GLUCOSE METABOLISM: GLUCONEOGENESIS

- Very important
- Extra explanation

"HOPE IS BEING ABLE TO SEE THAT THERE IS LIGHT DESPITE ALL OF THE DARKNESS."

هذا العمل لا يغني عن المصدر الأساسي للمذاكرة

OBJECTIVES:

- The importance of gluconeogenesis as an important pathway for glucose production
- The main reactions of gluconeogenesis
- The rate-limiting enzymes of gluconeogenesis
- Gluconeogensis is an energy-consuming, anabolic pathway

OVERVIEW OF GLUCONEOGENESIS

- Gluconeogenesis is an energy-consuming, anabolic pathway

Gluconeogenesis is important to provide the body with glucose when there is no external source of glucose (during prolonged fasting or starvation)

- Occurs in Liver mainly, and in Kidney

During Overnight fast:

- 90% of gluconeogenesis occurs in liver
- 10% of gluconeogenesis occurs in Kidneys

- Gluconeogenesis occurs in both mitochondria & cytosol .

EXCEPTION! if gluconeogenesis starts by **Glycerol**, it will need only the **cytosol**

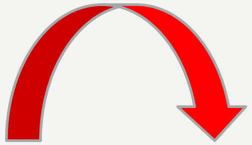
Gluconeogenic substrates

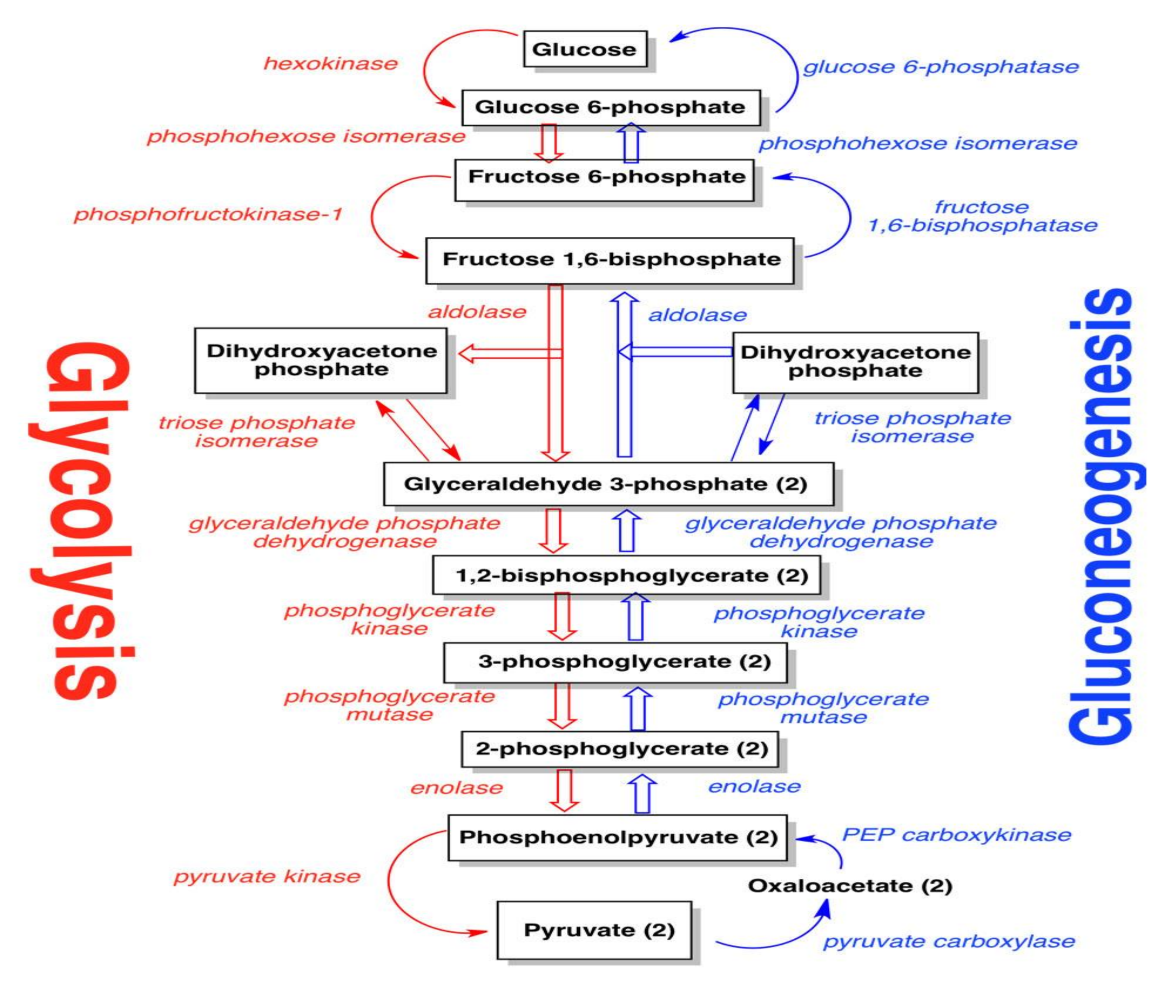
- Glycerol
- Lactate
- pyruvate
- Glucogenic amino acids

GLUCONEOGENIC PATHWAY

- **Seven** glycolytic reactions are **reversible** & are used in gluconeogenesis from lactate or pyruvate.
- **Three** glycolytic reactions are **irreversible** & must be reversed (by 4 alternate reactions) in gluconeogenesis.

