14

Biochemistry

Doctor 2017 | Medicine | JU

Sheet

Slides

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GLUCONEOGENESIS

Gluconeogenesis is the process of making glucose from non-carbohydrate precursors.

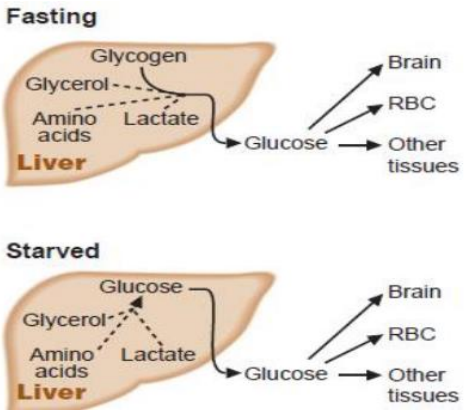
- Although **Gluconeogenesis** looks like **Glycolysis** in many steps, it is not the *simple* reversal of the glycolysis (because equilibrium strongly favors pyruvate formation), but the generation of glucose from non-carbohydrate precursors (like odd chain fatty acids and proteins). The reason why we have this process is because some organs and tissues can only use glucose as their energy source. These include the brain (although ketone bodies can be used here as well), erythrocytes, testes and the kidney medulla.
- Usually the glucose for the supply of these tissues comes directly from carbohydrates in food or storage carbohydrates as glycogen or starch, but when these are not available, the body has another way to get around this problem and to avoid the starvation of these tissues

Blood glucose can be obtained from three primary sources:

1) The diet

2) Glycogen degradation: it is fast but can only last for less than 24 hours because hepatic glycogen stores are depleted.

3) Gluconeogenesis: it is slow, used in starvation and it is also our main subject



- ❖ Some tissues, such as RBCs, kidney medulla, lens and cornea of the eye, testis, exercising muscle, and mostly **the brain (120g/day)** require a continuous supply of glucose as a metabolic fuel.

- ❖ **Body glucose reserve is limited:**
  1. Almost **20 g** as an extracellular fluid
  2. **75-100 g** stored as liver glycogen (to maintain blood glucose so it is not only for liver use) enough for 16 hours → recall point number 2
  3. **400 g** stored as muscle glycogen (more mass for muscles), it is only for muscle use, it is affected only when you are exercising.

- Main source of energy for resting muscle in *post-absorptive* state is fatty acids. 80% of glucose is used by brain & RBC
- At the first hours of fasting, muscle glycogen is not affected unlike liver glycogen which is highly affected.
- While fasting, fatty acids are the main source of energy to adipose tissue, muscles and liver, so utilization of fatty acids is increased 4-5 times **(by converting them to acetyl CoA and then TCA cycle)**, to preserve glucose for tissues that can't consume **FA** like the brain.
- in prolonged fasting *(starvation),* some fatty acids are converted into ketone bodies to supply the brain with an alternative source of energy
- Gluconeogenesis occurs mainly in the liver but in prolonged fasting kidneys also participate in gluconeogenesis.

A slim person weighing 70Kg has almost 15Kg of fat

Fatty acids can't be *directly* converted to glucose because Acetyl CoA from fats can't be reversed to pyruvate, while glucose and proteins are easily converted to fats.

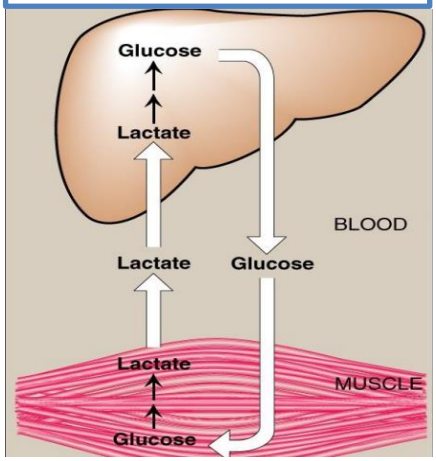
GLUCONEOGENESIS precursors

i. Lactate

- **Exercising muscles** undergo aerobic and anaerobic pathways to produce more energy, so lactate is produced
- **RBCs** lack mitochondria so they only undergo anaerobic pathway producing lactate.

