Gloconeogeniesis

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- Color Index:
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  - Important.
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  - Extra information

Biochemistry team 438

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

*Note: Enzymes are so important in this lecture don’t forget to memorize them!

Gluconeogenesis

- Gluconeogenesis is an energy consuming, anabolic pathway.
  It is a metabolic pathway that results in: the generation of glucose from certain **non**-carbohydrate carbon substrates . (it's one of the essential pathways of energy metabolism)

- Occurs in **Liver** mainly, and in **Kidney**
- During Overnight fast: 90% of gluconeogenesis occurs in **liver**.
  10% of gluconeogenesis occurs in **Kidneys** .

- occurs in both mitochondria and cytosol .
  EXCEPTION! if gluconeogenesis starts by Glycerol, it will need only the cytosol. * **so the RBC will be involved .**

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

436 : **Gluconeogenic substrates**

- **Glycerol**: The glycerol backbone is found in all lipids known as triglycerides
- **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.

*Extra:
We get triglycerides by the oxidation of fat stored in our bodies (that's how weight is lost)

	Glucogenic	Glucogenic and Ketogenic	Ketogenic
Nonessential	Alanine Arginine Asparagine Aspartate Cysteine Glutamate Glutamine Glycine Proline Serine	Tyrosine	
Essential	Histidine Methionine Threonine Valine	Isoleucine Phenyl-alanine Tryptophan	Leucine Lysine

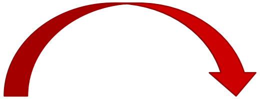
***Except**: lysine & leucine are ketogenic.
The rest may be glucogenic or both