Reversible 

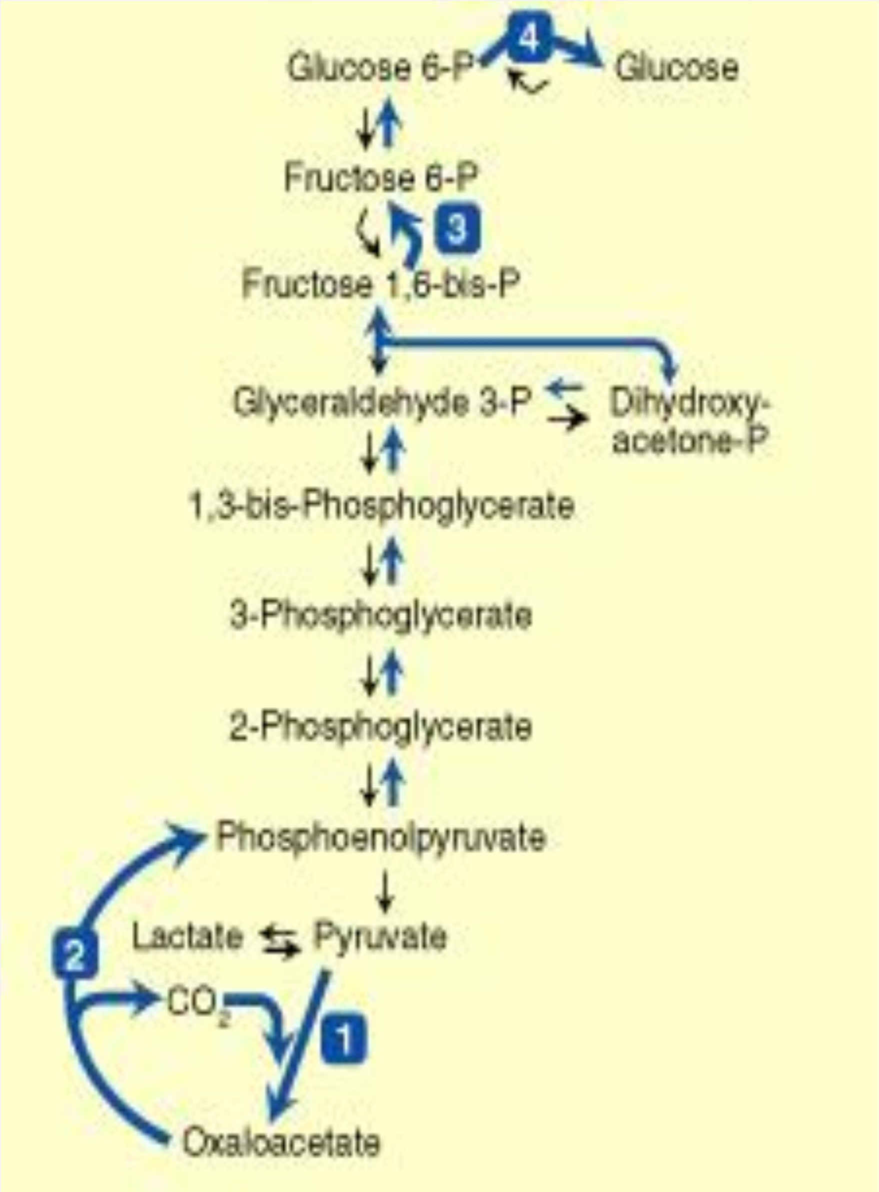
Irreversible 

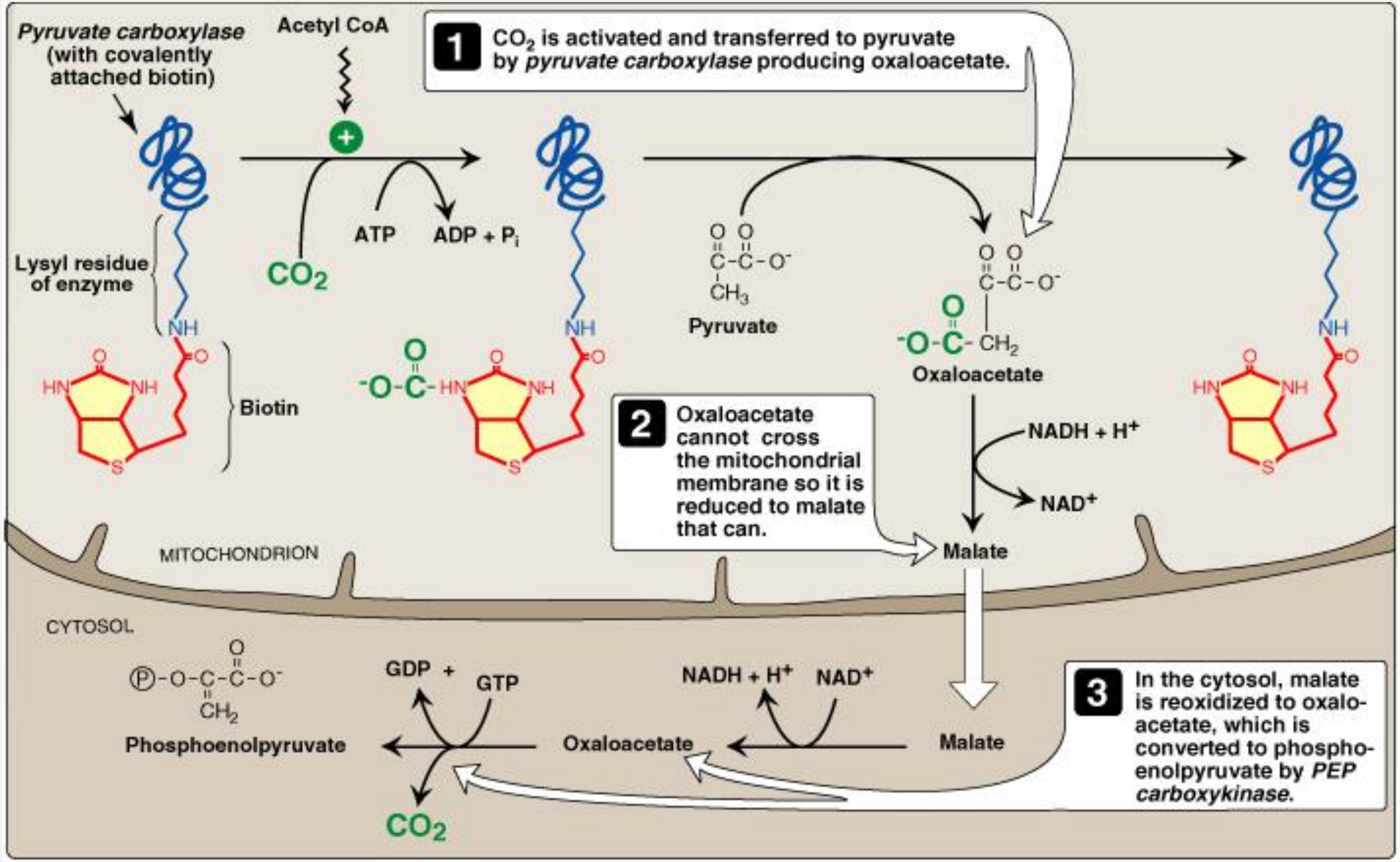


GLUCONEOGENESIS

The 4 alternate reactions in gluconeogenesis to the 3 irreversible glycolytic steps:

Glycolysis enzymes	Gluconeogenesis enzymes
Pyruvate kinase	1) Pyruvate carboxylase 2) PEP-CK
PFK-1	3) Fructose 1,6 bisphosphatase
Glucokinase	4) Glucose 6-phosphatase