This lactate enters the bloodstream and goes to the liver where it is converted into glucose. 6 molecules of ATP are needed for the conversion (metabolizing fat is the source of energy to make ATP here). Glucose then returns to muscles and RBCs for it to be metabolized again. This process is known as the **Cori cycle**

You should know that lactate can only be converted to pyruvate



ii. Glycerol

- from adipose tissue by breaking **triacyclglycerols**.
  Glycerol is converted to glycerol 3-phosphate in the liver by glycerol kinase (only found in liver), and then it is oxidized by glycerol 3-phsphate dehydrogenase to dihydroxyacetone phosphate (**DHAP** is an intermediate of glycolysis and gluconeogenesis)

iii. **Amino acids**

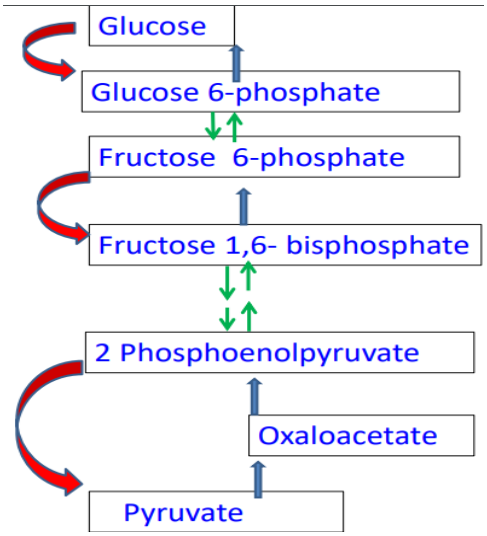
- their metabolism can generate α -keto acids such as pyruvate (converted to glucose) or α-ketoglutarate which enters the TCA cycle producing oxaloacetate (precursor for phosphoenolpyruvate *(PEP)* which is converted to glucose).

iv. **Propionate** ($C_3H_5O_2^-$)

- converted to propionyl CoA and then enters the TCA cycle as succinyl CoA which gives oxaloacetate (oxaloacetate is a precursor of PEP which is converted to glucose by gluconeogenesis).

v. **Sugars such as galactose and fructose:** always remember that sugars can be interconverted.

Reactions



Glycolysis is composed of 10 steps, 7 of them are reversible and are simply used in gluconeogenesis

3 glycolytic reactions are irreversible and must be circumvented by four alternate reactions called **typical gluconeogenesis reactions** that we are going to discuss in detail.

1. Pyruvate carboxylation

- In **Glycolysis** phosphoenolpyruvate (PEP) is converted to pyruvate by pyruvate kinase (irreversible reaction),
- In **Gluconeogenesis** pyruvate is carboxylated into oxaloacetate by pyruvate carboxylase.

This process is ought to happen in the mitochondria, but pyruvate is in the cytosol! pyruvate carrier protein transports pyruvate to the mitochondria.

Remember that glycolysis happens in the cytosol

Then Oxaloacetate is either converted to PEP by PEP-Carboxykinase (PEPCK) or enters the TCA cycle. (remember we are talking about a process that's exclusive to the liver and kidneys, in muscles it only enters TCA cycle, no gluconeogenesis)

- **Biotin** is the coenzyme required for carboxylation and here it is bound to lysine residue.

-At first CO_2 (from HCO_3^-) is connected to the biotin forming enzyme biotin-carbon dioxide intermediate, this requires ATP.

-then pyruvate is carboxylated to form oxaloacetate.