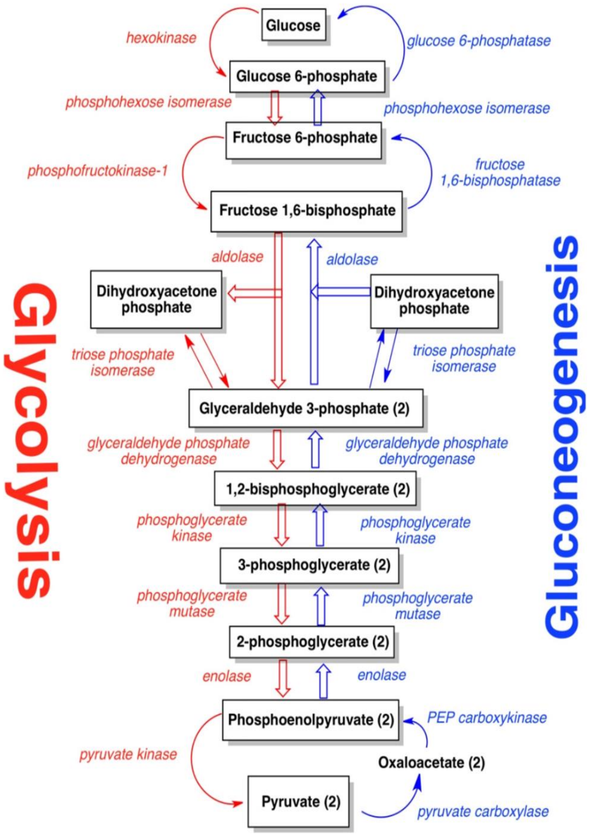
Gluconeogenic pathway

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 pathway

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

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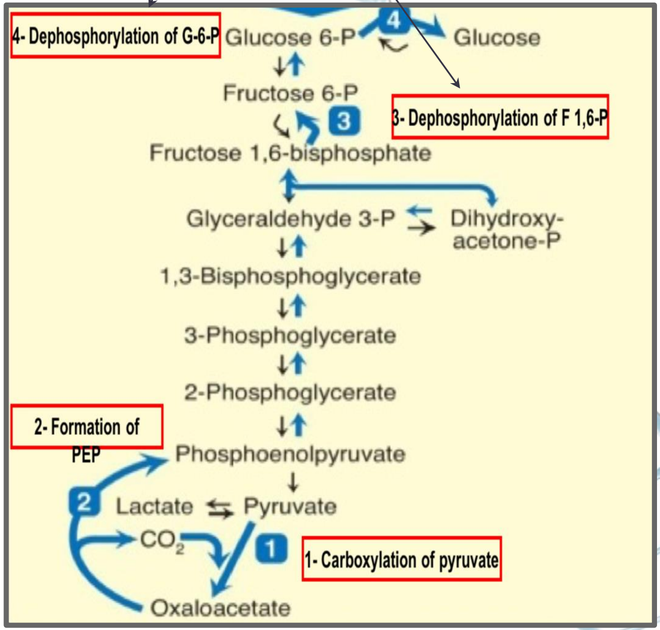
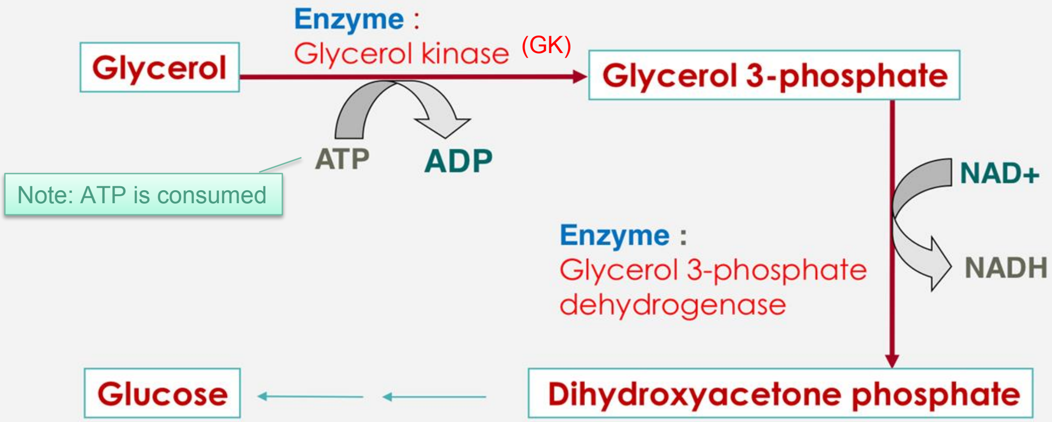


*Note: This Pathway occurs in the cytosol.

1. 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**

435:



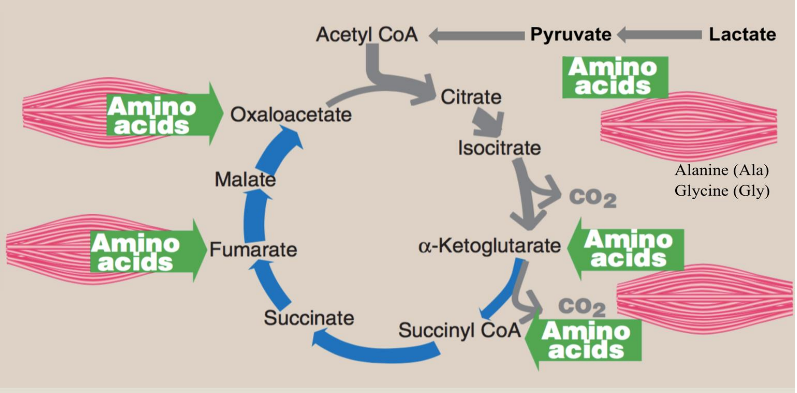
2. Gluconeogenic Substrates: Glucogenic Amino Acids (AAs)

435:
- AAs can be derived from **hydrolysis of tissue proteins**.
- The **anabolic** feature of gluconeogenesis.

436: مجموعة من الامينو اسد بتدخل كربس سايكل عن طريق

- The catabolism of glucogenic amino acids produces either:
  - pyruvate
  - **Or** one of the intermediates in the Krebs Cycle.

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

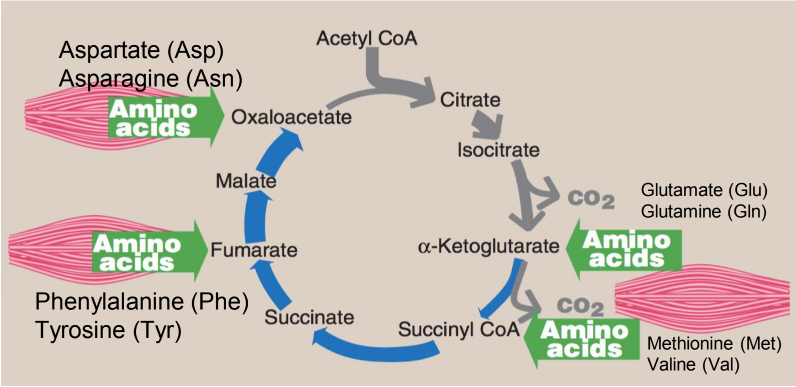


Alanine (Ala)
Glycine (Gly)

