Editing File

12

Gluconeogenesis

Color index :

Main text

IMPORTANT

Extra Info

Drs Notes

Foundation Block - Biochemistry Team

Revised & Approved by: Shaqra Abdullah Alghanim

Faisal Alotaibi

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A helpful video

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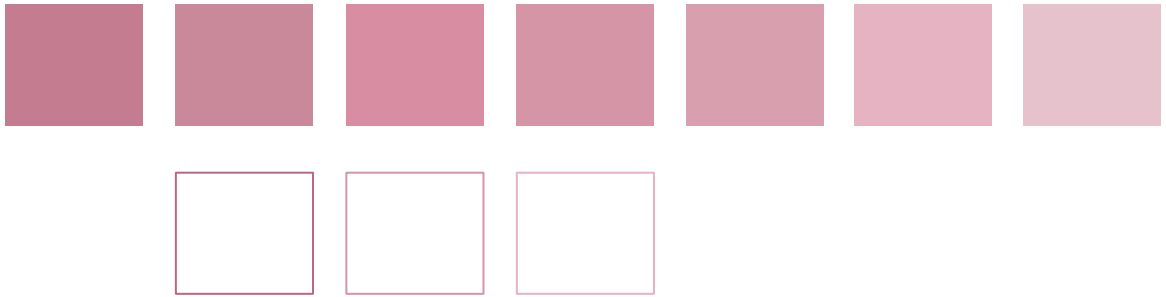
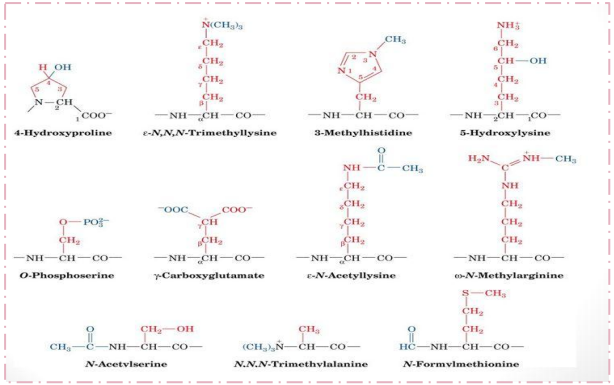


Non - polar	Polar	Charged
ProGAV PIL TM تخيلوها اسم جندي ثاني عاد Proline, Glycine, Alanine, Valine, Phenylalanine, Isoleucine, Leucine , Tryptophan, Methionine	SomeTimes Cats Try A Growl Serine, Threonine, Cysteine, Tryrosine , Asparagine, Glutamine	A Good Lawyer Aims High Aspartate, Glutamate, Lysine, Arginine, Histidine



1

2

3

Location of the nonpolar amino acids in proteins

In protein found in aqueous solution " hydrophilic " **(polar environment)**

- Inferior of the protein
- The nonpolar R-group fill up the interior of the folded protein and help give it its 3D shape

In protein located in hydrophobic region such as membrane (**non polar environment**)

- Outside surface of the Protein
- interacting with lipid environment to Stabilize protein structure

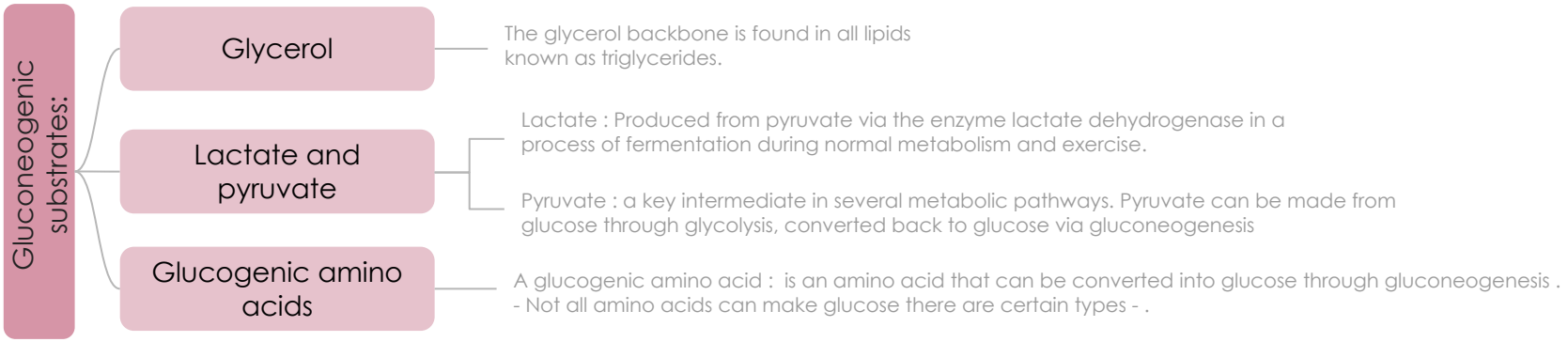
Types of DNA	A-DNA	B-DNA (Watson & Crick)	Z-DNA
direction	Right-handed They are clockwise	Right-handed They are clockwise	Left-handed They are anti-clockwise
Helix length	Short	Elongated "long"	More elongated
Major groove	Deep and narrow	Wide	Not a real groove
Minor groove	wide	Narrow	Narrow
Placements of bp	Displaced away from the helical axis	Centered over the helical axis	Zig-zag pattern (nearly perpendicular to the helical axis)
Bp per turn	11	10	12
Conformation of deoxyribose (the carbon where oxygen is removed)	C3	C2	G (C2) or C (C3)
Seen in	Seen in: - DNA replication - Non coding RNA	Most common in human body	Seen in the sites DNA is copied

Objectives:

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

Gluconeogenesis

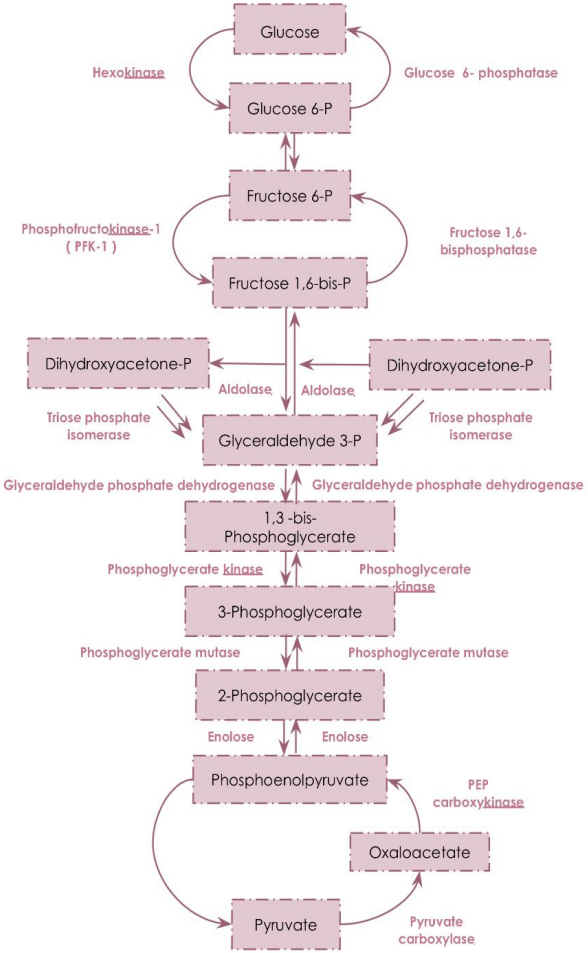
- The gluconeogenesis pathway is one of the essential pathways of energy metabolism.
- Gluconeogenesis is an energy consuming (anabolic pathway).
- Synthesis of glucose from non-carbohydrates molecules.
- Occurs in liver mainly , and in kidney .
- Both **mitochondria** and **Cytosol** are involved " Exception: if gluconeogenesis starts by Glycerol, it will need only the cytosol "



