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12

Gluconeogenesis

Color index :

Main text

IMPORTANT

Extra Info

Drs Notes

Foundation Block - Biochemistry Team

Revised & Approved by:
Shayma Abdullah Alghanoum
Faisal Alotaibi

MED439
KING SAUD UNIVERSITY

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 ".

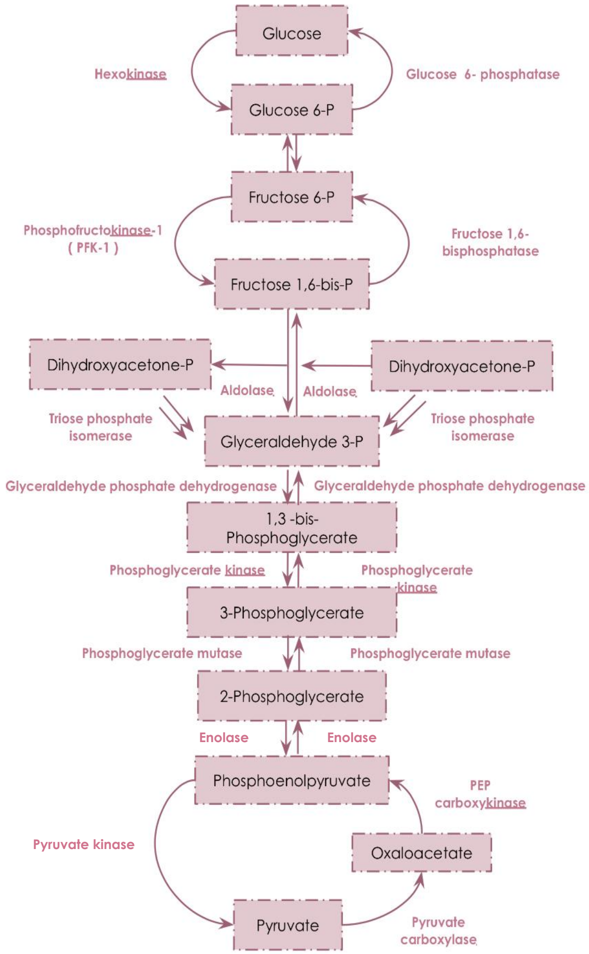
Gluconeogenic substrates:

- **Glycerol**
  - The glycerol backbone is found in all lipids known as triglycerides.
- **Lactate and pyruvate**
  - Lactate : Produced from pyruvate via the enzyme lactate dehydrogenase in a process of fermentation during normal metabolism and exercise.
  - Pyruvate : a key intermediate in several metabolic pathways. Pyruvate can be made from glucose through glycolysis, converted back to glucose via gluconeogenesis
- **Glucogenic amino acids**
  - A glucogenic amino acid : is an amino acid that can be converted into glucose through gluconeogenesis . - Not all amino acids can make glucose there are certain types - .

