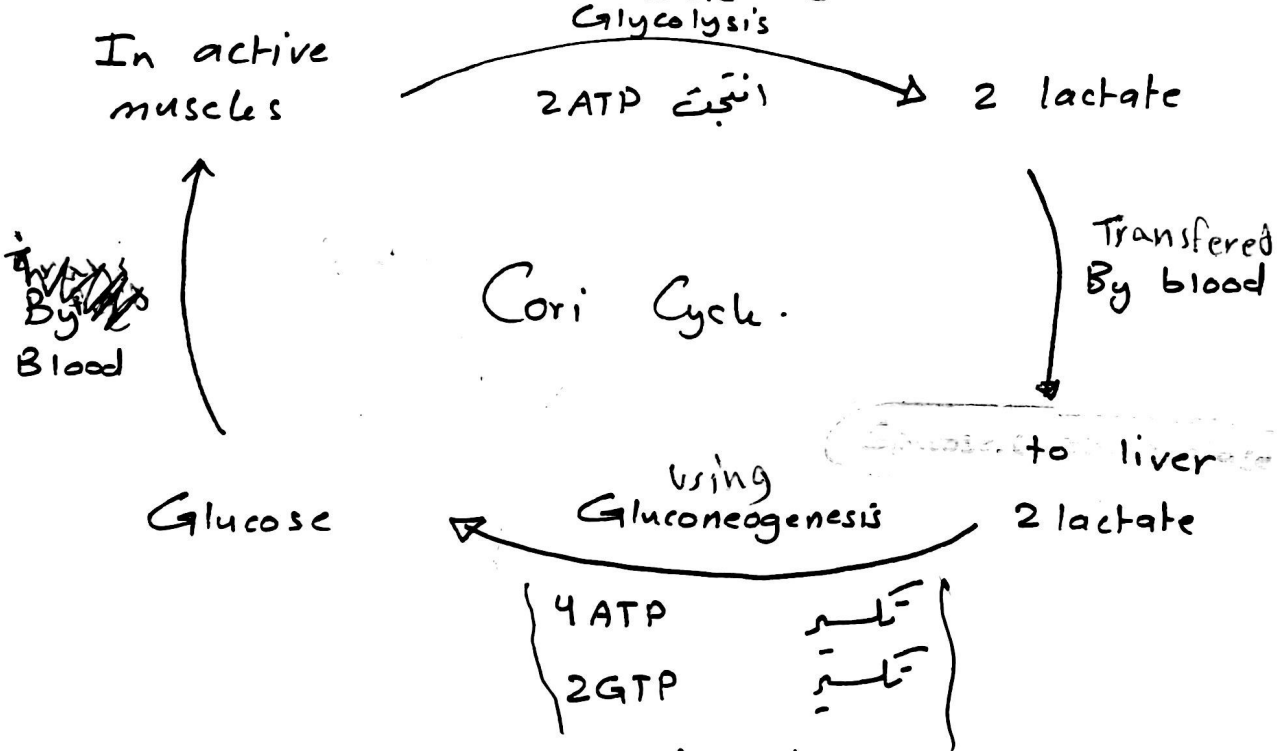
ΔG is -ve

~~Because of the Process~~ لتكوين Glucose من pyruvate

يحتاج لطاقة ولذلك يعكس ATP, GTP وينتج طاقة كبيرة

أكثر مما احتاجه ولذلك ΔG -ve

Cori Cycle



4 ATP تستهلك

2 GTP تستهلك

* this is the role of Massage

* 2 ATP تستهلك Cori Cycle كمرحلة

2 GTP وتستهلك

اذا ΔG لـ Cori Cycle -ve

Excergonic

which of the following concerning Biotin and gluconeogenesis is false?

a. Biotin is used to add CO_2 to certain intermediate in gluconeogenesis
b. CO_2 is incorporated into the glucose product
c. Biotin is capable of binding covelently to CO_2
d. Biotin helps synthesize an important precursor of phosphoenolpyruvate
e. ATP hydrolysis is required to attach CO_2 to biotin

Q: The enzyme glucose-6-phosphatase is only found in cells which have this function:-

a. Ability to utilize glucose anaerobically
b. Ability to replenish the level of glucose in the blood
c. Ability to produce lactic acid as an end product of metabolism
d. Glucose 6-phosphatase activity is found in almost all types of cells.