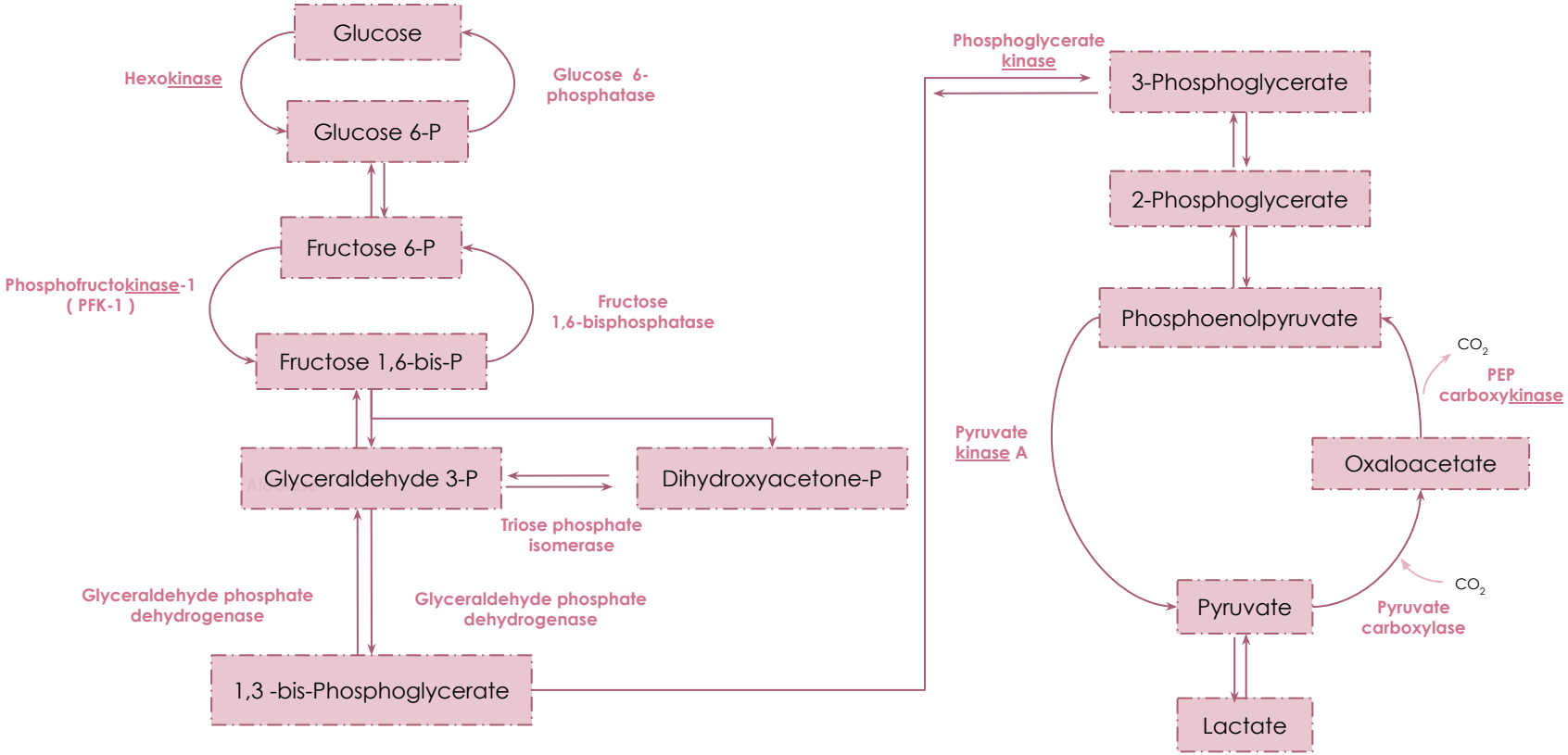
Gluconeogenesis , Contd....

- Seven glycolytic reactions are reversible and are used in the synthesis of glucose from lactate or pyruvate.
- Three of the reactions are irreversible and must be reversed by four alternate reactions that energetically favor the synthesis of glucose .

Glycolysis enzyme	Gluconeogenesis enzyme
Pyruvate kinase	1. Pyruvate carboxylase 2. PEP-CK
PFK-1	Fructose 1,6 bisphosphatase
Glucokinase / Hexokinase	Glucose 6-phosphatase



Glycolysis and Gluconeogenesis (overview)



A helpful video

Gluconeogenesis , Contd

- The **4 alternate reactions** in gluconeogenesis " reaction 1 , 3 and 10 in glycolysis are irreversible that's why it must be reversed ".

1 Pyruvate (3C) —(Pyruvate carboxylase)→ Oxaloacetate (4C)

- CO_2 + ATP In.
- ADP Out.
- Carboxylation " adds a carobin group " of pyruvate by **pyruvate carboxylase** and it occurs in mitochondria.

2 Oxaloacetate (4C) —(PEP carboxykinase)→ Phosphoenolpyruvate "PEP" (3C)

- GTP in
- GDP + CO_2 Out.

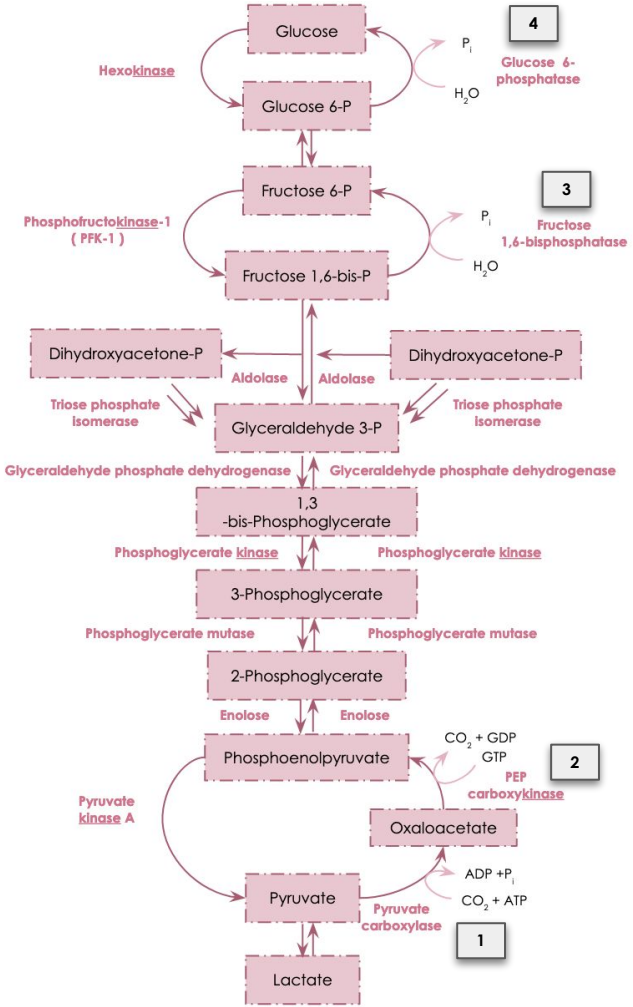
3 Fructose 1,6-bis-phosphate (6C) —(Fructose 1,6-bisphosphatase)→ Fructose 6-phosphate(6C)

- H_2O In.
- P_i Out.

4 Glucose 6-Phosphate (6C) —(Glucose 6-phosphatase)→ Glucose (6C)

- H_2O In.
- P_i Out.

هذي بكل بساطة اللي غيرناه بال gluconeogenesis الباقي نفس ال glycolysis .



★ extra explanation

Summary of the aerobic glycolysis In order for you to gain a better understanding In tables

Reaction 1	
Reactant	Pyruvate
Product	Oxaloacetate
Enzyme	**Pyruvate carboxylase**
Action	adding CO_2
Consume	1 ATP

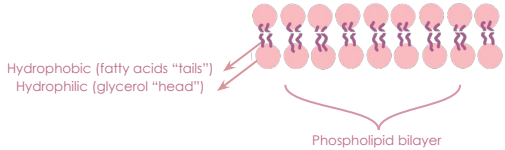
Reaction 2	
Reactant	Pyruvate
Product	Phosphoenolpyruvate "PEP"
Enzyme	**PEP carboxykinase**
Action	Adding s phosphate group
Consume	GTP

Reaction 3	
Reactant	Fructose 1,6-bisphosphate
Product	Fructose 6-phosphate
Enzyme	**Fructose 1,6-bisphosphatase**
Action	Removes a phosphate group
Consume	H_2O

Reaction 4	
Reactant	Glucose 6-phosphate
Product	Glucose
Enzyme	**Glucose 6-phosphatase**
Action	Removes a phosphate group
Consume	H_2O