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



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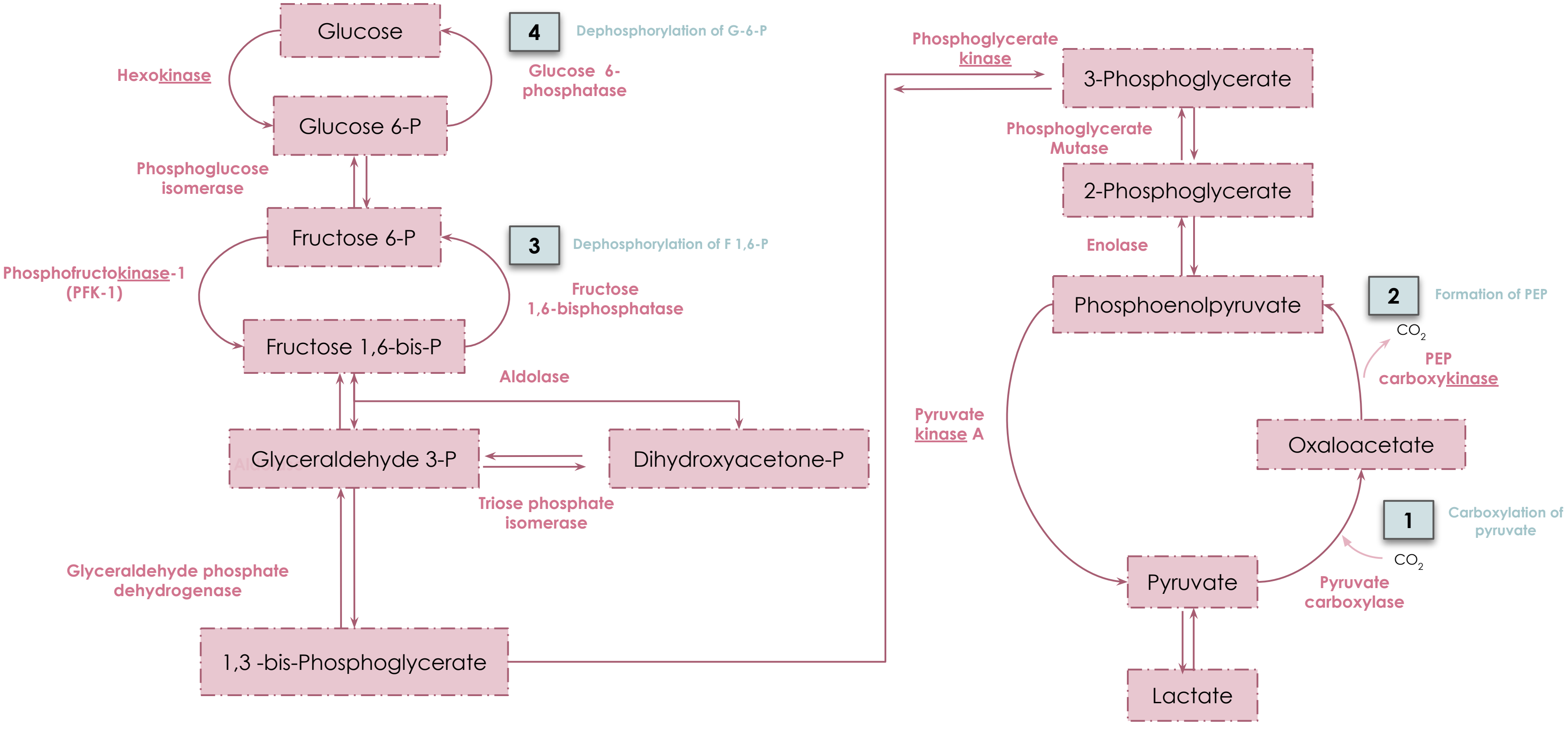
Glycolysis and Gluconeogenesis (overview)



We have 4 alternate reactions

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 with the help of **Pyruvate carboxylase** enzyme and it occurs in mitochondria.

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

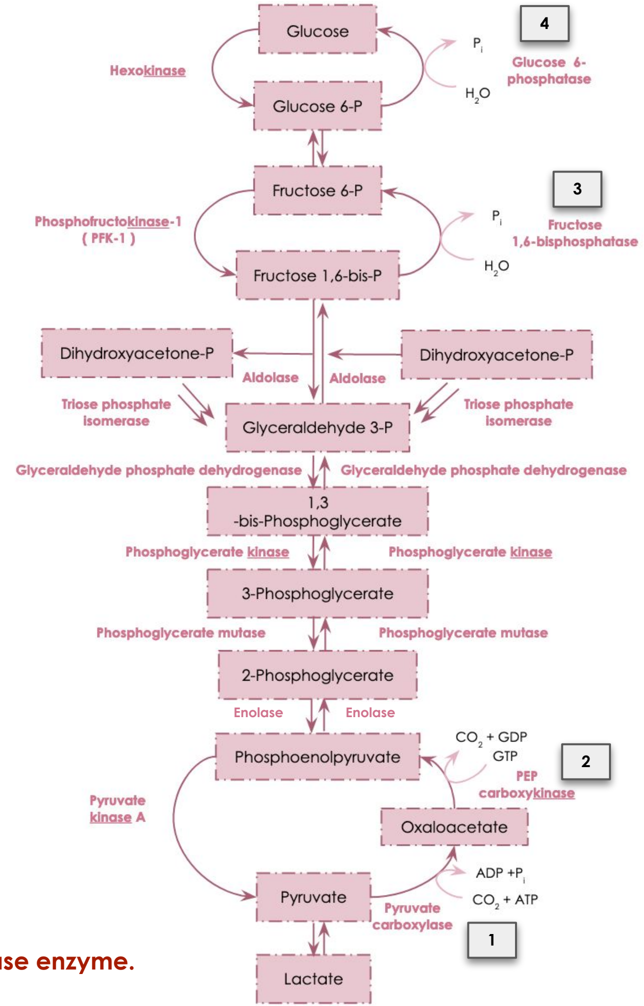
- GTP in
- GDP + CO_2 Out.
- **Formation of Phosphoenolpyruvate "PEP"** with the help of **PEP carboxykinase enzyme.**