Q: The NADH used for the reduction reactions during gluconeogenesis usually come from this reaction

a. Glyceraldehyde 3-Ⓟ dehydrogenase
b. Malate dehydrogenase activity in the cytoplasm
c. Pyruvate decarboxylase activity in the mitochondria
d. A variety of reactions which produce NADH in the mitochondria
e. none-of-these, Since it is NAD^+ that is used in gluconeogenesis

Q: How many ATP equivalent are expended to convert 2 pyruvate to 1 glucose?

a. 2
b. 4
c. 6
d. 8

: Which of the following is true ?

a. Gluconeogenesis from pyruvate involves simple reversal of all of glycolysis reactions, except for the reactions that consumed ATP during catabolism

b. Anabolic reactions are usually the reversal of catabolic ones

c. In gluconeogenesis, the effective reversal of the glycolytic reactions of hexokinase and phosphofructokinase involve the same sugar molecules but not the exact set of substrates and products

d. all of these are true

Q : It is imposible to reverse ang Kinase reaction under physiological conditions

True False

Q: if you're running away from a bear :-

a. Both your Liver cells and leg muscles will be running glycolysis

b. Both your Liver cells and leg muscles will be running gluconeogenesis

c. your liver cells will be running gluconeogenesis and your leg muscles will be running glycolysis

d. your liver cells will be running glycolysis and your leg muscles will be running gluconeogenesis.

Step 1 Glucose $\xrightarrow[Mg^{+2}]{\text{Hexokinase}}$ Glucose-6-P

* If Glucose-6-P ↑ → inhibit Hexokinase

* Glucokinase in Liver Cells Only, NOT inhibited by Glucose 6-P

⇒ Km Glucokinase > Km Hexokinase

↓

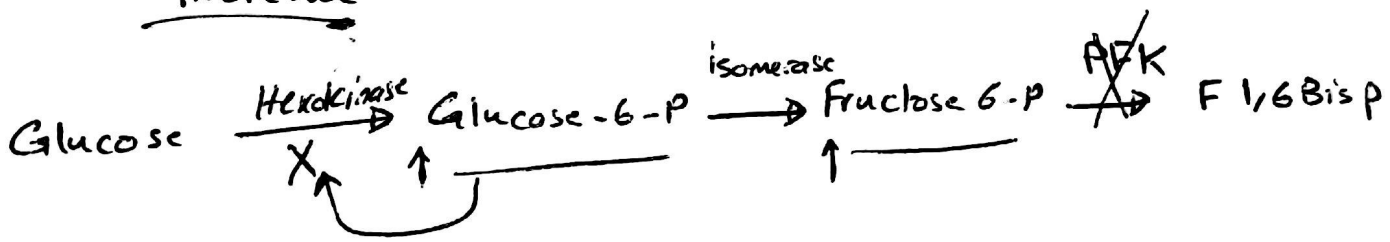
has higher affinity to glucose

* when [Glucose] is low Hexokinase will be functioning

* when [Glucose] is high Glucokinase will be functioning

So, when Glucose is low, it will not be consumed metabolized by liver.

Q: If PFK is inhibited, what happend to [Glucose-6-P] increase Or decrease



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PEP $\xrightarrow{\text{Pyruvate Kinase/Mg}^{+2}}$ Pyruvate

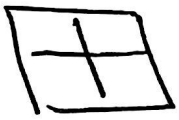
ADP $\longrightarrow$ ATP

* allosteric Control

↑ ATP
↑ Alanine
} inhibit the enzyme

* alanine is an Amino-version of pyruvate ↑ pyruvate ↑ Ala

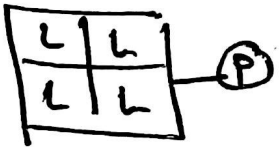
Fructose 1,6 Bisphosphate → activate this Enzyme

Pyruvate Kinase is Tetramer 

M: muscle
L: Liver
A: other tissue.