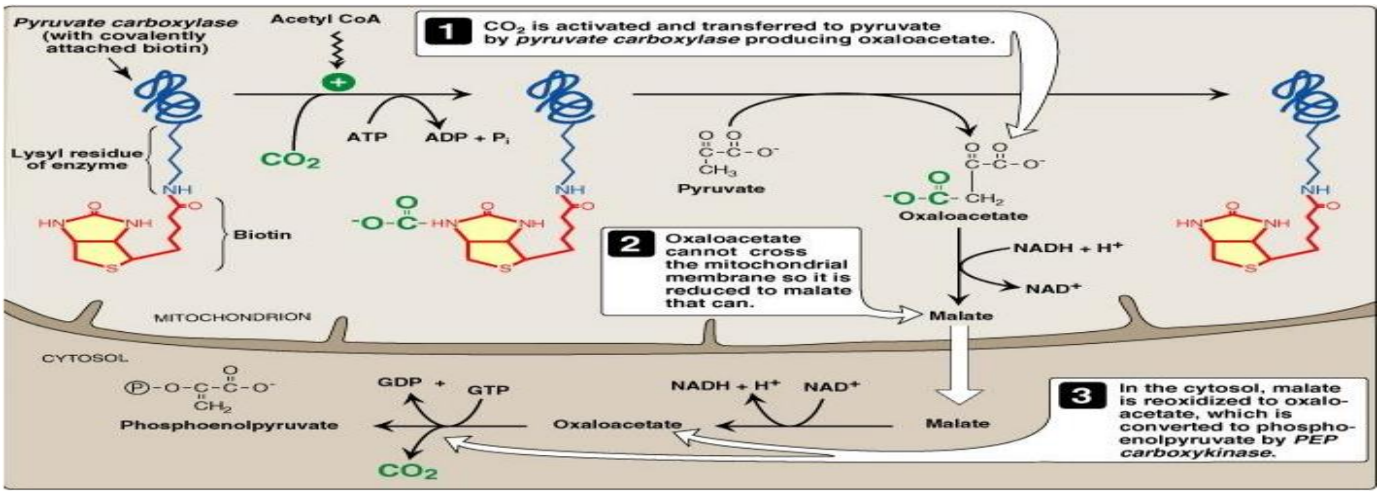
2. Oxaloacetate to PEP

- Oxaloacetate can't pass the inner mitochondrial membrane (we need it there because the reversal of glycolysis happens in the cytosol).
- It is converted into malate by malate dehydrogenase found in the mitochondria, malate can cross the membrane and be reoxidized into oxaloacetate by the cytosolic malate dehydrogenase.

Remember the shuttling system

- Finally, oxaloacetate becomes PEP by PEPcarboxykinase**,** the reaction is driven by hydrolysis of GTP to GDP.

Study this diagram for a better understanding



3. Fructose 1,6-bisphosphate dephosphorylation.

- In **Glycolysis**, fructose 6-phosphate is converted to fructose 1,6-bisphosphate by phosphofructokinse-1 (PFK-1).
- In **Gluconeogenesis** fructose 1,6-bisphosphate is converted to fructose 1-phosphate by **fructose 1,6-bisphosphatase.**
  It is an important regulatory reaction.

4. Glucose 6-phosphate dephosphorylation

- In **Glycolysis** glucose is converted to glucose 6-phosphate by hexokinase/glucokinase.
- In **Gluconeogenesis** the reversed reaction happened by glucose 6-phosphatase.

This process requires a complex of two proteins:

1. **glucose 6-phosphate translocase** which transports glucose 6-phosphate through the endoplasmic reticulum membrane to dephosphorylate it inside the ER.
2. glucose 6-phosphatase in the ER which removes the phosphate producing **free glucose** (mainly in the liver)
   Free glucose goes to the cytosol and then to the blood.

- The previous process also requires **GLUT7** that transports glucose outside of the ER towards the cytosol, and **GLUT2** that transports glucose from the cytosol to leave the cell.