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

- H_2O In.
- P_i Out.
- **Dephosphorylation of Fructose 1,6-Phosphate** with the help of **Fructose 1,6-bisphosphatase** enzyme.

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

- H_2O In.
- P_i Out.
- **Dephosphorylation of Glucose -6-Phosphate** with the help of **Glucose 6- phosphatase enzyme.**



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

★ extra explanation

Summary of the 4 alternate reactions 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	Oxaloacetate
Product	Phosphoenolpyruvate "PEP"
Enzyme	**PEP carboxykinase**
Action	Adding a 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

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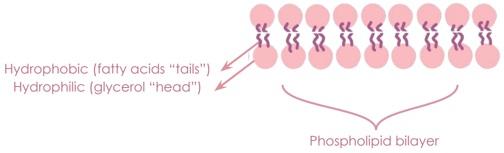
Gluconeogenic Substrates: Glycerol



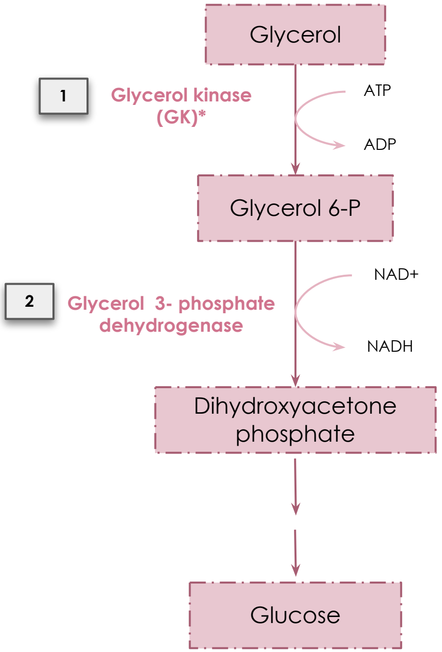
- Glycerol kinase present only in liver and kidneys.
- Gluconeogenesis of glycerol occurs in only the cytosol.
- Glycerol is released during the hydrolysis of Triacylglycerol (TAG) in adipose tissue.

1 Glycerol —(**Glycerol kinase**)→ Glycerol 3-Phosphate

- ATP In.
- ADP out.
- Phosphorylation "adds a phosphate group to Glycerol with the help of **Glycerol kinase**"enzyme.

2 Glycerol 3-Phosphate —(**Glycerol 3-phosphate dehydrogenase**)→ Dihydroxyacetone phosphate

- NAD+ In.
- NADH out.
- Oxidation of Glycerol 3-Phosphate with the help of **Glycerol 3-phosphate dehydrogenase** enzyme. (oxidation reaction which involves the reduction of NAD+ to NADH)



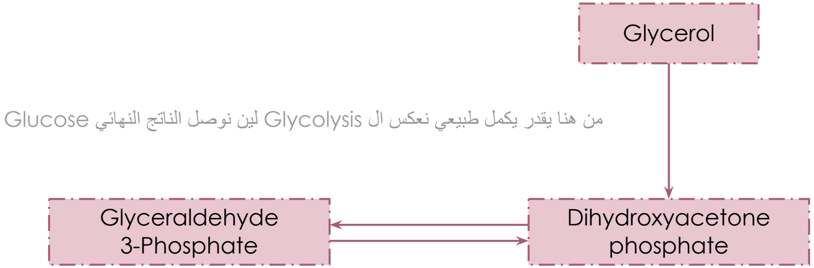
Glycerol kinase (GK)*: Present only in liver and kidney