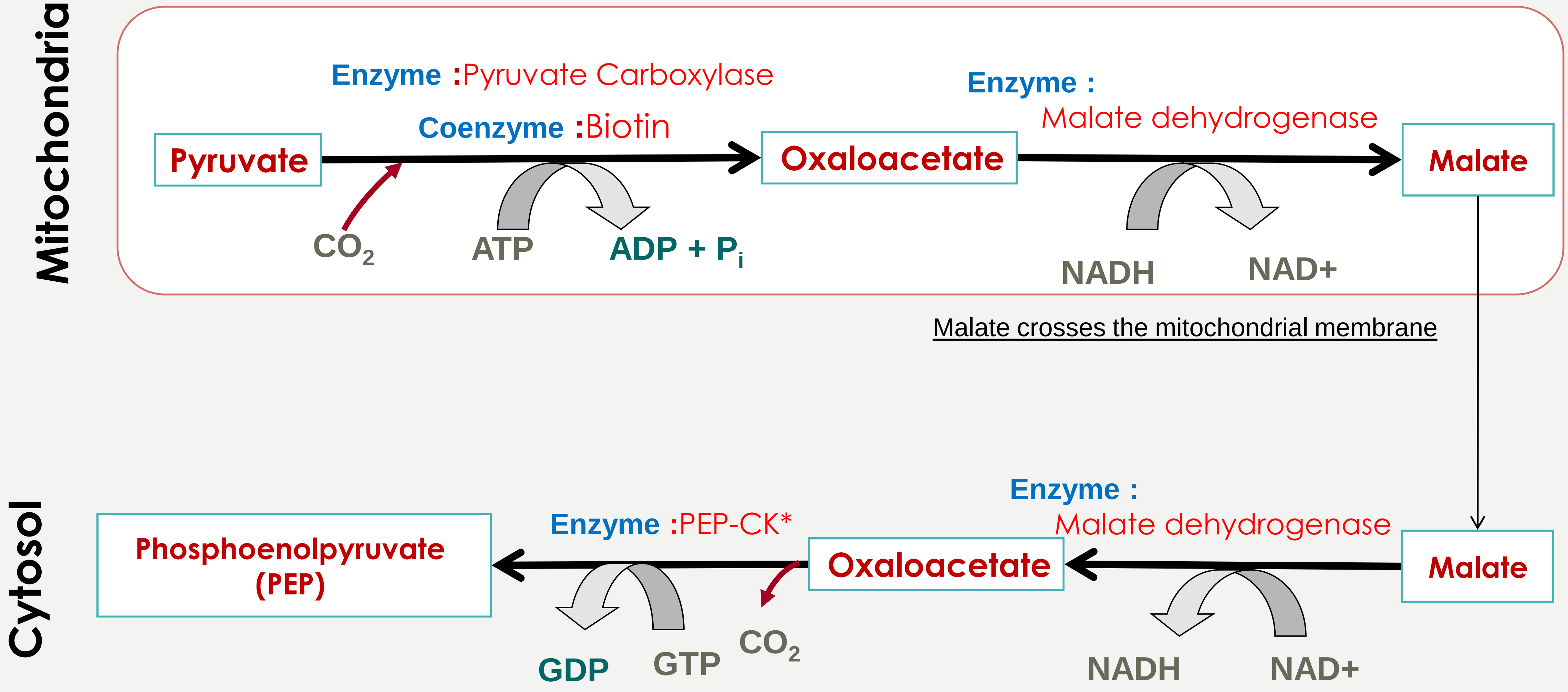


Pyruvate carboxylase (with covalently attached biotin)
Acetyl CoA
1 CO2 is activated and transferred to pyruvate by pyruvate carboxylase producing oxaloacetate.
Lysyl residue of enzyme
Biotin
CO2
ATP
ADP + Pi
Pyruvate
Oxaloacetate
NADH + H+
NAD+
2 Oxaloacetate cannot cross the mitochondrial membrane so it is reduced to malate that can.
Malate
MITOCHONDRION
CYTOSOL
Phosphoenolpyruvate
GDP +
GTP
CO2
Oxaloacetate
NADH + H+
NAD+
Malate
3 In the cytosol, malate is reoxidized to oxaloacetate, which is converted to phosphoenolpyruvate by PEP carboxykinase.

- Pyruvate Carboxylase is induced by Acetyl-CoA

During Fasting:
↑ **Acetyl-CoA (From FAO)***

***Fatty Acid Oxidation**

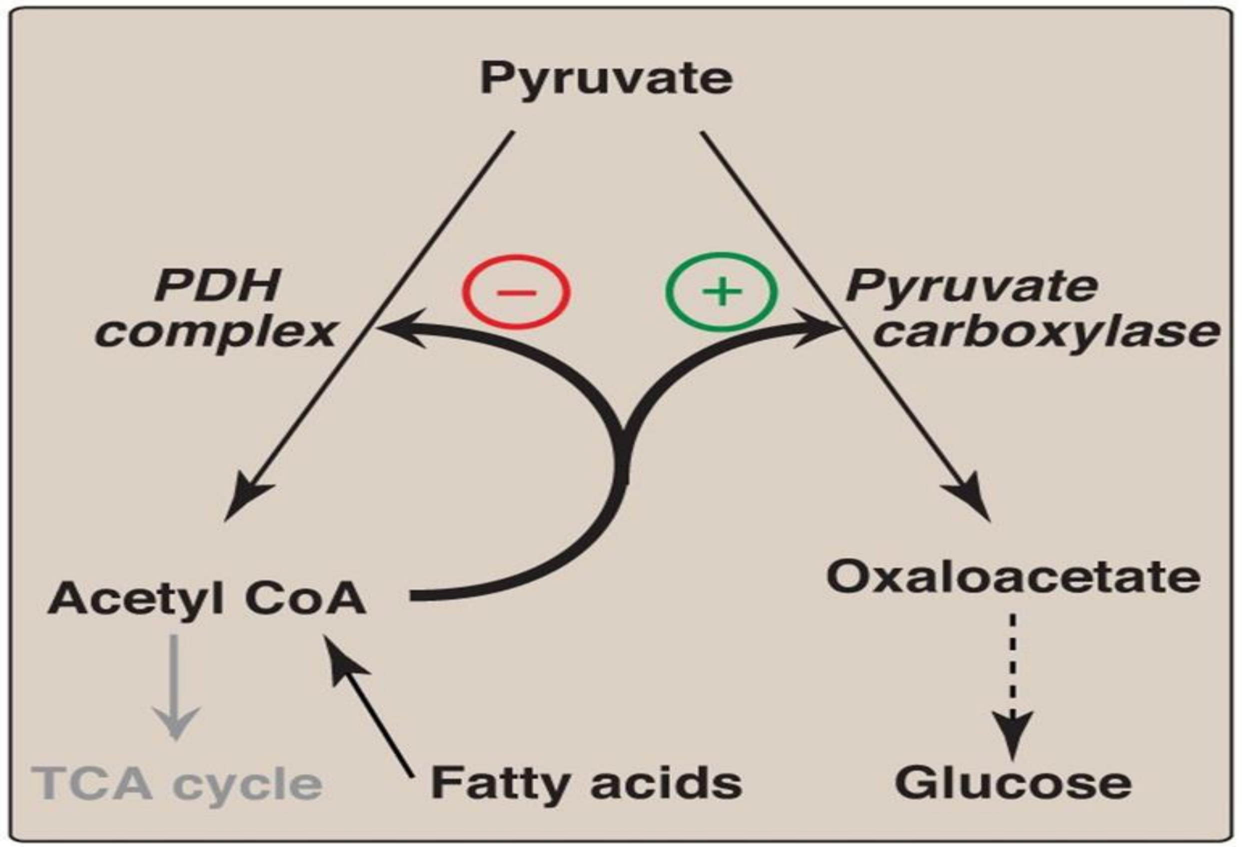


*PEP-CK= Phosphoenolpyruvate CarboxyKinase

Pyruvate carboxylase + PEP-CK ≠ Pyruvate kinase

REGULATION OF PYRUVATE CARBOXYLASE

- Acetyl CoA diverts pyruvate away from oxidation and toward gluconeogenesis



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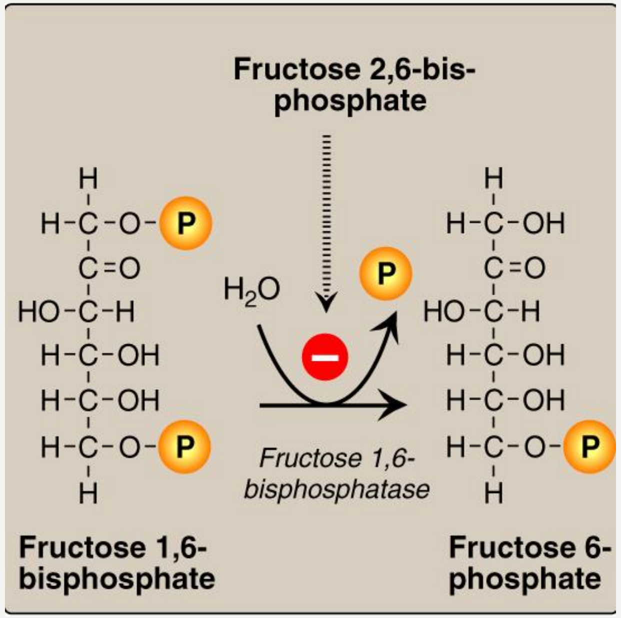
Fructose 1,6- bisphosphate