> Refer to sheet 11 for more information about GLUT proteins

Remember the coupling system (using energy from exergonic reactions to facilitate endergonic ones)

$$\text{Glc.} + \text{Pi} \longrightarrow \text{Glc. 6-phosphate} + H_2O \quad \Delta G = +ve$$
$$ATP + H_2O \longrightarrow ADP + P_i \quad \Delta G = -ve$$

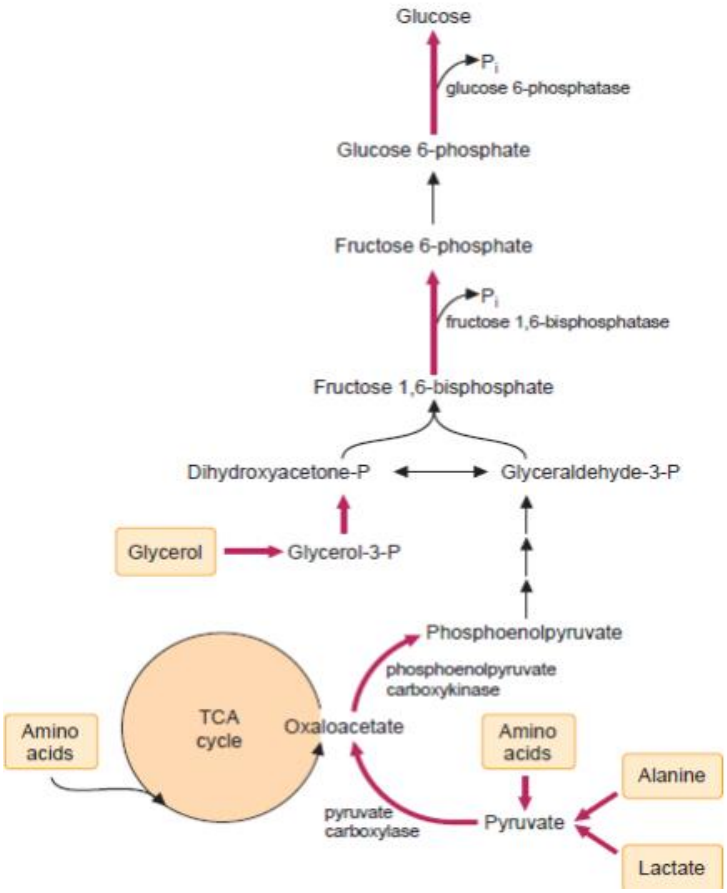
$$\text{Glc.} + ATP \xrightarrow{HK} \text{Glc. 6-phosphate} + ADP \quad \Delta G = -ve$$

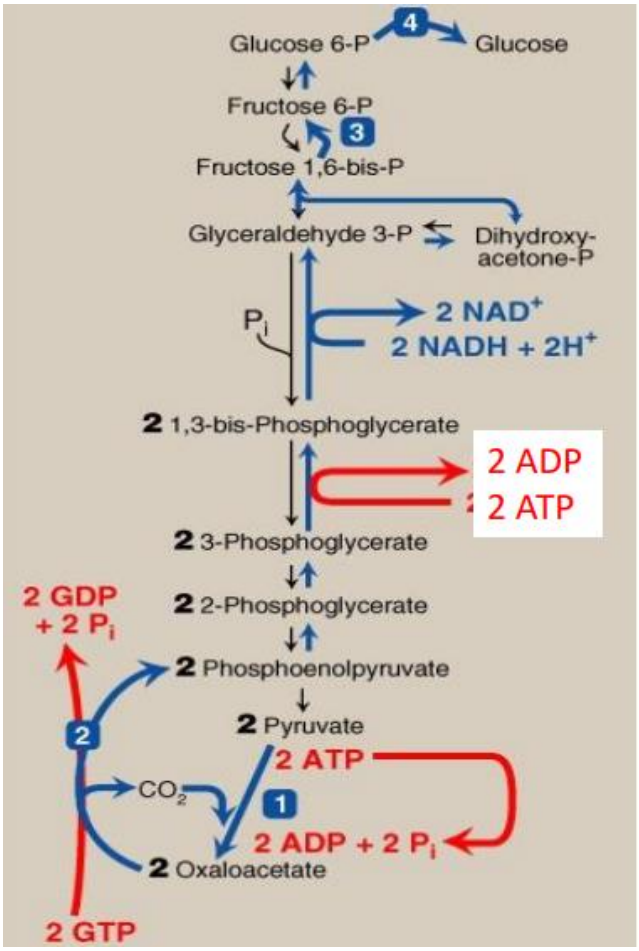
$$\text{Glc. 6-phosphate} + H_2O \xrightarrow{\text{Phosphatase}} \text{Glc.} + P_i \quad \Delta G = -ve$$

A small summary for gluconeogenesis →

it shows the consumption of 6 ATP (usually from fat metabolism)

Since we have a lot of fats in our body ATP is easily obtained to produce glucose which is essential.