They are converted to **pyruvate** then to **oxaloacetate** then to **malate**

Notes:

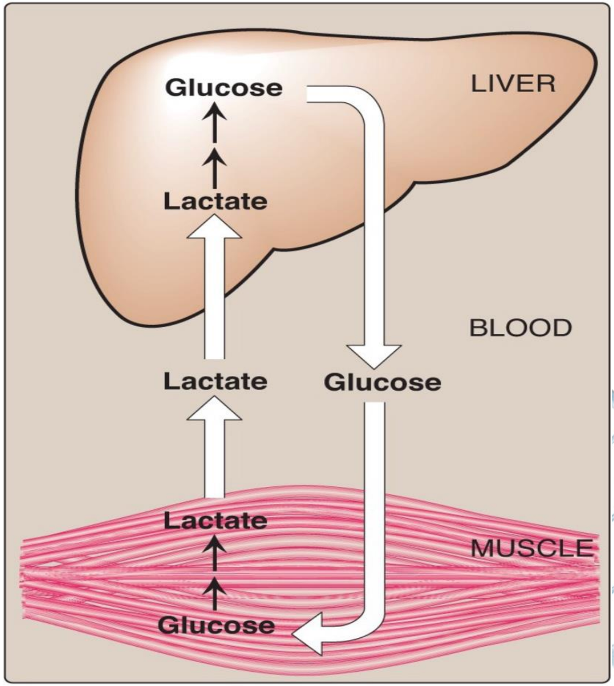
- Acetyl CoA can't be converted directly to pyruvate and therefore can't be converted to glucose
- Acetyl coA is converted to Oxaloacetate
- Oxaloacetate can be oxidized to form phosphoenolpyruvate
- After getting phosphoenolpyruvate the steps are the same in glycolysis which are reversible so we're getting close to getting glucose



3. Gluconeogenic Substrates: Lactate (Cori Cycle)

436: 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.

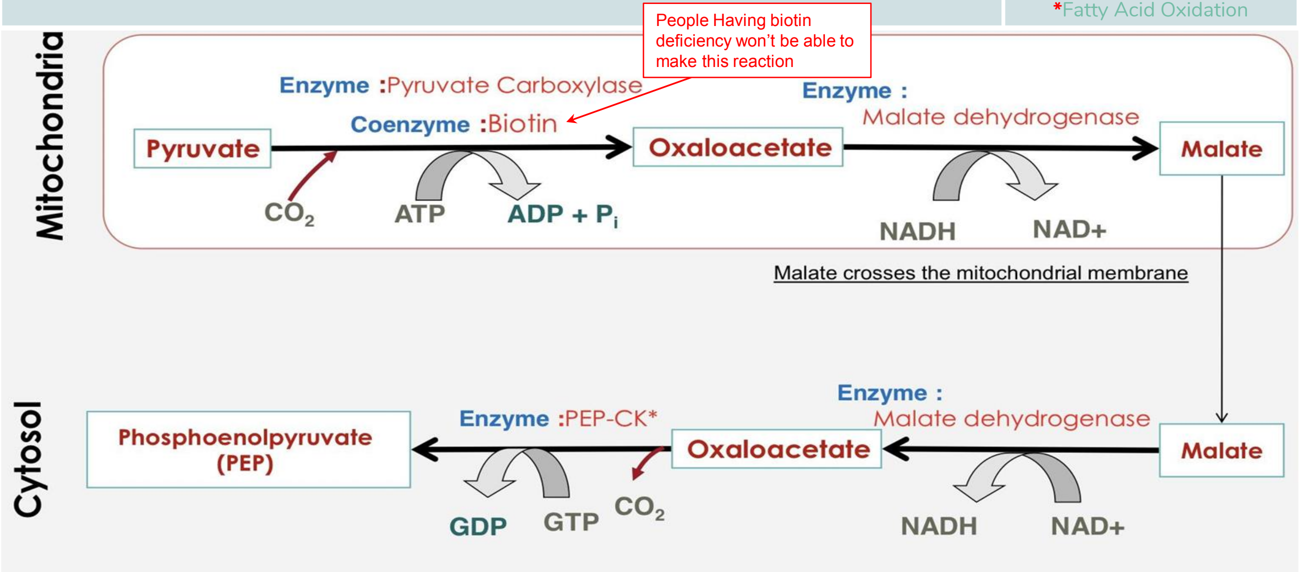


4. Gluconeogenic Substrates: Pyruvate Carboxylation

435 ♡:

- **Pyruvate Carboxylase** is induced by **Acetyl-CoA**

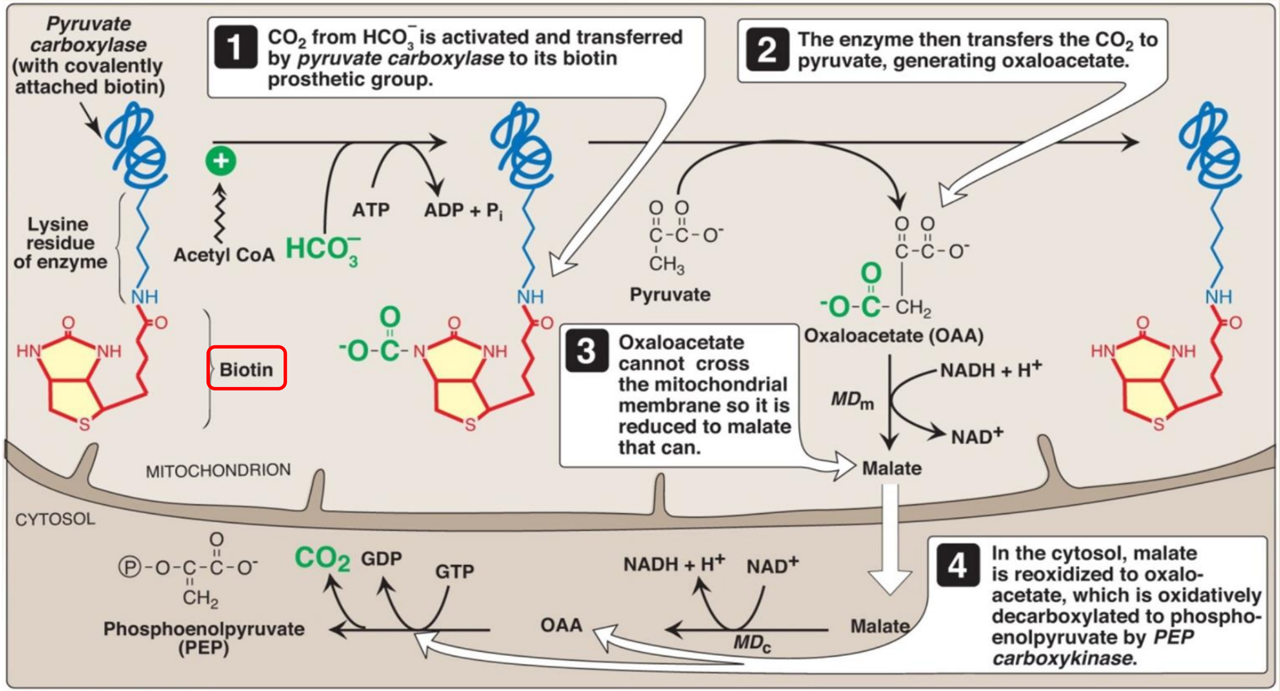
During Fasting:
↑Acetyl CoA
(From FAO)*
*Fatty Acid Oxidation



*PEP-CK= Phosphoenolpyruvate CarboxyKinase

Pyruvate carboxylase + PEP-CK ≠ Pyruvate kinase

Pyruvate Carboxylation & PEP-CK



Alternative way

Pyruvate carboxylase + PEP-CK = Pyruvate kinase

Notes:

- PEP-Ck = PhosphoEnolPyruvateCytoKinase
- MDm = Maltate Dehydrogenase (in mitochondria)

Regulation of Pyruvate Carboxylase reaction

Acetyl CoA diverts pyruvate away from **oxidation** (by PDH complex to produce acetyl coA) and toward **gluconeogenesis**