★ extra explanation

Summary of pathway “Glycerol as gluconeogenic substrate” In order for you to gain a better understanding (In tables)

Reaction 1	
Reactant	Glycerol
Product	Glycerol 3-Phosphate
Enzyme	**Glycerol Kinase**
Action	Adding one phosphate
Consume	1 ATP

Reaction 2	
Reactant	Glycerol 3-Phosphate
Product	Dihydroxyacetone phosphate
Enzyme	**Glycerol 3-phosphate dehydrogenase**
Action	Oxidation
Produce	NADH



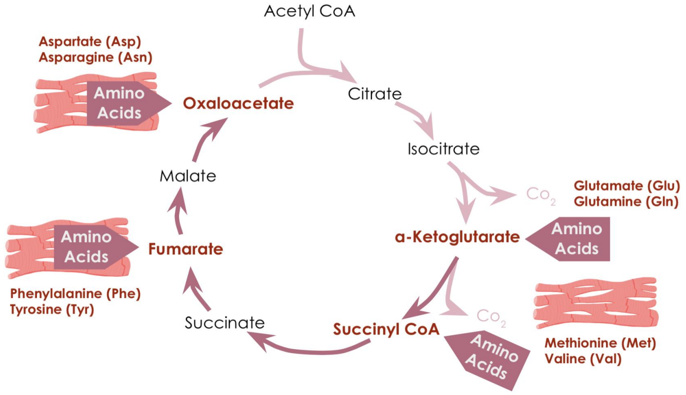
Gluconeogenic Substrates: Glucogenic Amino Acids

★ Everything in red, You have to memorize it
★ You have to know the names of the 4 entrance points and the amino acids

The catabolism of glucogenic amino acids produces either:

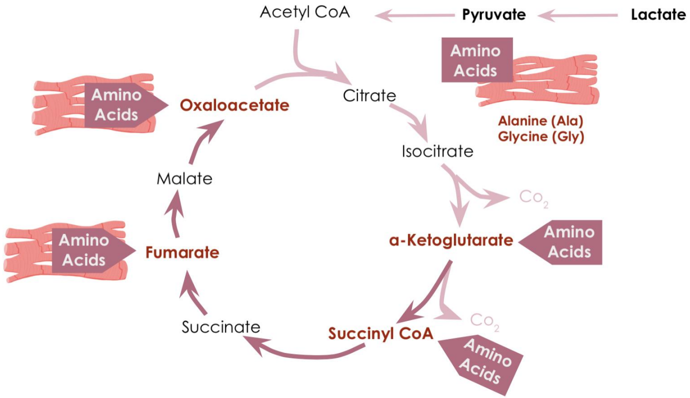
- One of the intermediates in the Krebs Cycle

  For example: catabolizing Asparagine and Aspartate produces Oxaloacetate (an intermediate) which can converted later to glucose



- Pyruvate

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



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

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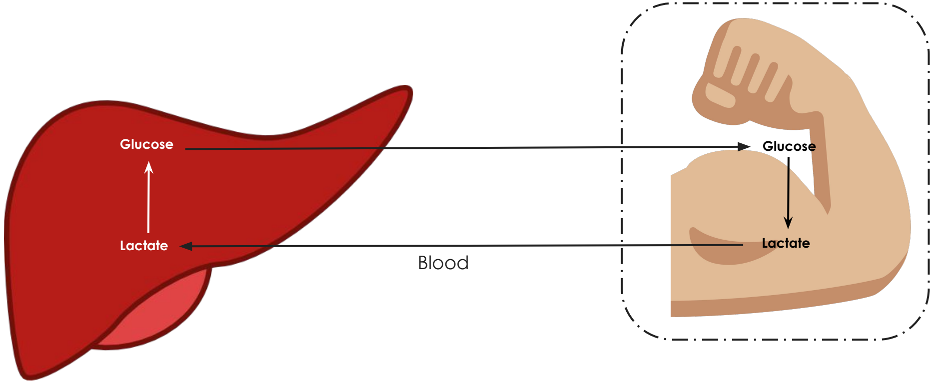
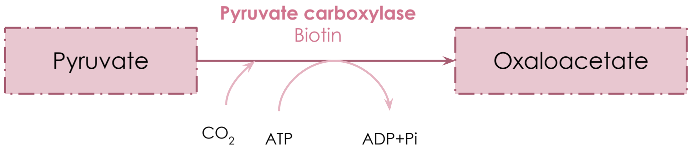
Gluconeogenic Substrates: Lactate (Cori Cycle)

- 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 Carboxylation

- 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 CO_2 more active to bind.