Enzyme :Fructose 1,6- bisphosphatase

Fructose 6- phosphate

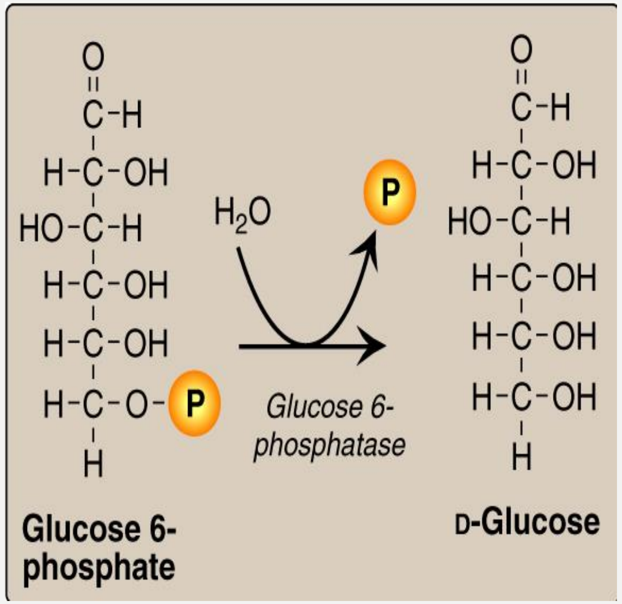


- This enzyme inhabited by AMP & Fructose 2,6- bisphosphate
- induced by ATP
- Fructose 1,6- bisphosphatase ≠ PFK-1