Gluconeogenic Substrates: Glycerol

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



Gluconeogenic Substrates : Glycerol

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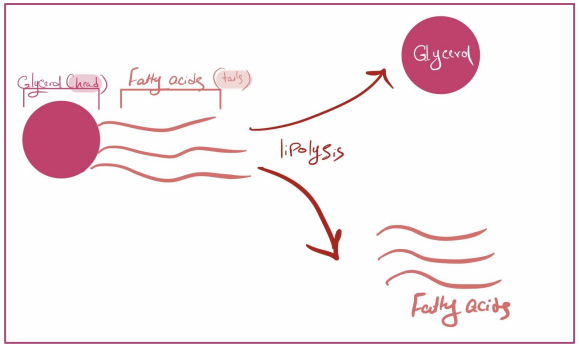
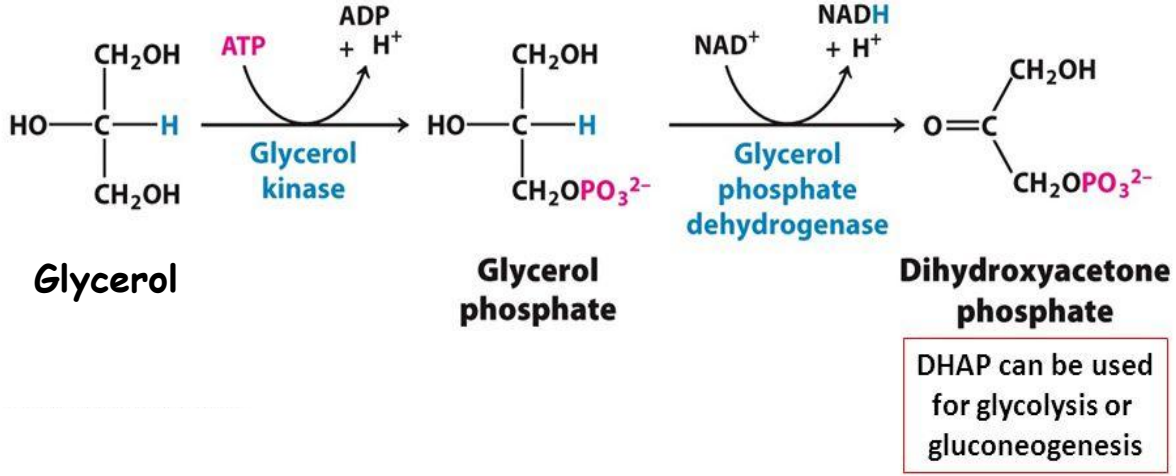
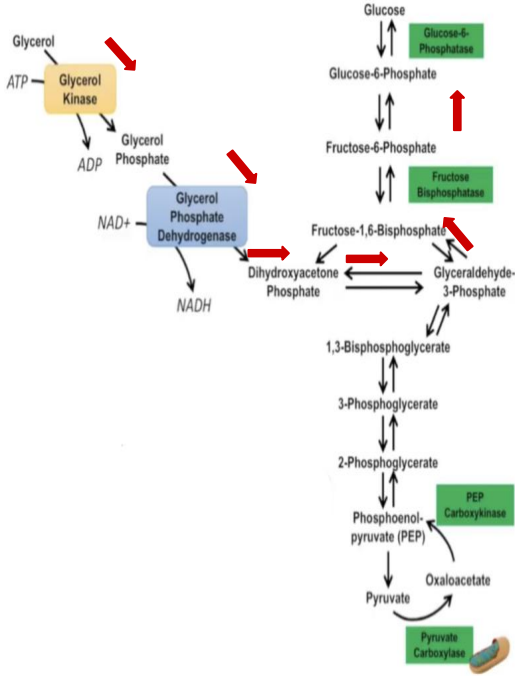






Gluconeogenic Substrates : Glycerol

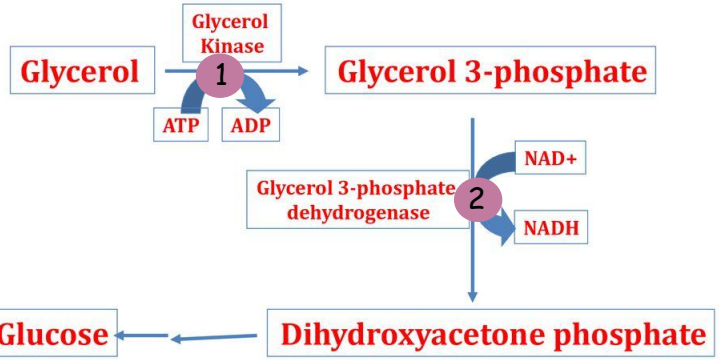
To sum up

Reaction 1	
Reactant	Glycerol
Product	Glycerol-3-phospha te
Enzyme	Glycerol kinase
Action	Adding one phosphate
Consume	ATP

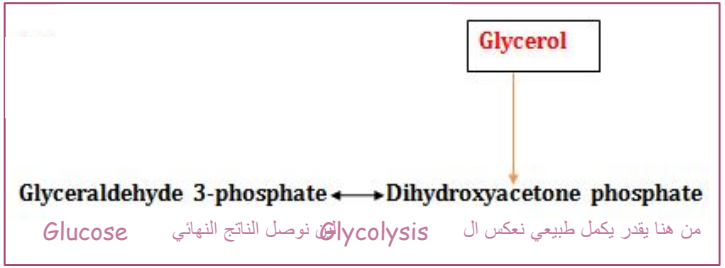
Reaction 2	
Reactant	Glycerol-3-phosphate
Product	Dhydroxyacetone phosphate
Enzyme	Glycerol-3-phosphate dehydrogenase
Action	Oxidation
Produce	NADH

*Reaction 2 is an oxidative reaction which involves the reduction of NAD to NADH

Glycerol as a gluconeogenic Substrate



GK: Glycerol kinase only in liver & kidneys



Gluconeogenic Substrates: Glucogenic Amino Acids

You have to memorize it

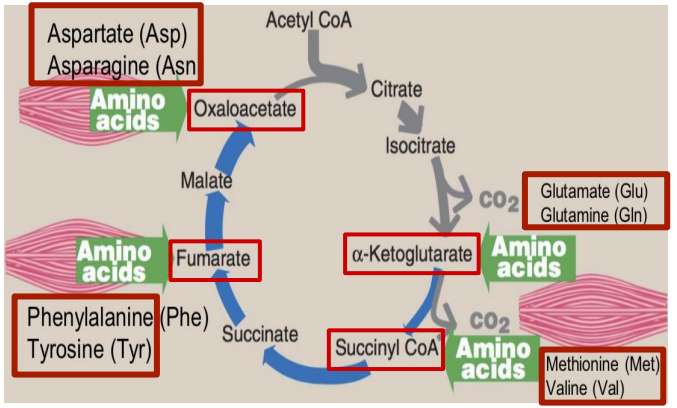
The catabolism of glucogenic amino acids produces either:

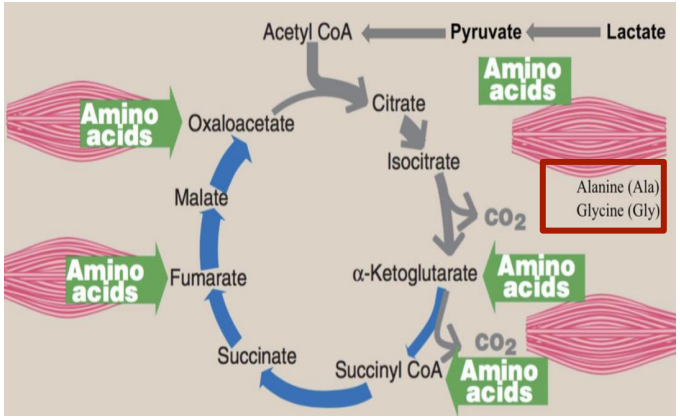
- one of the intermediates in the Krebs Cycle

  For example: catabolizing asparagine & aspartate produces oxaloacetate
  (an intermediate) which can be converted later to glucose.

- Pyruvate

  Some of the amino acids Enter Krebs cycle by transfer into pyruvate (glycine & alanine)





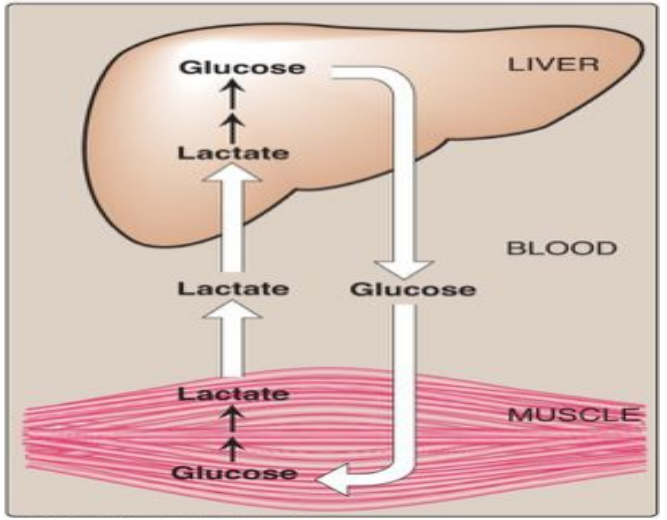
All amino acids are Glucogenic (make glucose) except: Leucine & Lysine (the Lazy L's)

*You have to know the names of the 4 entrance points and the amino acids

Gluconeogenic Substrates: Lactate (cori cycle)

Glucose in the liver travels through the blood to the **muscle** where it is turned into lactate then the lactate re-travels through the blood and back into the **liver** where it is turned back into glucose

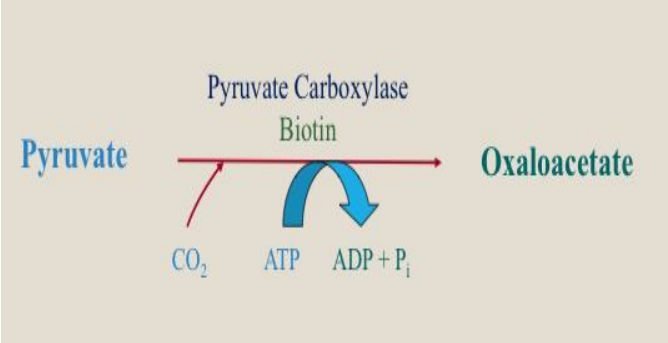
Lactate is released into the blood by exercising skeletal muscle and by cells that lack mitochondria such as RBCs.
In the Cori cycle, bloodborne glucose is converted by exercising muscle to lactate, which diffuses into the blood. The lactate is taken up by the liver and reconverted to glucose, which is released back into circulation