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Pyruvate Carboxylase and PEP-CK

1 CO_2 from HCO_3^- and transferred by pyruvate carboxylase to its biotin prosthetic group.

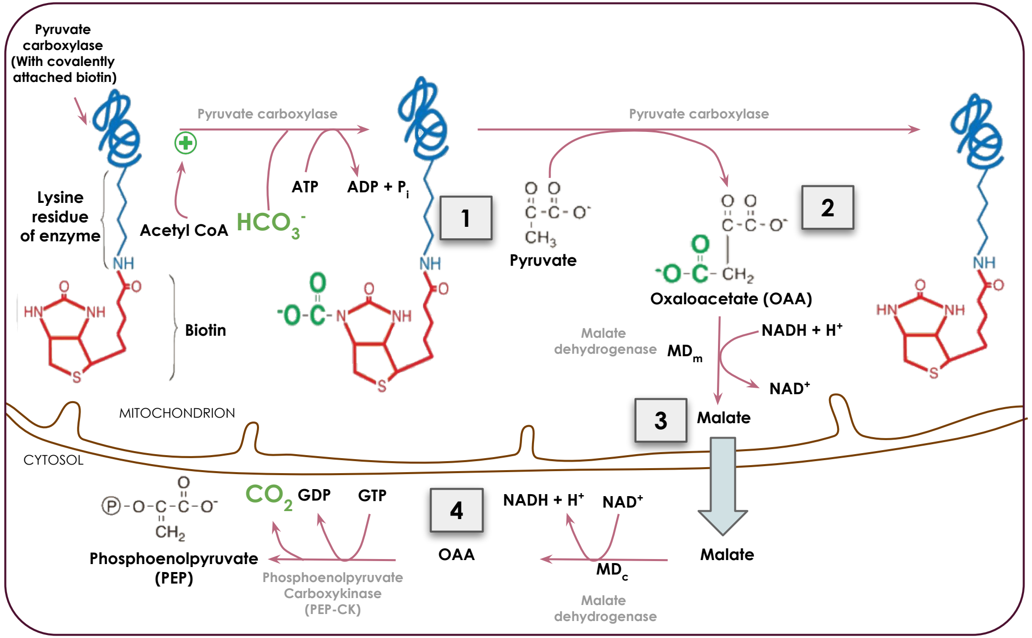
2 The enzyme "pyruvate carboxylase" then transfers the CO_2 to pyruvate, generating oxaloacetate .

3 Oxaloacetate cannot cross the mitochondrial membrane so it is reduced to malate that can cross.

4 In the cytosol, malate is reoxidized to oxaloacetate, which is oxidatively decarboxylated to phosphoenolpyruvate by PEP carboxykinase.