Glucose 6- phosphate

Enzyme :Glucose 6- phosphatase

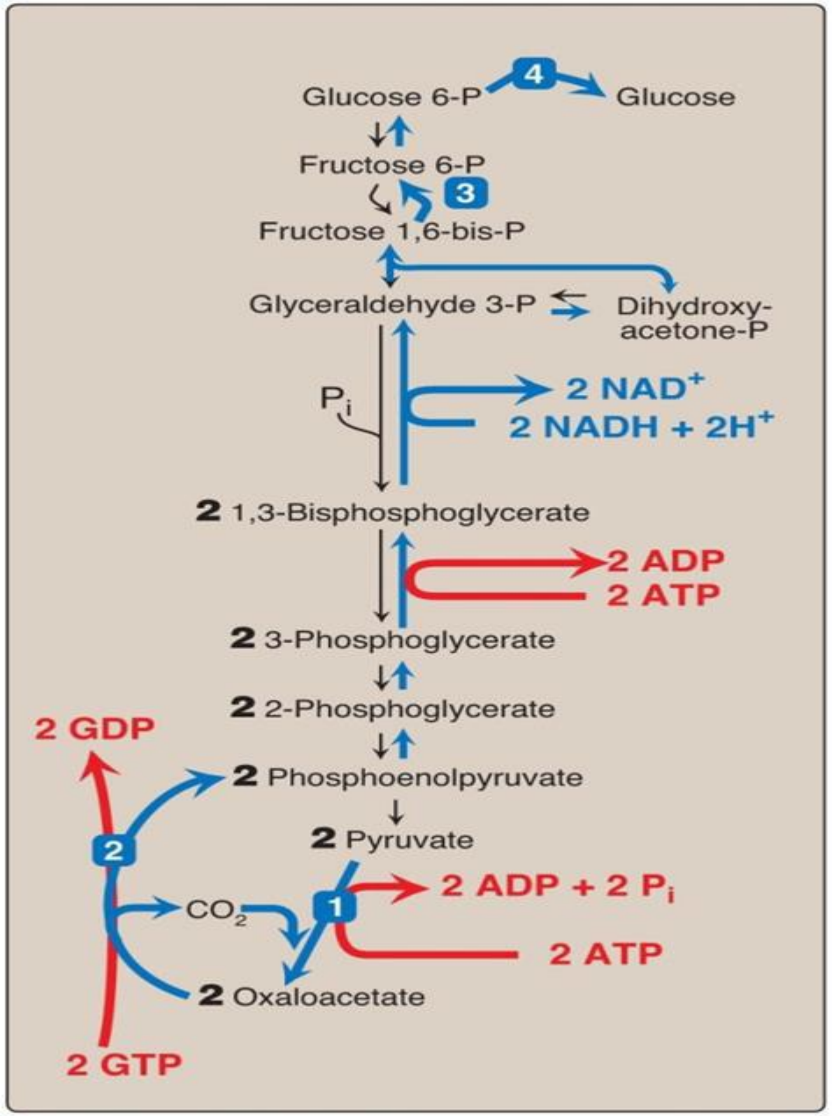
D-Glucose



- Glucose 6-phosphatase ≠ Glucokinase

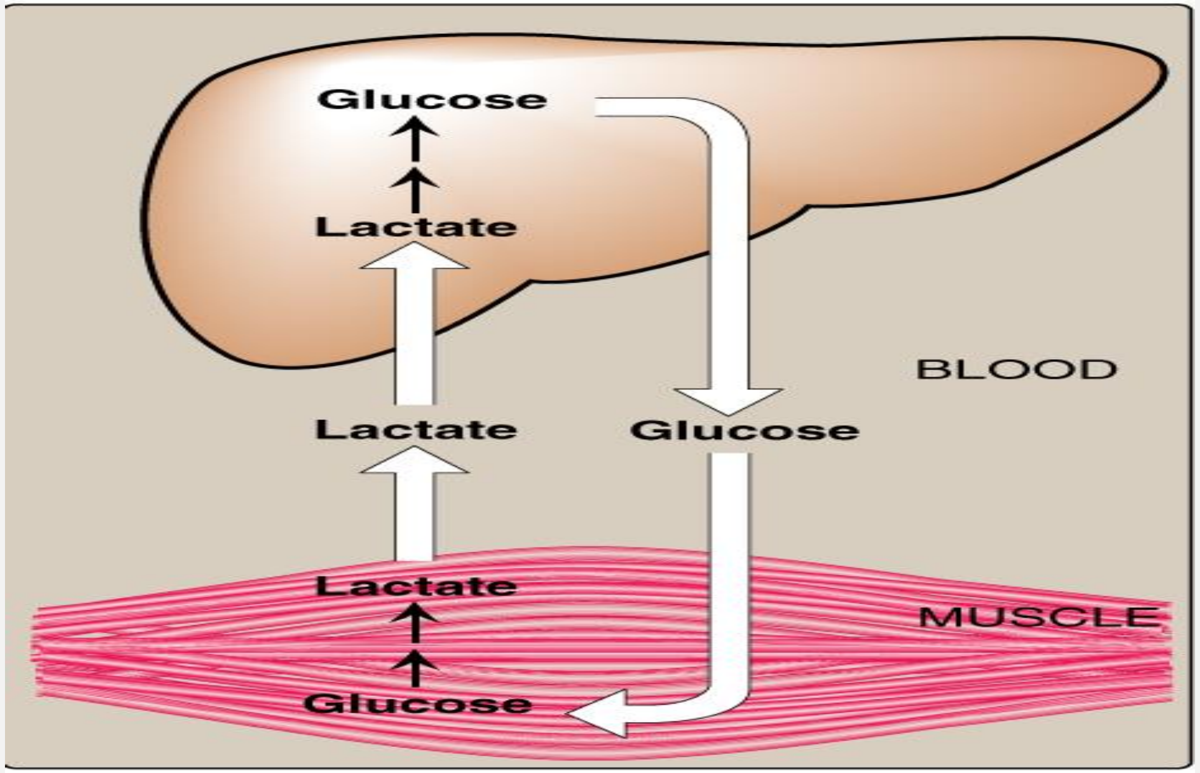