Pyruvate carboxylase

- The carboxylation occurs in the **liver** and **kidney**, exactly in **mitochondria** so pyruvate has to travel from cytoplasm to mitochondria why ? Because pyruvate carboxylase is only found in matrix of mitochondria

- Biotin coenzyme that makes CO2 more active to bind



Pyruvate carboxylase and PEP-CK

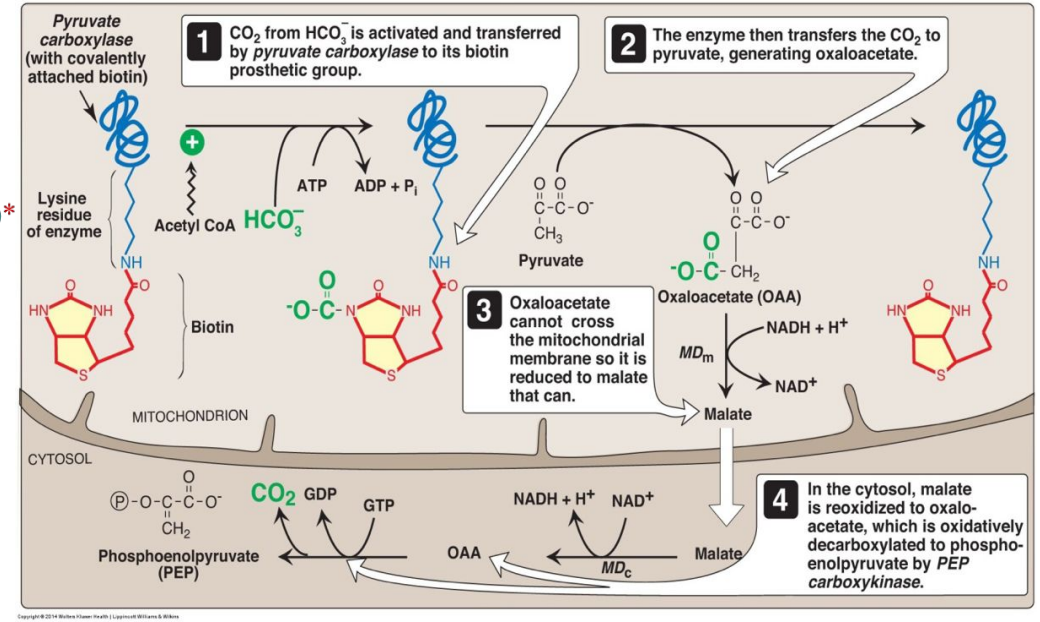
Note : to compare

In glycolysis to convert from PEP into pyruvate we need just one enzyme which is (pyruvate kinase)

In gluconeogenesis to convert pyruvate into PEP we need two enzymes in two steps these enzymes are (pyruvate carboxylase + PEP-CK)

↑ Fasting: Acetyl CoA (From FAO)*

*Fatty Acid Oxidation



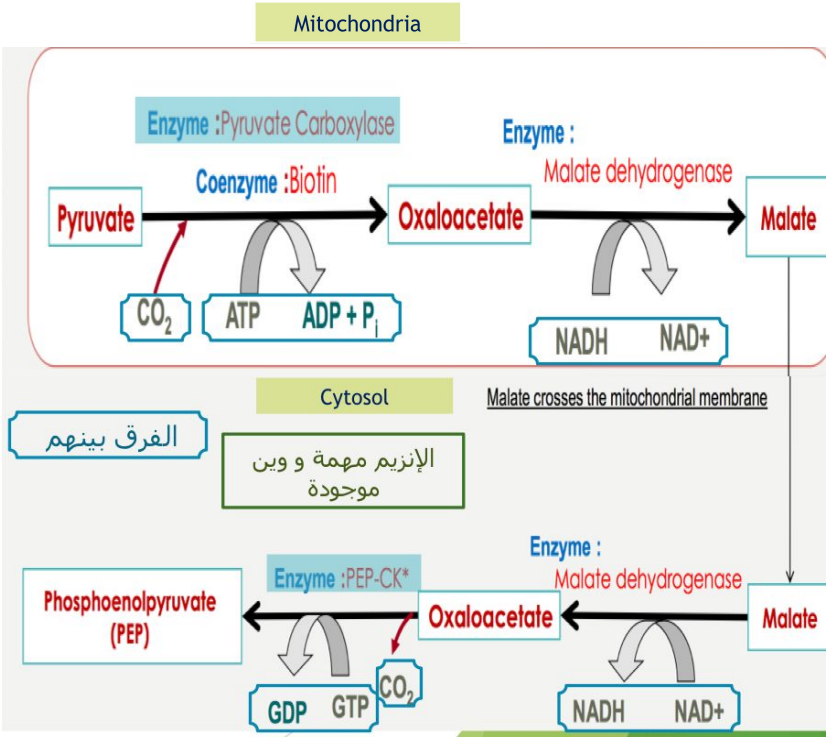
Pyruvate carboxylase + PEP-CK ≠pyruvate kinase

Explained in next slide

Explanation for the two steps

الحين زي ما قلنا Pyruvate لازم يدخل الميتوكندريا ليش ؟
عشان هناك راح يلقى الانزيم Pyruvate Carboxylase اللي راح يحوله الى Oxaloacetate طيب المشكلة ان هذا Oxaloacetate ما يقدر يطلع من الميتوكندريا بصورته هذي والحل طيب ؟ فيه انزيم ثاني اسمه Malate dehydrogenase. راح يحوله بشكل مؤقت الى Malate بالاختزال نفس الانزيم اللي كان موجود بكربس سايكل (الخطوة الأولى)

الحين هذا Malate يقدر يطلع من الميتوكندريا ويروح للسيتوبلازم ليش ؟
لأن الهدف من هذا كله هو اني اكون جلوكوز وأنزله على الدم ويروح للخلايا الثانية تستخدمه وتنتج طاقة، طيب في السيتوبلازم يصير له اكسدة بنفس الانزيم Malate dehydrogenase ويرجع يتحول إلى Oxaloacetate
هذا اللي نبغاه ليش ؟ لان فيه انزيم مهم PEP-CK راح يحوله اخيرًا الى PEP اللي بدوره بيكمل السالفة (الخطوة الثانية)



(PEP-CK) = Phosphoenolpyruvate Carboxykinase

Regulation of Pyruvate Carboxylase reaction

Acetyl CoA diverts pyruvate away from oxidation in Krebs cycle and toward gluconeogenesis

+ positive regulation

High Acetyl coA will **stimulate the enzyme pyruvate carboxylase biotin** to make more oxaloacetate Then, the oxaloacetate will produce more glucose

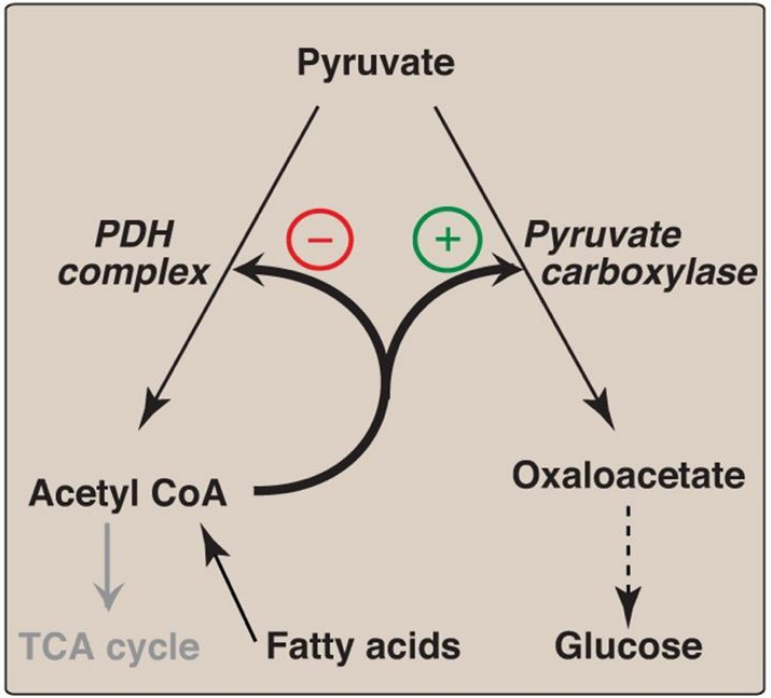
- negative regulation

High level of Acetyl-coA **inhibit PDH complex** and stop or reduce the Glycolysis.