Liver isoenzyme

L_4 also has covalent Control

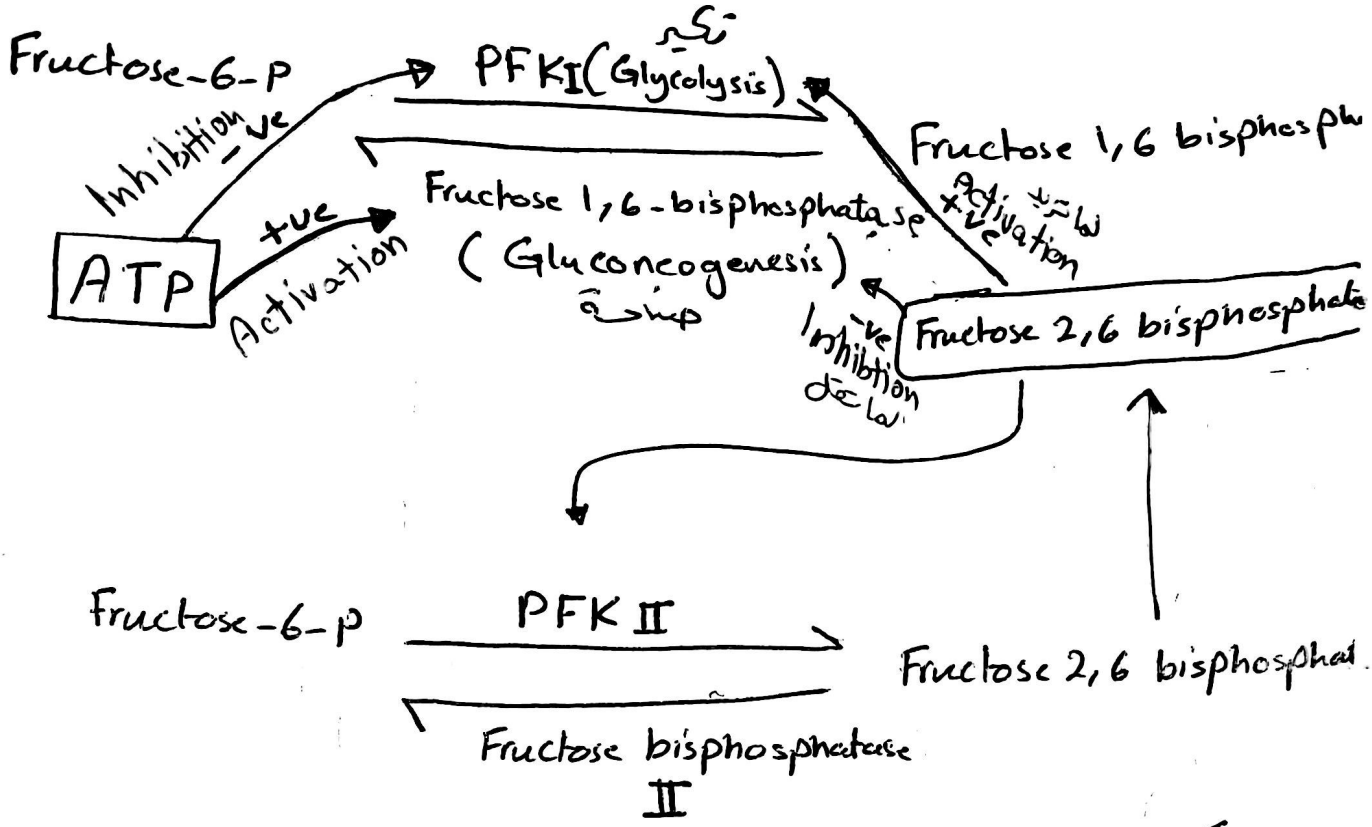


Phosphorylated form is less active.