Gluconeogenesis: Energy-Consumed

- Six High-Energy Phosphate Bonds Are Consumed for the Conversion of Pyruvate to Glucose



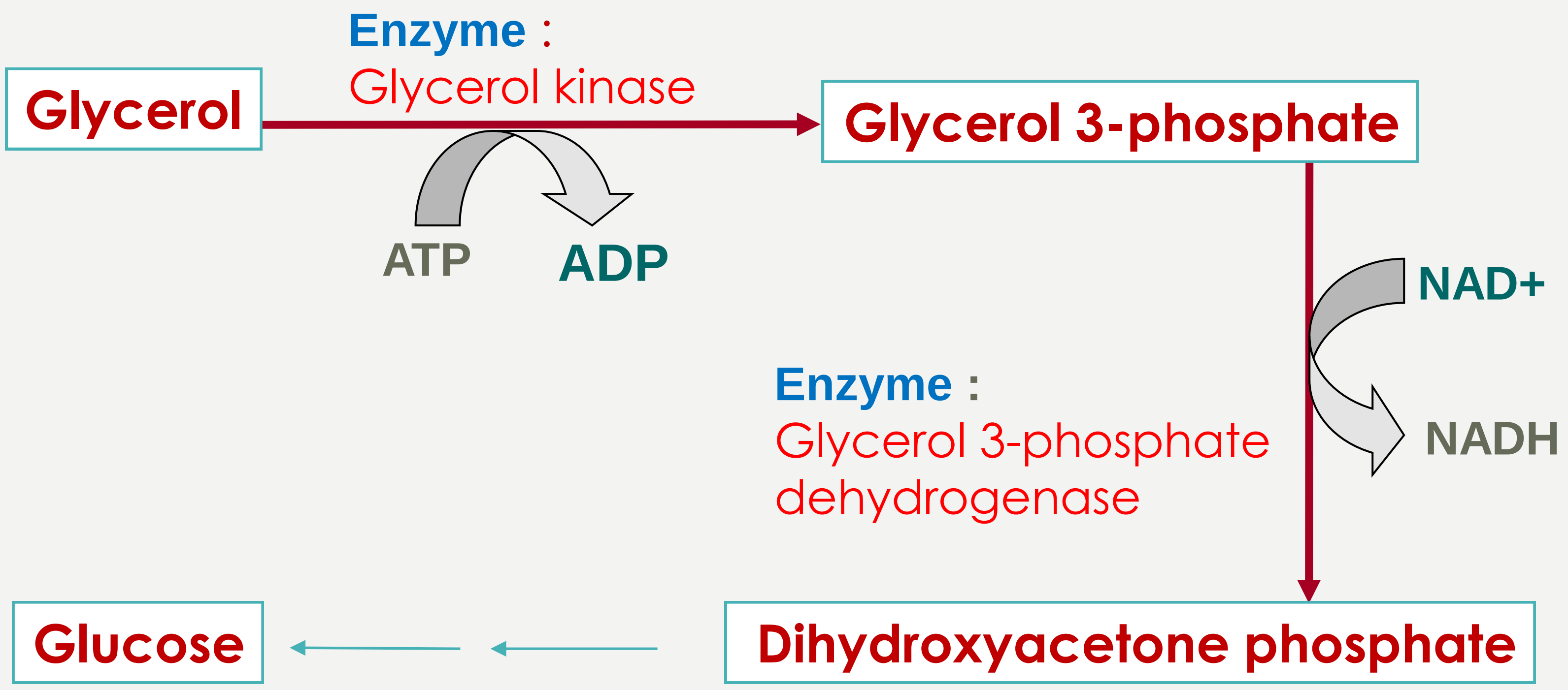
Gluconeogenic Substrates: Lactate (Cori Cycle)