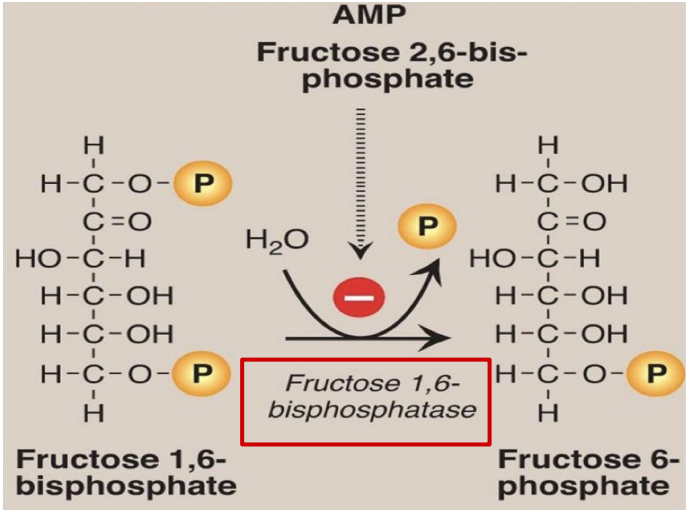
PDH function: converts pyruvate to Acetyl coA

+ : Activation - : Inhibition

Biotin is essential for the pyruvate carboxylase action thus we call it pyruvate carboxylase biotin (biotin is attached to the enzyme)



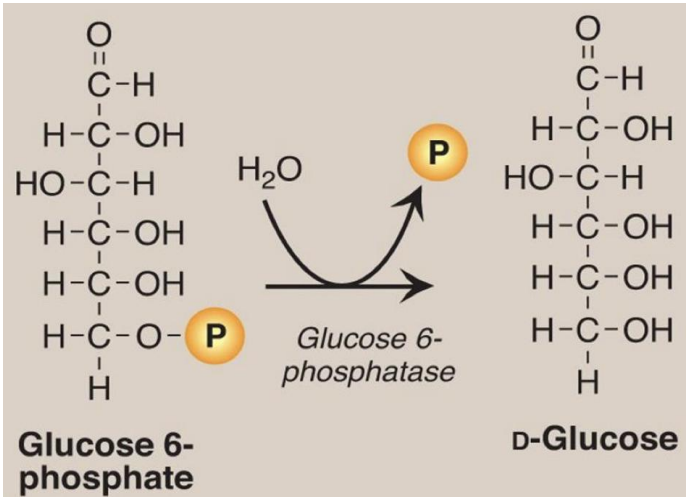
PDH: Pyruvate dehydrogenase complex: is a complex of three enzymes



Dephosphorylation of fructose 1,6-bisphosphate

- Fructose 1,6- phosphatase: inhibited by **AMP** & **Fructose 2,6- bisphosphate**
- Induced by **ATP**
- Fructose 1,6- bisphosphatase ⇌ PFK-1

Fructose 2,6-bisphosphate:
inhibits fructose 1,6-bisphosphatase (Gluconeogenesis)
Activates PFK-1 (Glycolysis)



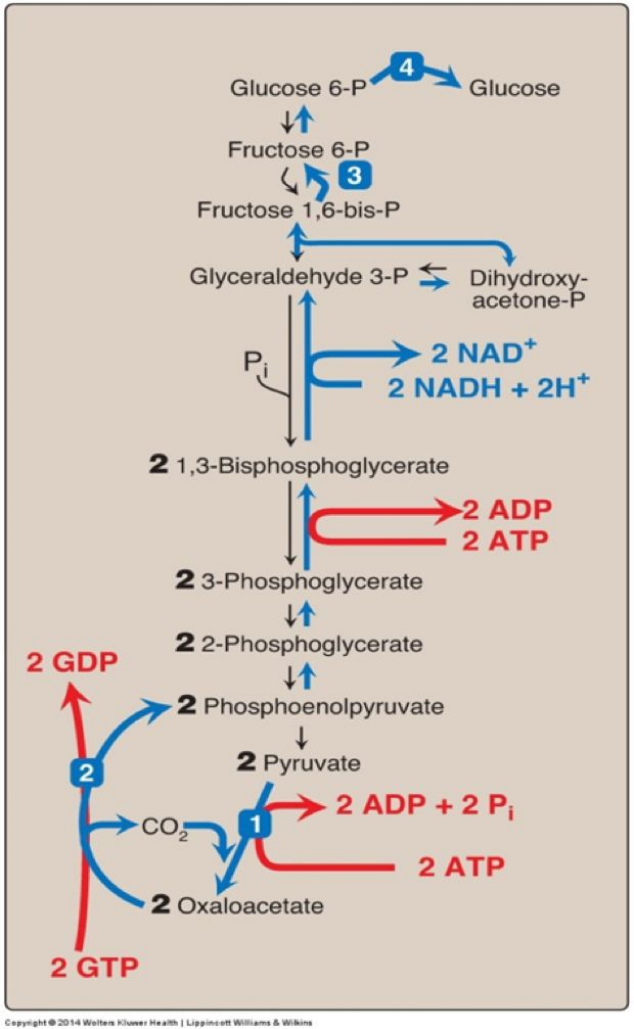
Dephosphorylation of glucose 6-phosphate

- Allows release of free glucose from the liver and kidney into blood by (GLUT-2)
- Glucose 6-phosphate ⇌ Glucokinase

Gluconeogenesis: Energy-Consumed

Six High-Energy Phosphate Bonds From Pyruvate to Glucose

12 ATP molecules are required to produce 1 Glucose from 2 Pyruvate



Gluconeogenesis: Regulation

Reciprocal control

- Gluconeogenesis & Glycolysis

Allosteric

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

F 1,6-bisphosphatase

Glucagon (↓I/G* ratio)

*I = Insulin , G = glucagon

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

⇩ Repression ⇧ Induction

Take home messages

- Gluconeogenesis is an important pathway for glucose production from non-carbohydrate sources during prolonged fasting .
- Lactate, Glycerol and glucogenic amino acids are the major gluconeogenesis substrate .
- Gluconeogenesis is not a simple reversal of glycolysis. In fact gluconeogenesis requires 4 unique reactions to circumvent the 3 irreversible reactions of glycolysis .
- Gluconeogenesis and glycolysis are reciprocally controlled, allowing efficient glucose metabolism .
- It is mainly anabolic pathway that consumes ATP for the synthesis of glucose .

QUIZ ♥

MCQs

Q1: The main site of gluconeogenesis ?

A) Spleen B) Liver C) Kidney D) Lymph node

Q2: Which of the following amino acids Enter Krebs cycle by transfer into pyruvate?

A) Aspartate B) Phenylalanine C) Glycine D) Methionine

Q3: All amino acid can converted into glucose except ?

A) Lysine B) Glycine C) Leucine D) Both A&C

Q4: Gluconeogenesis of glycerol occurs only in the ?

A) Cytosol B) liver C) lymph node D) spleen

SAQ

Q1 :What substrates can be used for gluconeogenesis?

Q2 :What are the three unique irreversible reactions in gluconeogenesis?

MCQs answers

4) A
3) D
2) C
1) B

SAQ answer:

1. ~~Glycerol , Lactate & Pyruvate, Glucogenic amino acids~~
2. ~~Slide4~~

Quiz

Q1 : Oxidative phosphorylation happens in			
A) Nucleus	B) Cytosol	C) Mitochondria	D) Rough ER
Q2 : The net ATP production in Aerobic Glycolysis is			
A) 8 ATP	B) 4 ATP	C) 7 ATP	D) 5 ATP
Q3 : Which of the following biochemical pathways does NOT require oxygen ?			
A) Krebs cycle	B) Glycolysis	C) ETC	D) Calvin cycle
Q4 : The final product of Anaerobic Glycolysis is			
A) Pyruvate	B) Lactate	C) Citrate	D) Acetyl coenzyme A
Q5 : There are ..... steps reaction in aerobic glycolysis			
A) 13	B) 20	C) 10	D) 15
Q6 : The first 3 steps in glycolysis are			
A) Irreversible	B) Reversible	C) Both of them	D) None of them

SAQs :

Q1: What is the function of enolase enzyme ?

Q2: How many NADH are produced by glycolysis per glucose ?

★ **MCQs Answer key:**

1) C 2) A 3) B 4) B 5) c 6) A

★ **SAQs Answer key:**

1) Remove water, so it will convert phosphoglycerat to Phosopheonolpyruvate
2) 2 NADH

Girls team:

Alia Zawawi
Nada Babilli
Rania Aqil
Reem alamri
Reema Alomar
Reem Alqahtani
Renad Alhumaidi
Shaden Alobaid
Noura Alsalem
Lama Alahmadi
Sadem Alhazmi
Somow Abdulrahman
Budoor Almubarak
Samar Almohammedi
Nuha Alkudsi
Norah Alsheikh
Muneerah Alssdhan
Mayasem Alhazmi
Noura alshathri
Duaa Alhumoudi

Boys team:

Mansour albawardi
Hassan alshuraf
Abdulrahman almbki
Mohammed alsayari
Abdullaziz alomar
Abdulaziz alrabiah
Saud alrasheed
Abdullah almazro
Hamad almousa
Ahmad alkhayat

A goal should scare you a little and excite you a lot!.