Fasting: ↑ Acetyl CoA (From FAO)*

* Fatty Acid Oxidation



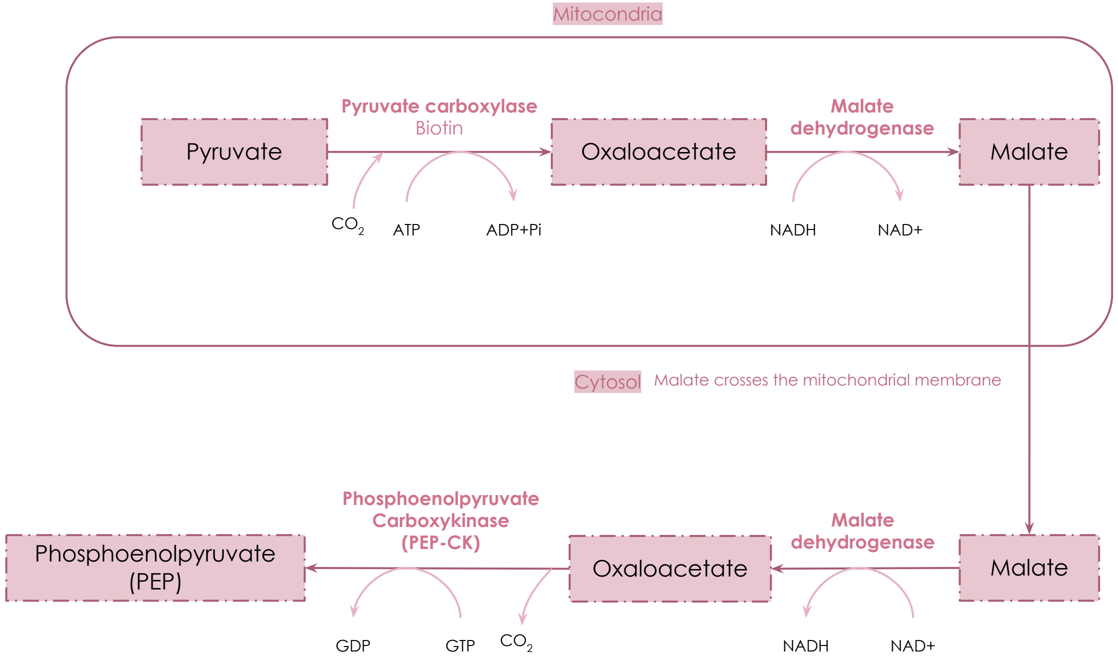
Pyruvate carboxylase + PEP-CK ≠pyruvate kinase

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)

★ extra explanation
Thanks to #Med436

1. الـ Pyruvate زي ماقلنا لازم يدخل الـ Mitochondria، ليش ؟
عشان هناك راح يلقى الـ Pyruvate Carboxylase اللي يحوله إلى Oxaloacetate
المشكلة ان الـ Oxaloacetate مايقدر يطلع من الـ Mitochondria بصورته هذي، والحل طيب؟
راح يجي الـ Malate Dehydrogenase ويحوله بشكل مؤقت إلى Malate بالاختزال

2. الحين الـ Malate يقدر يطلع من الـ Mitochondria ويروح لـ cytoplasm، ليش؟
لأن الهدف من هذا كله هو اني أكوّن Glucose وأنزله على الدم ويروح للخلايا الثانية عشان تستخدمه وتنتج طاقة، في الـ Cytoplasm يصير له أكسدة بنفس الإنزيم Malate Dehydrogenase ويرجع يتحوّل إلى Oxaloacetate و هذا اللي نبغاه، ليش؟
لأن فيه انزيم مهم وهو Phosphoenolpyruvate carboxykinase (PEP-CK) راح يحوّله أخيراً إلى Phosphoenolpyruvate اللي بدوره بيكمل السالفة



Regulation of Pyruvate Carboxylase Reaction

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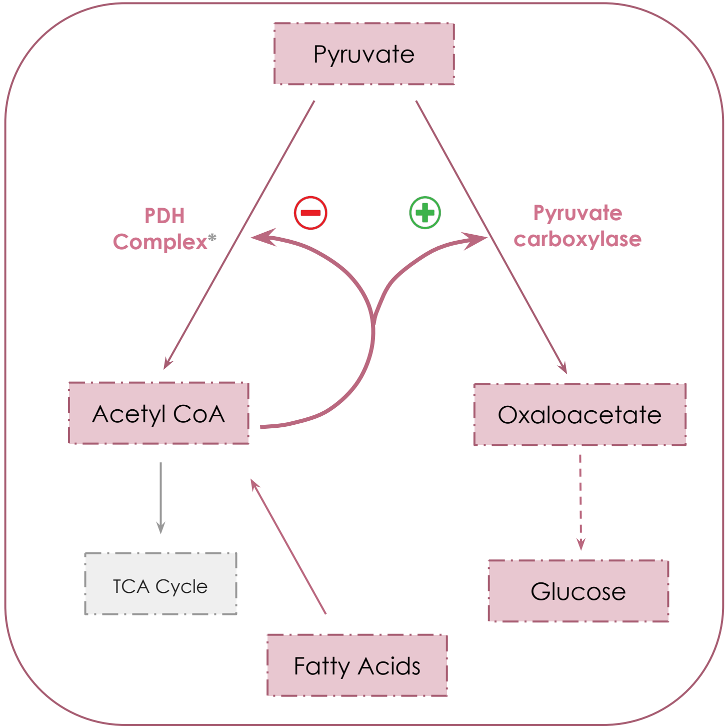
- Acetyl CoA diverts pyruvate away from oxidation in Krebs cycle and toward gluconeogenesis