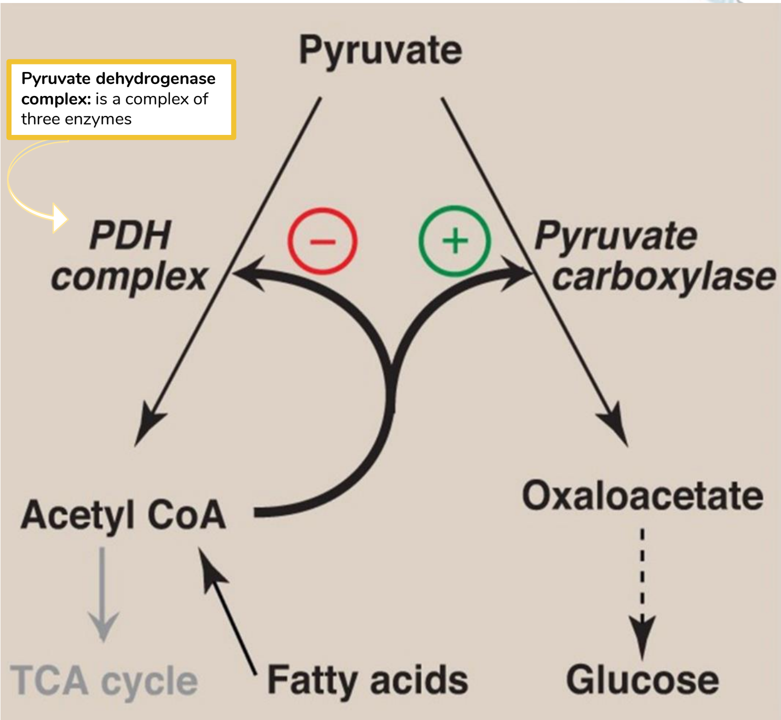
How? **High level of Acetyl-CoA** will **inhibit** **PDH complex** and stop or reduce the Glycolysis. And stimulate Pyruvate Carboxylase to start Gluconeogenesis.

+ positive regulation

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

-negative regulation

High level of Acetyl-coA inhibit PDH complex. PDH function: converts **pyruvate carboxylase** to **Acetyl coA**



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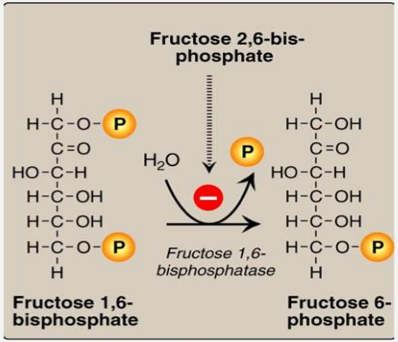
Fructose 1,6- bisphosphate

Enzyme :Fructose 1,6-bisphosphatase

Fructose 6- phosphate



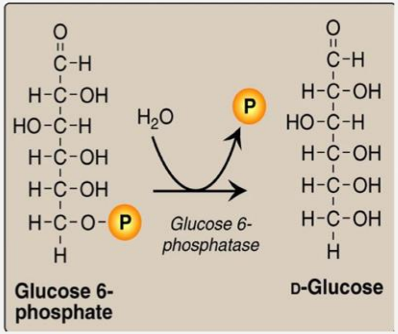
Dephosphorylation of fructose 1,6-bisphosphate

- 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



Dephosphorylation of glucose 6-phosphate

- allows release of free glucose from the liver and kidney into blood (By GLUT-2)
- Glucose 6-phosphatase ≠ Glucokinase

Notes:

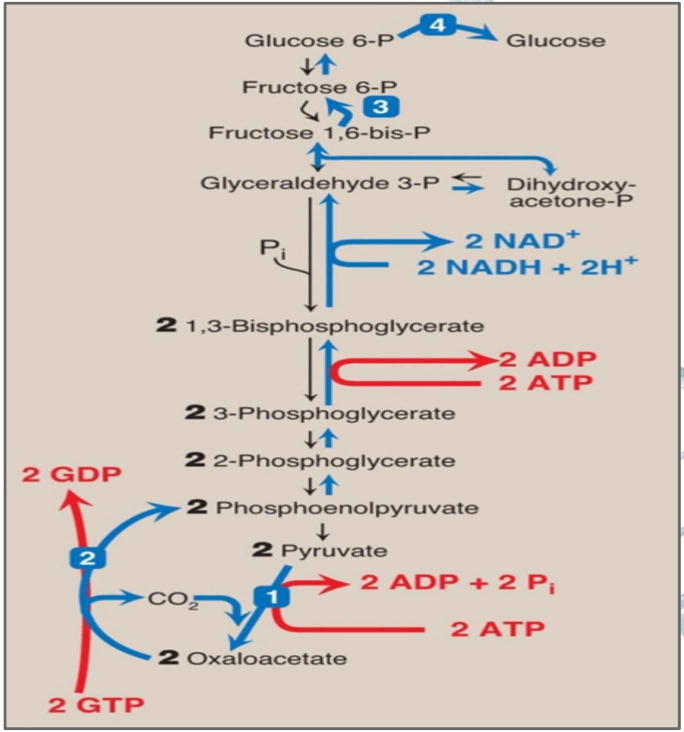
Fructose 2,6-bis-phosphate:

- **INHIBITS** fructose 1,6-bisphosphotase **(Gluconeogenesis)**
- **ACTIVATES** PFK-1 **(Glycolysis)**

Gluconeogenesis: Energy-Consumed

Six High-Energy Phosphate Bonds are consumed for the conversion of Pyruvate to Glucose

2Purvate convert to 2 Oxaloacetate	-2 ATP
2GTP convert to 2GDP	-2ATP
2 (3-Phosphoglycerate) convert to	-2ATP 2(1.3bisphosphoglycerate)
2 NADH converted to 2 NAD	6ATP
NET :	**0 ATP**



Gluconeogenesis: Regulation

Reciprocal control of :

Gluconeogenesis (محفز) & glycolysis (مثبط)

436 ♡:
Important!!!
Pyruvate carboxylase is only found in **matrix of mitochondria**

Gluconeogenesis rate-limiting enzymes:
- **Pyruvate carboxylase**
- **PEP-CK**

Allosteric regulation:

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

→ **F 1,6-bisphosphatase**

Hormonal Control

Glucagon (↓ I/G* ratio)
Allosteric (**F 2,6-Bisphosphate**)
Induction (**PEP-CK**)

If the insulin increase this deriving to glycolysis

If the insulin decrease (glucagon increase) this deriving to gluconeogenesis

*I = Insulin , G = glucagon

Review 435:

	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

Take Home Message

- Gluconeogenesis is an important pathway for glucose production from non-carbohydrate sources during prolonged fasting.

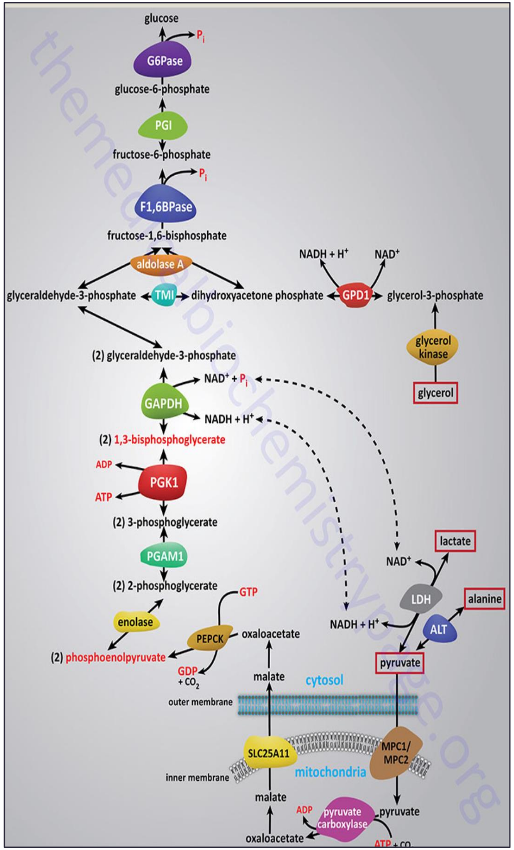
  •Lactate, glycerol and glucogenic amino acids are the major gluconeogenic substrates.

  •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.

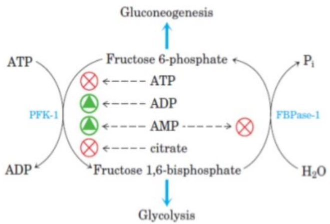
  •It is mainly anabolic pathway that consumes ATP for the synthesis of glucose.