Shatha Aldhohair

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Team members

Girls Team :

- Alia Zawawi
- Nada Babilli
- Rania Aqil
- Reem alamri
- Reema Alomar
- Reem Alqahtani
- Renad Alhumaidi
- Samar Almohammedi
- Shaden Alobaid
- Budoor Almubarak
- Somow Abdulrahman
- Noura Alsalem
- Lama Alahmadi
- Sadem Alhazmi
- Nuha Alkudsi
- Norah Alsheikh
- Muneerah Alsadhan
- Mayasem Alhazmi

Boys Team :

- Mansour albawardi
- Hassan alshurafa
- Abdulrahman almebki
- Mohammed alsayyari
- Abdullaziz alomar
- Ahmed Alkhayat
- Bander alharbi
- Abdulaziz alrabiah
- Saud alrasheed
- abdullah almazroo
- Hamad almousa

Team leaders

- Shatha Aldhohair
- Mishal Althunian

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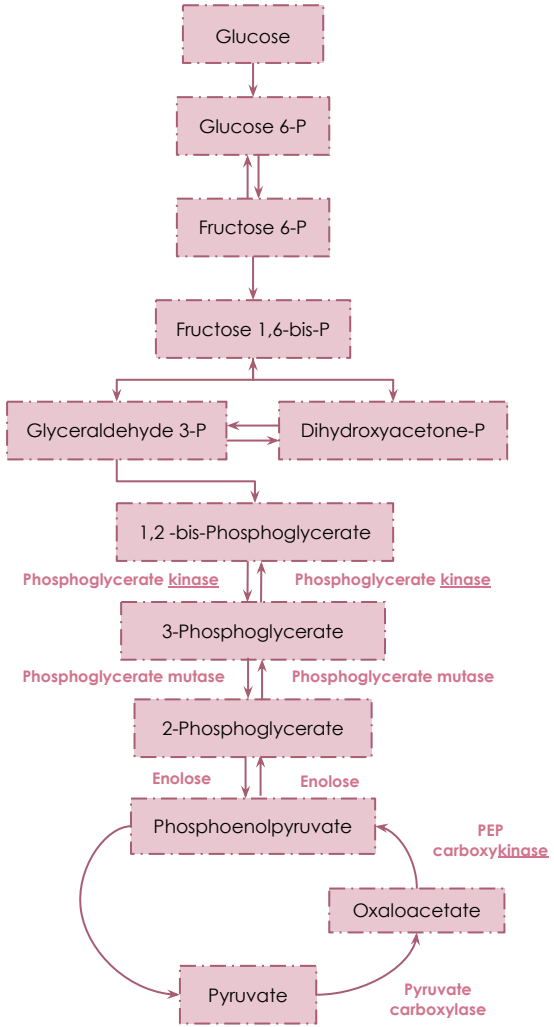
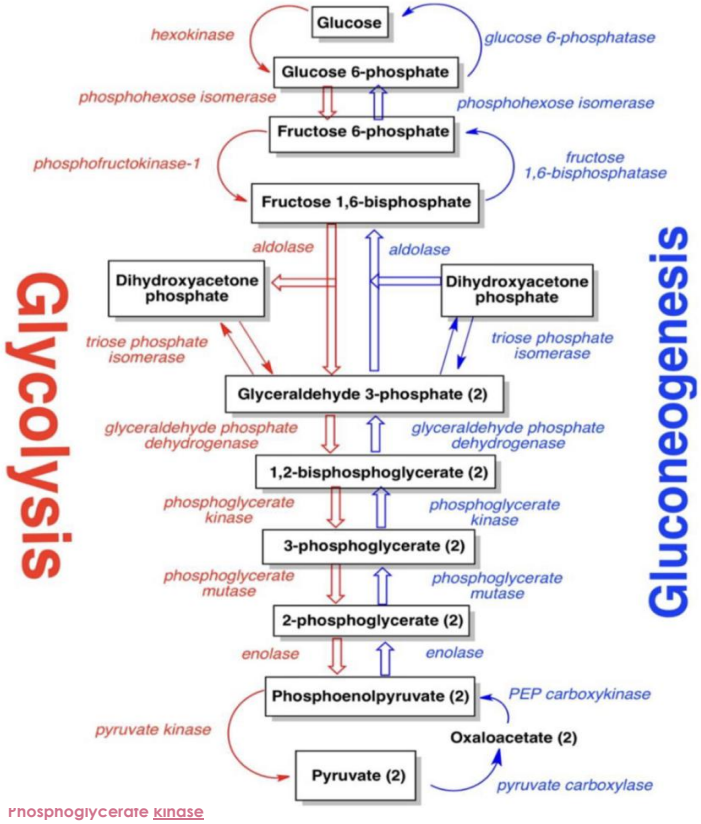
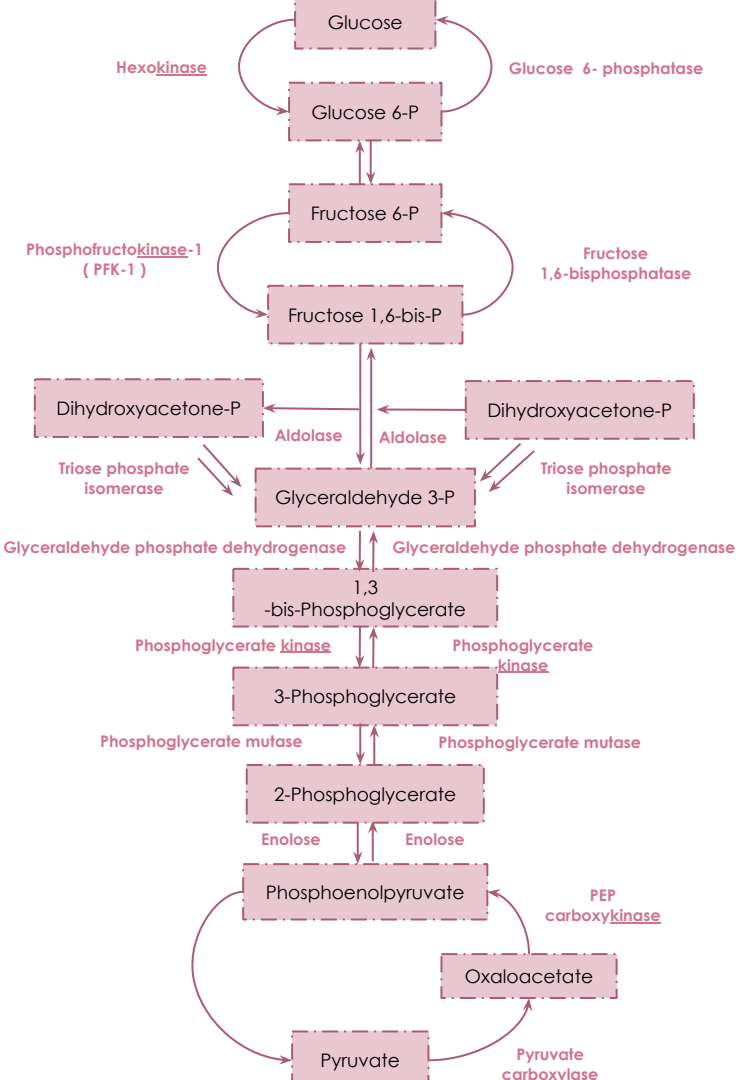
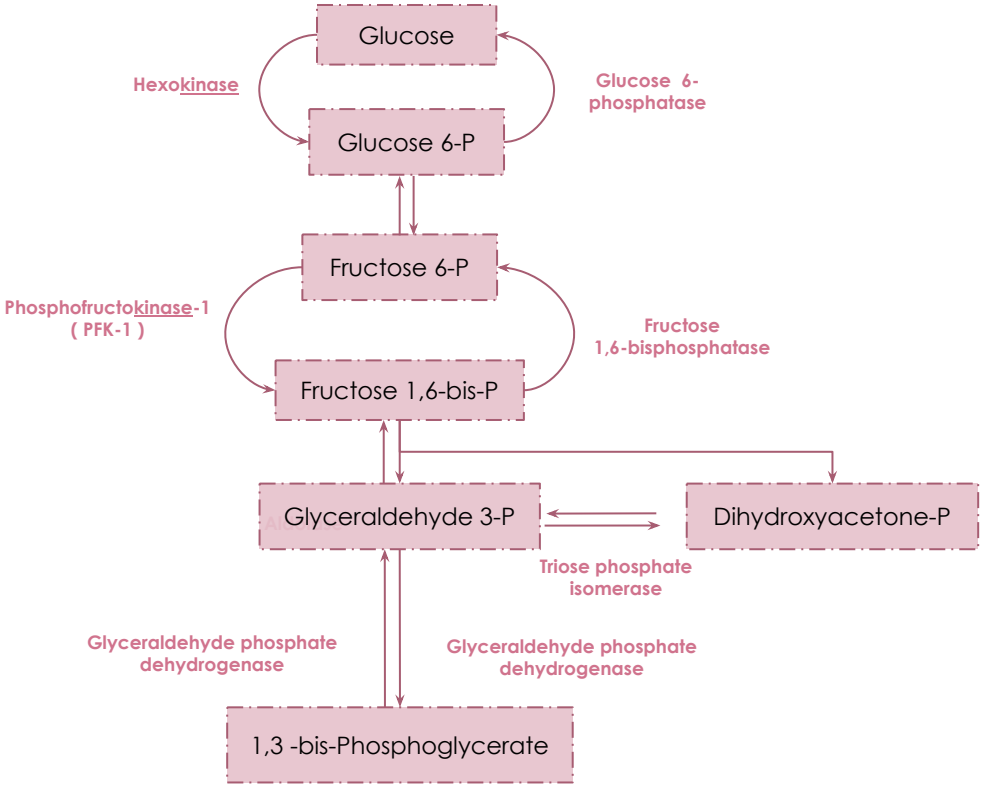
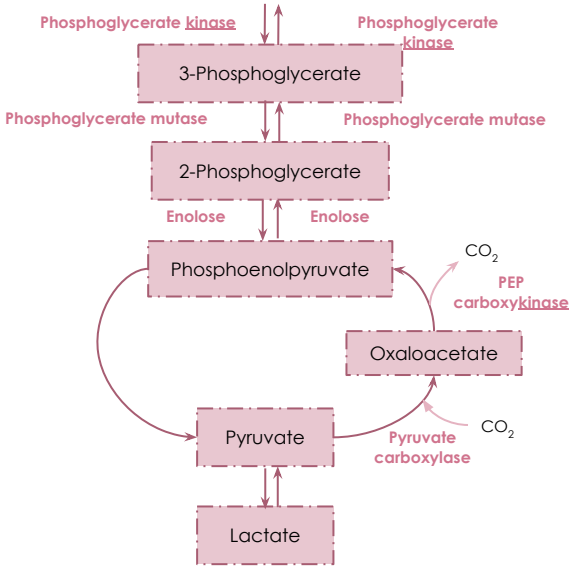