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 (Pyruvate dehydrogenase complex) and stop or reduce the Glycolysis.
- PDH function: converts Pyruvate to Acetyl coA

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

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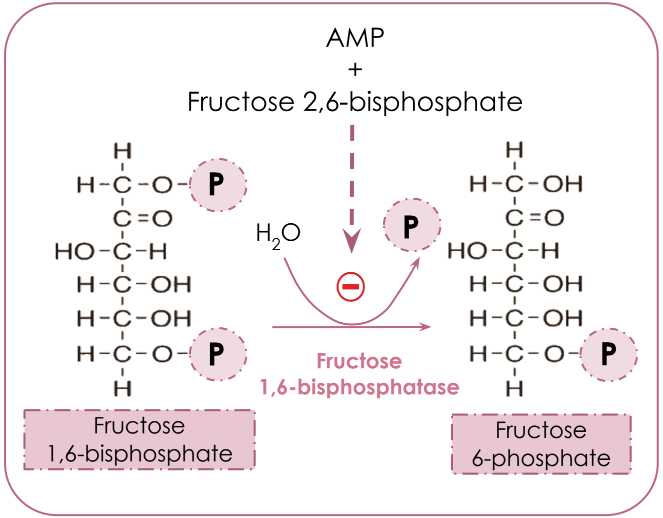
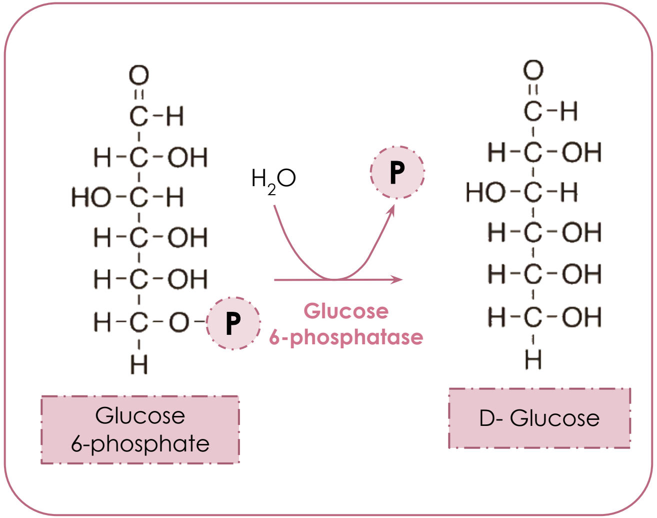
Dephosphorylation of Fructose 1,6-bisphosphate



- 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
- Glucokinase is an enzyme that facilitates phosphorylation of glucose to glucose-6-phosphate.

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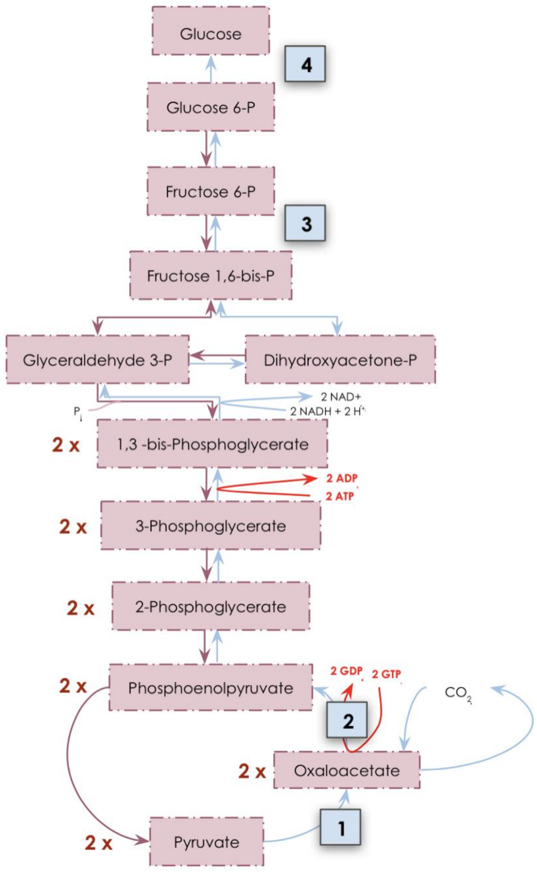
Gluconeogenesis: Energy-consumed