Note: The lactate is formed when the muscle does not have enough oxygen, do to the difference in the amount of oxygen entering the body by breathing and the amount needed to perform an exercise, so muscle form the lactate" by the know anaerobic pathway" to extend the exercise time, after finishing the exercise lactate" toxic" will be converted to glucose again by the liver.

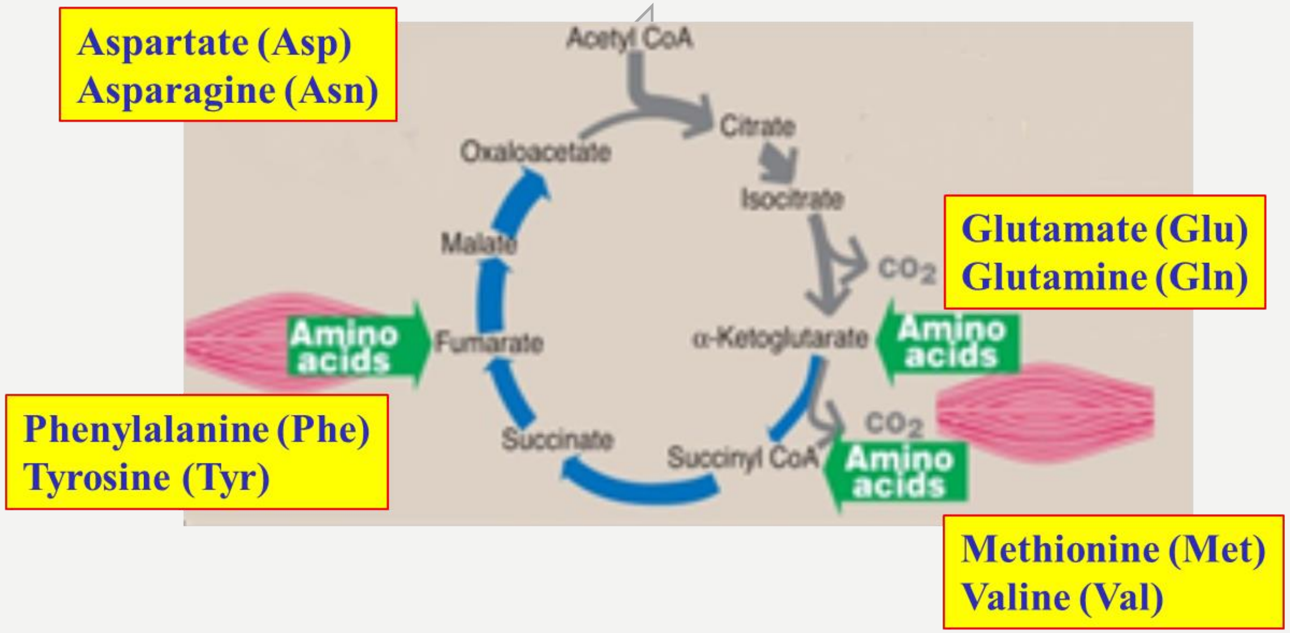


Gluconeogenic Substrates: Glycerol

- Glycerol is released during the hydrolysis of Triacylglycerol (TAG) in adipose tissue.
- Glycerol kinase only in **liver** & **kidneys**
- Gluconeogenesis of glycerol occurs in only the cytosol



Gluconeogenic Substrates: Glucogenic Amino Acids (AAs)



- AAs can be derived from hydrolysis of tissue proteins.
- The anabolic feature of gluconeogenesis.

Aspartate (Asp) Asparagine (Asn	Phenylalanine (Phe) Tyrosine (Tyr)	Methionine (Met) Valine (Val)	Glutamate (Glu) Glutamine (Gln)	Alanine (Ala) Glycine (Gly)
They are converted into oxaloacetate then it converts to malate then it goes to other pathway	They are converted into fumarate then it completes Krebs cycle to malate then it goes to other pathway	They are converted into succinyl CoA then it completes Krebs cycle to malate then it goes to other pathway	They are converted to a-ketoglutarate then it completes Krebs cycle to malate then it goes to other pathway	They are converted to pyruvate then to oxaloacetate then to malate

Gluconeogenesis: Regulation

- Reciprocal control of :

Gluconeogenesis (محفز) & Glycolysis(مثبط)

- Allosteric regulation:

(↑)Acetyl CoA (Pyruvate carboxylase)
(↓)AMP or (↑)ATP
(↓)F 2,6-Bisphosphate
} F 1,6-bisphosphatase

- Glucagon (↓ I/G ratio)