Glucose
Glucose 6-P
Fructose 6-P
Fructose 1,6-bis-P
Glyceraldehyde 3-P
Dihydroxyacetone-P
1,2 -bis-Phosphoglycerate
Phosphoglycerate kinase
Phosphoglycerate kinase
3-Phosphoglycerate
Phosphoglycerate mutase
Phosphoglycerate mutase
2-Phosphoglycerate
Enolose
Enolose
Phosphoenolpyruvate
PEP carboxykinase
Oxaloacetate
Pyruvate
Pyruvate carboxylase


Glycolysis
Gluconeogenesis
Glucose
hexokinase
glucose 6-phosphatase
Glucose 6-phosphate
phosphohexose isomerase
phosphohexose isomerase
Fructose 6-phosphate
phosphofructokinase-1
fructose 1,6-bisphosphatase
Fructose 1,6-bisphosphate
aldolase
aldolase
Dihydroxyacetone phosphate
Dihydroxyacetone phosphate
triose phosphate isomerase
triose phosphate isomerase
Glyceraldehyde 3-phosphate (2)
glyceraldehyde phosphate dehydrogenase
glyceraldehyde phosphate dehydrogenase
1,2-bisphosphoglycerate (2)
phosphoglycerate kinase
phosphoglycerate kinase
3-phosphoglycerate (2)
phosphoglycerate mutase
phosphoglycerate mutase
2-phosphoglycerate (2)
enolase
enolase
Phosphoenolpyruvate (2)
PEP carboxykinase
pyruvate kinase
Oxaloacetate (2)
Pyruvate (2)
pyruvate carboxylase
Phosphoglycerate kinase


Glucose
Hexokinase
Glucose 6- phosphatase
Glucose 6-P
Fructose 6-P
Phosphofructokinase-1
(PFK-1)
Fructose
1,6-bisphosphatase
Fructose 1,6-bis-P
Dihydroxyacetone-P
Aldolase
Aldolase
Dihydroxyacetone-P
Triose phosphate
isomerase
Triose phosphate
isomerase
Glyceraldehyde 3-P
Glyceraldehyde phosphate dehydrogenase
Glyceraldehyde phosphate dehydrogenase
1,3
-bis-Phosphoglycerate
Phosphoglycerate kinase
Phosphoglycerate
kinase
3-Phosphoglycerate
Phosphoglycerate mutase
Phosphoglycerate mutase
2-Phosphoglycerate
Enolose
Enolose
Phosphoenolpyruvate
PEP
carboxykinase
Oxaloacetate
Pyruvate
Pyruvate
carboxylase


Glucose
Hexokinase
Glucose 6-phosphatase
Glucose 6-P
Fructose 6-P
Phosphofructokinase-1 (PFK-1)
Fructose 1,6-bisphosphatase
Fructose 1,6-bis-P
Glyceraldehyde 3-P
Dihydroxyacetone-P
Triose phosphate isomerase
Glyceraldehyde phosphate dehydrogenase
Glyceraldehyde phosphate dehydrogenase
1,3 -bis-Phosphoglycerate


Phosphoglycerate kinase
Phosphoglycerate kinase
3-Phosphoglycerate
Phosphoglycerate mutase
Phosphoglycerate mutase
2-Phosphoglycerate
Enolose
Enolose
Phosphoenolpyruvate
CO_2
PEP carboxykinase
Oxaloacetate
Pyruvate
CO_2
Pyruvate carboxylase
Lactate

A helpful video

Gluconeogenesis , Contd....

- The **4 alternate reactions** in gluconeogenesis " reaction 1 , 3 and 10 in glycolysis are irreversible that's why it must be reversed ".

1 Pyruvate (3C) —(Pyruvate carboxylase)→ Oxaloacetate (4C)

- CO_2 + ATP In.
- ADP out.
- Carboxylation " adds a carobin group " of pyruvate by **pyruvate carboxylase** and it occurs in mitochondria.

2 Oxaloacetate (4C) —(PEP carboxykinase)→ Phosphoenolpyruvate "PEP" (3C)

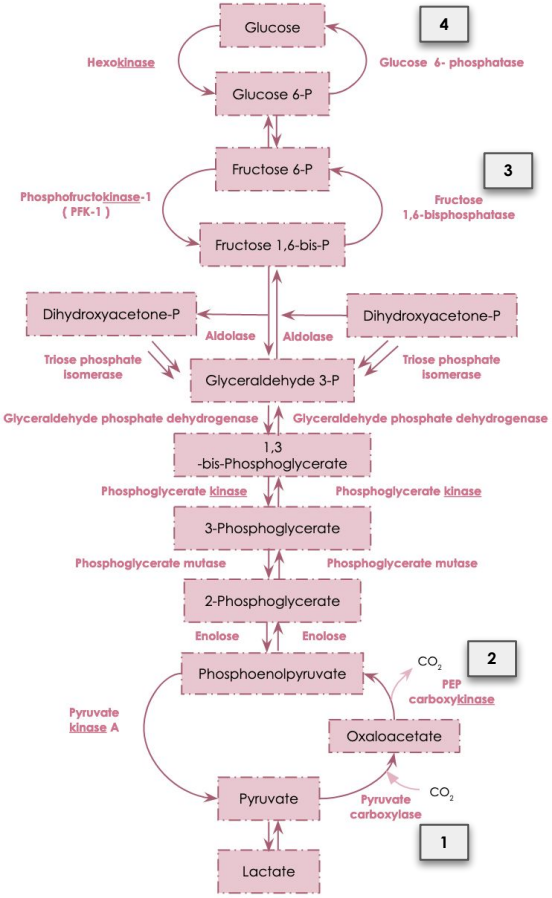
- GTP in
- GDP + CO_2 Out.

3 Fructose 1,6-bis-phosphate (6C) —(Fructose 1,6-bisphosphatase)→ Glucose 6-phosphate(6C)

- Dephosphorylation of Fructose 1,6-bis-phosphate.

4 Glucose 6-Phosphate (6C) —(Glucose 6-phosphatase)→ Glucose 6-phosphate (6C)

- Dephosphorylation of Glucose 6-Phosphate.



هذي بكل بساطة اللي غيرناه بال gluconeogenesis الباقي نفس ال glycolysis .