This slide is EXTRA

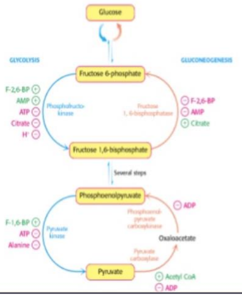


Allosteric regulation

- **Fructose 1,6- bisphosphatase-1 (FBPase1)**
  - Inhibited by AMP, when energy currency ATP is less
  - Thus there gluconeogenesis is down regulated because it is a energy consuming process.
  - The opposing effect of PFK-1 and FBPase-1 helps to regulate glycolysis and gluconeogenesis according to current need of cell



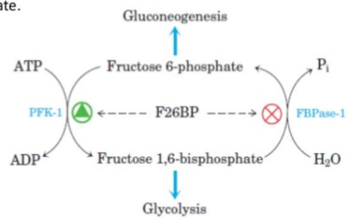
Reciprocal Regulation of Gluconeogenesis and Glycolysis in the Liver



- Glycolysis and Gluconeogenesis are reciprocally regulated .
- When glycolysis is on Gluconeogenesis is turned off especially in the fed state, whereas under conditions of starvation, gluconeogenesis is fully on and glycolysis is turned off.
- Both the cycles are never active at the same pace at the same time.

Hormonal Regulation

- hormonal regulation of glycolysis and gluconeogenesis is mediated by **fructose 2,6-bisphosphate.**
- F2,6-BP binds to allosteric site on PFK-1 increases that its affinity for substrate F 6-P, & reduces its affinity for the allosteric inhibitors ATP and citrate.



- PFK-1 is virtually inactive in the absence of F2,6-BP
- F2,6-BP *activates PFK-1 and stimulates* glycolysis in liver
- F2,6-BP *inhibits* FBPase-1 slowing gluconeogenesis.

Summary Chart- Regulation of Gluconeogenesis

Enzyme	Effect of substrate concentration	Allosteric modification/ Feed back Inhibition	Induction/ Repression	Clinical Significance
Pyruvate carboxylase	Inhibited by high carbohydrate diet Stimulated during fasting	**Activator**-Acetyl CoA **Inhibitor** ADP	**Induced by** Glucocorticoids, glucagon, epinephrine **Repressed by** Insulin	Activity increases in Diabetes Mellitus
Fructose 1,6 bisphosphatase	Inhibited by high carbohydrate diet Stimulated during fasting	**Activator**-Citrate **Inhibitor** AMP, Fr 2,6 bisphosphate	**Induced by** Glucocorticoids, glucagon, epinephrine **Repressed by** Insulin	Activity increases in Diabetes Mellitus

MCQs

Q1; all amino acid can converted into glucose except

A-Alainine & theronine
B-lysine & leucine
C-glycine

Q2; the main site of glucogoneogenesis is:

A-liver
B-kidney
C-spleen

Q3; gluconeogenesis always occurs in both mitochondria and cytosol

A-true
B- false

Q4; oxaloacetate can't cross the cell membrane so it is converted to……, then back to oxaloacetate

A-malate
B-fumarate
C- phosphoenolpyruvate

Answer key:

1-B
2-A
3-B
4-A

SAQs

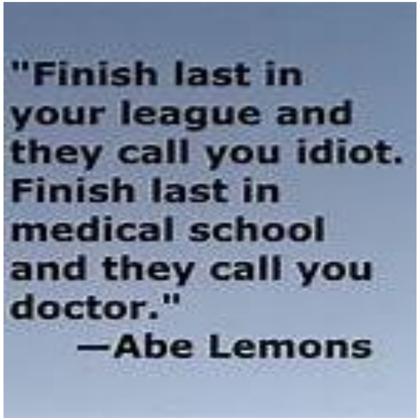
- One of the unique enzyme of gluconeogenesis is………

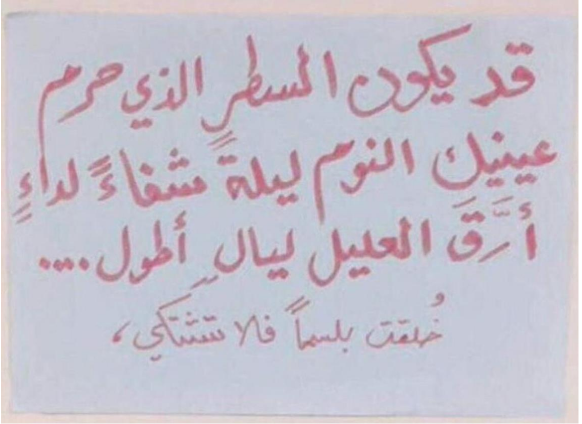
glucose-6-phosphatase

And we're done with FOUNDATION block !!!

See you next block

A very very special thanks to the best team in the world!!





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