Q: pyruvate is an allosteric inhibitor For Pyruvate Kinase

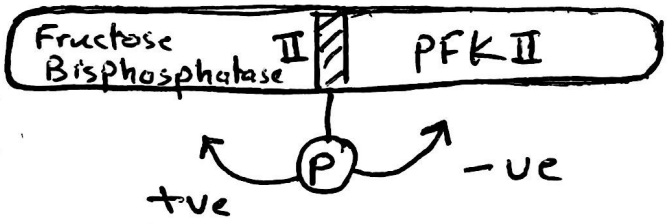
True

False



if PFK II activated → ↑ F 2,6 Bis Ⓟ → PFK I activated

if Fructose Bisphatase II activated → ↓ F 2,6 Bis Ⓟ → Fructose 1,6 Bisphosphatase activated



Q: if PFK II, Fructose bisphosphatase II complex is dephosphorylated which pathway will be activated?

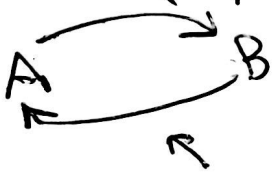
Glycolysis Or Gluconeogenesis

Types of Control

① Allosteric : any effector (rapid response) الاسرع Ex: ATCase

② Covalent : mainly phosphorylation (rapid response) Ex: Na^+-K^+ pump, Glycogen phosphorylase

③ Substrate Cycle Control : 2 opposing reactions Catalyzed by different enzymes which can be activated or inhibited separately (Rapid response)



Ex:- Glycolysis and Gluconeogenesis
- Steps 1, 3, 10

④ Genetic Control :- on Gene (DNA) of the enzyme
the amount of enzyme ↑
(Long term)

Ex:- Induction
β-galactosidase Gene.

The formation and breakdown of fructose 2,6-bisphosphate :-

a. is catalyzed by the same protein dependant upon whether it is phosphorylated or not.

b. is catalyzed by the same protein dependant allosteric regulator

c. is catalyzed by different proteins.

Q: Which of the following is not true concerning control of pyruvate kinase?

a. the phosphorylated form is less active

b. It is inhibited by ATP

c. It is activated by fructose 1,6 Bisphosphate

d. It is inhibited by low blood glucose level

e. All of these

Glycolysis

Glucose
↓ Hexokinase (ATP → ADP) ★ (1)
Glucose-6-P
⇌ Glucophospho isomerase (2)
Fructose-6-P
↓ PFK (ATP → ADP) ★ (3)
Fructose 1,6 Bis phosphate
⇌ Aldolase (4)
Dihydroxyacetone-P + Glyceraldehyde 3-P
Triose isomerase (5) (2)
⇌ Glyceraldehyde dehydrogenase (6) (2NAD+ → 2NADH)
(2) 1,3 Bis phosphoglycerate
⇌ Phosphoglycerate Kinase (7) (2ADP → 2ATP)
(2) 3-phosphoglycerate
⇌ mutase (8)
(2) 2-phosphoglycerate
⇌ Enolase (9)
(2) phosphoenol pyruvate
↓ Pyruvate Kinase (2ADP → 2ATP) ★ (10)
(2) Pyruvate

Gluconeogenesis

Glucose
↑ Glucose-6 phosphatase
Glucose-6-P
⇌ Glucophosphate isomerase
Fructose 6-P
↑ Fructose 1,6 Bis phosphatase
Fructose 1,6 Bis phosphate
⇌ Aldolase
Dihydroxyacetone + (2) Glyceraldehyde 3-P
Triose isomerase
(2NAD+ → 2NADH) ⇌ Glyceraldehyde Dehydrogenase
(2) 1,3 Bisphosphoglycerate
(2ADP → 2ATP) ⇌ phosphoglycerate Kinase
(2) 3-phosphoglycerate
⇌ mutase
(2) 2-phosphoglycerate
⇌ Enolase
(2) Phosphoenol pyruvate
PEPCK (2GDP → 2GTP, 2CO2)
(2) oxaloacetate
Pyruvate Carboxylase (2CO2, 2ATP → 2ADP)
(2) pyruvate