Gluconeogenesis in general metabolism

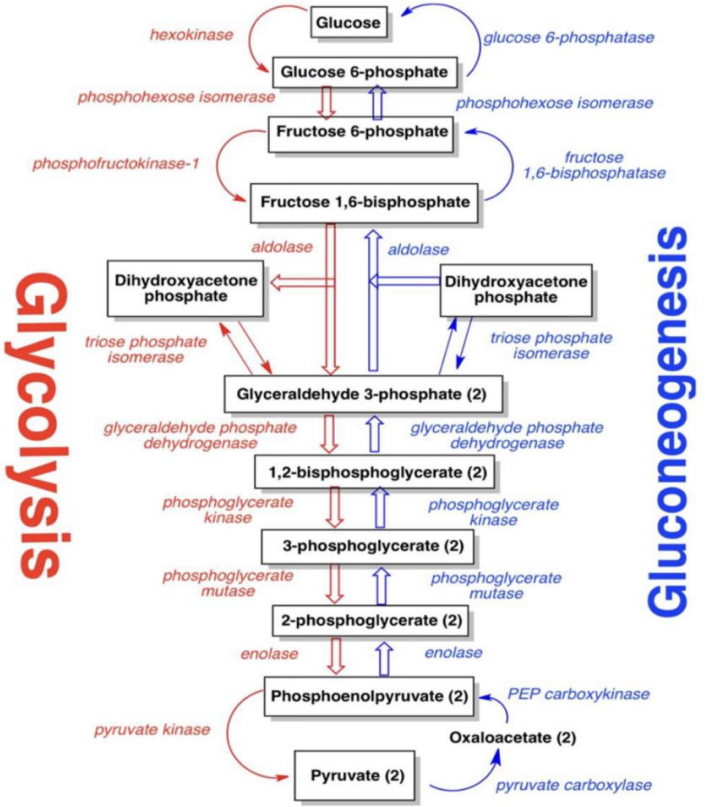
- The gluconeogenesis pathway is one of the essential pathways of energy metabolism.
  - Gluconeogenesis is an **energy consuming** (anabolic pathway).
  - Synthesis of glucose from non-carbohydrates molecules.

Site:
- **Liver** (mainly)
- **Kidneys**

- Both **mitochondria** and **Cytosol** are involved

Exception: if the substrate is **Glycerol**: only in **cytosol**

- **Gluconeogenic substrates:**
  - Glycerol
  - Lactate and Pyruvate
  - Glucogenic amino acids



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.

Gluconeogenesis Pathway

reactions 1 & 3 & 10 in glycolysis are irreversible

Helpful video

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

1) **Pyruvate** → **Oxaloacetate**

- Carboxylation of pyruvate by **pyruvate carboxylase**
- In **mitochondria**

2) **Oxaloacetate** → **PEP**

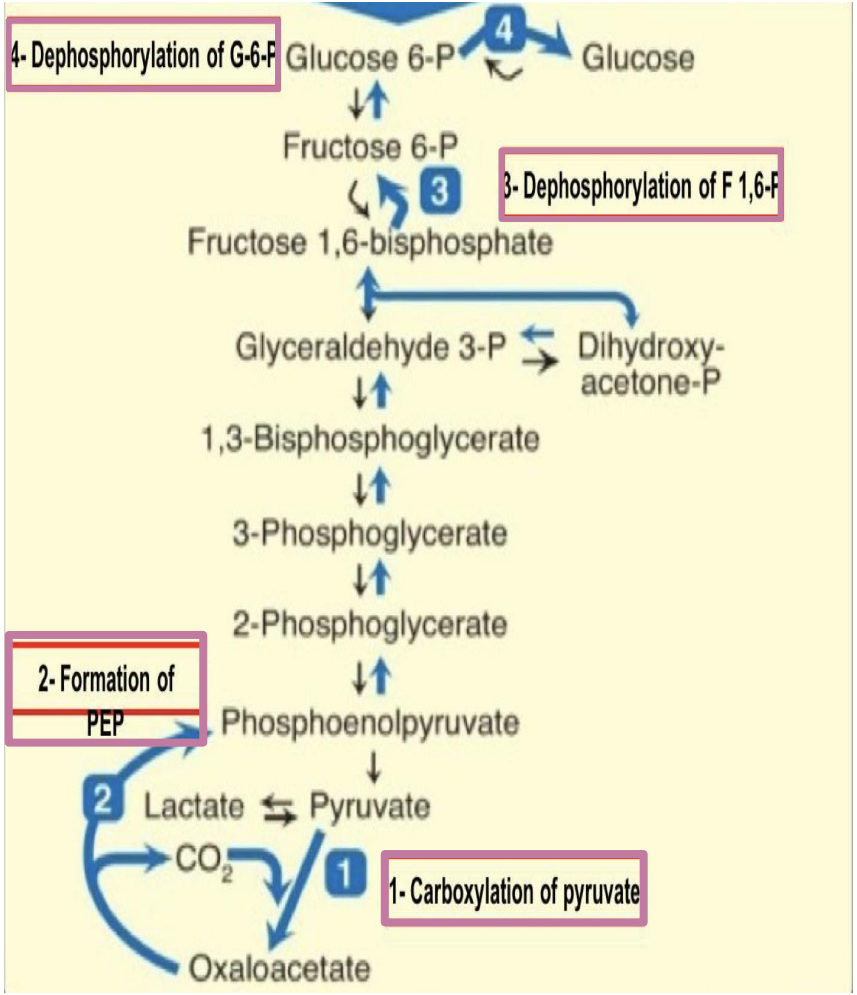
- By PEP-CK (phosphoenolpyruvate carboxykinase)

3) **Fructose 1,6-bisphosphate** → **Fructose 6-P**

- Dephosphorylation of F 1,6-P
- By Fructose 1,6 bisphosphatase

4) **Glucose 6-P** → **Glucose**

- Dephosphorylation of G-6-P
- By Glucose 6-phosphatase



Gluconeogenesis Pathway

هذي عشان نعكس تفاعل ١٠ لانه Irreversible فنحتاج نحوس

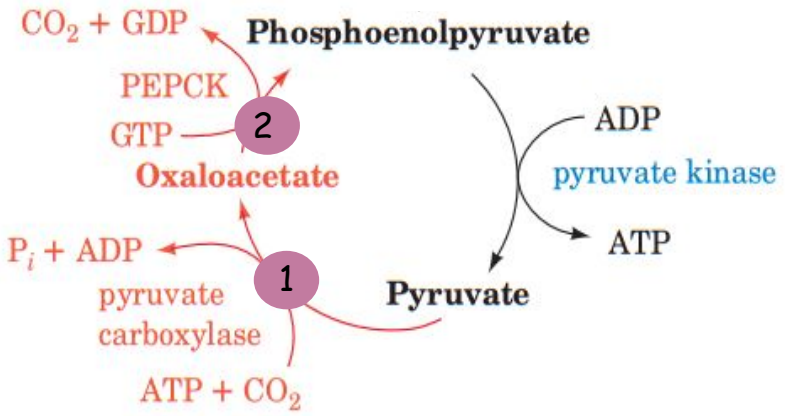
reactions 1 & 3 & 10 in glycolysis are irreversible

To sum up

Reaction 1	
Reactant	Pyruvate
Product	Oxaloacetate
Enzyme	Pyruvate carboxylase
Action	Adding CO2 Converts 3c → 4c*
Consume	1 ATP

Reaction 2	
Reactant	Oxaloacetate
Product	PEP (Phosphoenolpyruvate)
Enzyme	PEPCK (phosphoenolpyruvate carboxykinase)
Action	Removing CO2 and adding one phosphate
Consume	1 GTP

PEP to pyruvate is reaction 10 in glycolysis



We need to go in the exact opposite of glycolysis but since the reactions 1,3 and 10 in glycolysis are irreversible we have to take a detour (go **around**)

*carbons

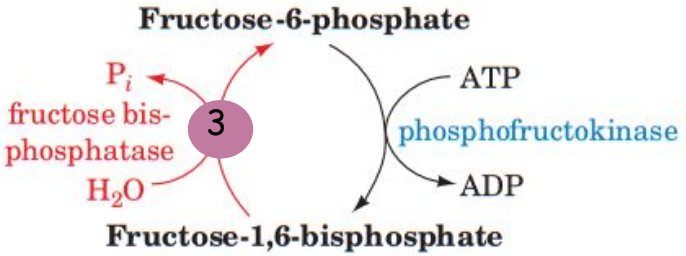
Gluconeogenesis Pathway

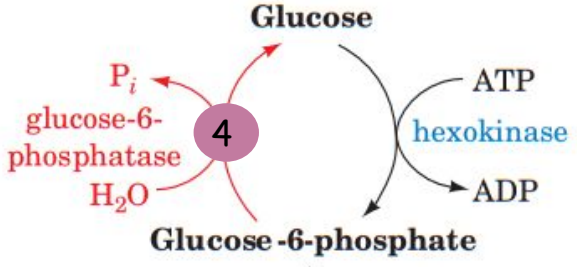
To sum up

Reaction 3	
Reactant	Fructose-1,6-bis phosphate
Product	Fructose-6-phos phate
Enzyme	Fructose bisphosphatase
Action	Removing one phosphate
Consume	H2O

Reaction 4	
Reactant	Glucose-6-pho sphate
Product	Glucose
Enzyme	Glucose-6-pho sphatase
Action	Removing one phosphate
Consume	H2O

Fructose-6-phosphate to fructose -1,6-bisphosphate is reaction 3 in glycolysis





Glucose to glucose-6-phosphate is reaction 1 in glycolysis