Total of Energy consumed	
2 Pyruvate convert to **2** Oxaloacetate	**-2** ATP
2 GTP convert to 2 GDP	**-2** ATP
2 (3-Phosphoglycerate) convert to **2** (1-3 bisphosphoglycerate)	**-2** ATP
2 NADH converted to NAD+	**+6** ATP
Net	**0** ATP

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



Gluconeogenesis: Regulation

1 Reciprocal control

- Gluconeogenesis and Glycolysis
- The processes of gluconeogenesis and glycolysis are regulated in a reciprocal fashion, Which means that when one process is highly active, the other one is inhibited

2 Allosteric

- Acetyl CoA ⊕ (Pyruvate carboxylase)

  Which means pyruvate carboxylase enzyme will be activated by high levels of Acetyl CoA

- AMP ⊖ or ATP ⊕
- F 2,6-Bisphosphate ⊖

} F 1,6-bisphosphatase

1. When we have high levels of AMP (indicating low level of energy) we don't want to store glucose ,we want break down glucose to create ATP (more energy) so low energy state will inhibit Gluconeogenesis by inhibiting Fructose 1,6-bisphosphatase
2. When we have high levels of Fructose 2,6-Bisphosphate (indicating high levels of glucose) we don't need to make more of it cuz we already have more of it so it will inhibit Gluconeogenesis by inhibiting Fructose 1,6-bisphosphatase
3. When we have high levels of ATP (indicating high level of energy) we want to store glucose (store energy) so we will activate Gluconeogenesis by activating Fructose 1,6-bisphosphatase

3 ↑ Glucagon (↓ I/G* ratio) Stimulates gluconeogenesis

*I = Insulin , G = glucagon

- **Allosteric** (↓ F 2,6-Bisphosphate)

  When we have high levels glucagon it will decrease Fructose 2,6-Phosphate that leads to inhibition of Phosphofructokinase-1"PFK-1" and activation of Fructose 1,6-bisphosphatase which will stimulate gluconeogenesis
- **Induction** (PEP-CK)

  We we have high levels of glucagon it will induce Phosphoenolpyruvate Carboxykinase "PEP-CK"

Important note:

- Pyruvate carboxylase is only found in matrix of mitochondria
- Gluconeogenesis rate-limiting enzymes:
  - A. Pyruvate carboxylase
  - B. Phosphoenolpyruvate Carboxykinase (PEP-CK)

What does I/G ratio mean?

- The function of Glucagon is to rise blood glucose level in the blood whereas Insulin lowers blood glucose level in the blood, So to enhance Gluconeogenesis we need a huge amount of glucagon

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

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
Q5 : Where is the site of conversion of Lactate into Glucose?			
A) The Blood	B) Pancreas	C) Kidney	D) Liver
Q6 : What is the reciprocal pathway to Gluconeogenesis (opposite pathway)?			
A) Glycogenolysis	B) Hexose Inversion	C) Glycolysis	D) Cori Cycle

SAQs :

Q1: What substrates can be used for gluconeogenesis?

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

★ **MCQs Answer key:**

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

★ **SAQs Answer key:**

1) Glycerol , Lactate and Pyruvate, Glucogenic amino acids
2) Slide 6

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

Shatha Aldhohair

Boys team:

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

Mishal Althunayan

"Do good and good will come to you."

Made by

Biochemistry439@gmail.com
@Biochemistry439