  Allosteric (F 2,6-Bisphosphate)
  Induction (PEP-CK)

I = Insulin , G = glucagon#
#دائما_وأبدا : الجلوكاجون والانسولين عكس بعض واحد ارتفع الثاني ينزل

Take Home Message

- **Gluconeogenesis:**
  -Synthesis of glucose from noncarbohydrates
  -Anabolic
  -Energy-consuming

- Four unique enzymes are required for reversal of the 3 irreversible reactions of glycolysis

- Both gluconeogenesis & glycolysis are reciprocally-regulated

Glycolysis

	Reactions	From	Into	Enzyme used (by)	Type	Type of Step
1	Phosphorylation	Glucose	Glucose 6-p	1- Hexokinase (in most tissues 2- Glucokinase (in liver)	Irreversible	Regulatory
2	Isomerization	Glucose 6-P	Fructose 6-P	Phosphoglucose isomerase	Reversible	Not regulated
3	Phosphorylation	Fructose 6-P	Fructose 1,6 bisphosphate	Phosphofructokinase1 (PFK-1)	Irreversible	Most important
4	Cleavage	Fructose 1,6 bisphosphate	Dihydroxyacetone phosphate (DHAP)	Aldolase	Reversible	Not regulated
5	Isomerization	Dihydroxyacetone phosphate (DHAP)	2 molecules of glyceraldehyde 3-P.	Triose-P isomerase	Reversible	Not regulated
6	Oxidation	Glyceraldehyde 3-P	1,3-bisphosphoglycerate (1,3-BPG)	Glyceraldehyde 3-P dehydrogenase	-	-
7	Synthesis	1,3-BPG	3-phosphoglycerate	Phosphoglycerate kinase	Reversible	Not regulated
8	Shift P group	Carbon 3	Carbon 2	Phosphoglycerate mutase	Reversible	Not regulated
9	Dehydration	2-P glycerate	Phosphoenolpyruvate (PEP)	Enolase	Reversible	Not regulated
10	Formation	PEP	Pyruvate	Pyruvate kinase (PK)	Irreversible	Regulatory

Reactions of Krebs Cycle

	Reactions	From	Into	Enzyme used (by)	Type of Step
1	Synthesis	acetyl CoA + OAA	Citrate	citrate synthase	inhibits PFK-1
2	Isomerization	Citrate	isocitrate	aconitase	-
3	Oxidation & decarboxylation	Isocitrate	αKG	isocitrate dehydrogenase	oxidative phosphorylation
4	Oxidation & decarboxylation	αKG	succinyl CoA	αKG dehydrogenase complex	oxidative phosphorylation
5	Cleavage	succinyl CoA	succinate	succinate thiokinase	substrate-level phosphorylation
6	Oxidation	succinate	fumarate	succinate dehydrogenase	oxidative phosphorylation
7	Hydration	fumarate	L-malate	fumarase	-
8	Oxidation	L-malate	OAA	malate dehydrogenase	oxidative phosphorylation

Gluconeogenesis

	Glycolysis step (Enzyme)	From→ Into	Gluconeogenesis	Information
1 2	PEP → Pyruvate (Pyruvate Kinase) 1-(Carboxylation reaction) 2-(Decarboxylation & phosphorylation reaction)	1-Pyruvate→Oxaloacetate	Pyruvate Caroxylase	Requires ATP,Biotin Happens in Mitochondria
		2-Oxaloacetate → PEP	PEPCK	Requires GTP, happens in Cytosol
3	Fructose 6-P → Fructose 1,6 Bisphosphate (PFK-1) (Dephosphorylation reaction)	Fructose 1,6 Bisphosphate→Fructose 6-P	Fructose 1,6 Bisphosphatase	Inhibited by high levels of AMP Activated by high levels of ATP
4	Glucose → Glucose 6-P (Hexokinase) (Dephosphorylation reaction)	Glucose 6-P → Glucose	Glucose 6-Phosphatase	Enzyme is found only in liver and kidney

QUIZ

Q1: Gluconeogenesis occurs mainly in

a. Liver
b. Kidney
c. Bone marrow

Q2: Glutamate enters Krebs cycle by being converted to

a. Succinate
b. Fumarate
c. Alpha ketoglutarate

Q3:Glucneogenesis is

a. Catabolic
b. Anabolic
c. Energy-yielding

QUIZ

Q4: Pyruvate carboxylase is induced by

a. Oxaloacetate
b. Acetyl co a
c. AMP

Q5:Oxaloacetate can’t cross the cell membrane so it is converted to………….. , then back to oxaloacetate

a. Malate
b. Fumarate
c. Phosphoenolpyruvate

Q6: One of the unique enzymes of gluconeogenesis

a. Glucokinase
b. Glucose-6-phosphatase
c. Phosphoglycerate mutase

QUIZ

True or False

Q7: Gluconeogenesis and glycolysis are reciprocally regulated

Q8: Gluconeogenesis always occurs in both mitochondria and cytosol

Q9: An increase in Insulin Glucagon ratio means induction of gluconeogenesis

Q10: Fructose 1,6-bisphosphatase converts Fructose 1,6-bisphosphate to Fructose 6-phosphate

ANSWERS

1. A
2. C
3. B
4. B
5. A
6. B
7. T
8. F
9. F
10. T

Biochemistry Team

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 لصديقتنا : نوف التويجري.

Boys Team:

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

* نستقبل إقتراحاتكم وملاحظاتكم على:

@435biochemteam

435biochemistryteam@gmail.com

@biochemteam435

435 Biochemistry Team