← A small summary #2 ☺

It shows some precursors which have been explained earlier.

remember the enzymes the convert glycerol to dihydroxyacetone

Don't try to study this lecture from other references, the sheet is adequate (assem style)

Save your time for Community ☹

Regulation

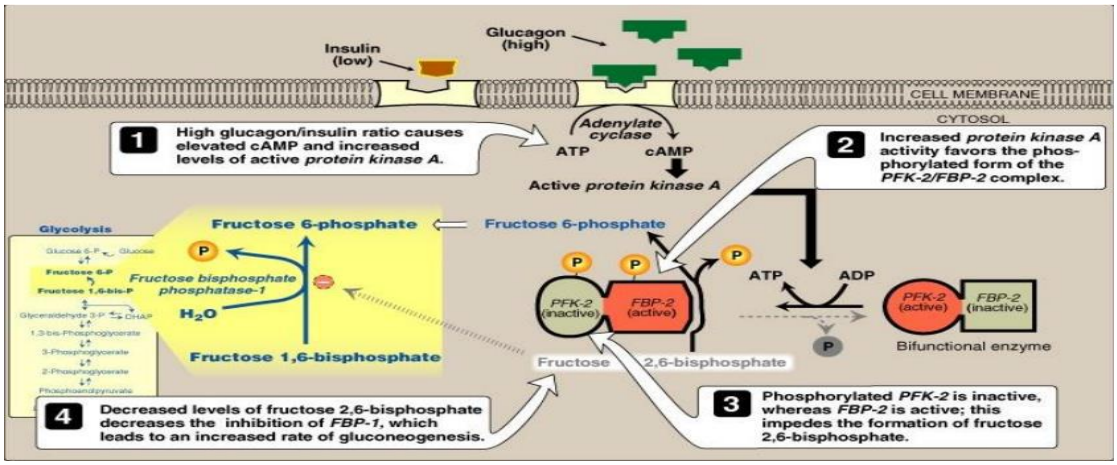
Fructose 2,6-bisphosphate activates glycolysis and inhibits gluconeogenesis

So, decreasing its concentration will activate gluconeogenesis

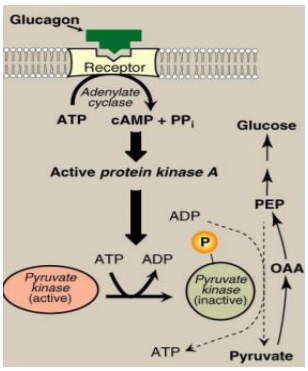
Glucagon stimulates Gluconeogenesis by 3 mechanisms:

1. Changes in allosteric effects:
   - ❖ Glucagon (secreted from alpha pancreatic cells) has the reverse effect of insulin, so its function is to increase glucose in **blood** (Gluconeogenesis again and again)
   - ❖ Glucagon elevates cAMP level → Increased protein kinase A activity which phosphorylates the bifunctional enzyme.
   - ❖ when it is phosphorylated (the opposite to glycolysis), **fructose 2,6-bisphosphatase** is the active one that decreases fructose 2,6-bisphosphate concentration, thus inhibiting glycolysis → activates gluconeogenesis.

In sheet 13 it was explained that when insulin binds it activates glycolysis. Here glucagon is binding which activates gluconeogenesis (the reverse effect)



2. Covalent modification of enzyme activity: glucagon increases cAMP level and protein kinase A activity which phosphorylates pyruvate kinase making it in its inactive form, this decreases conversion of PEP to pyruvate and stimulates the other pathway (Gluconeogenesis).



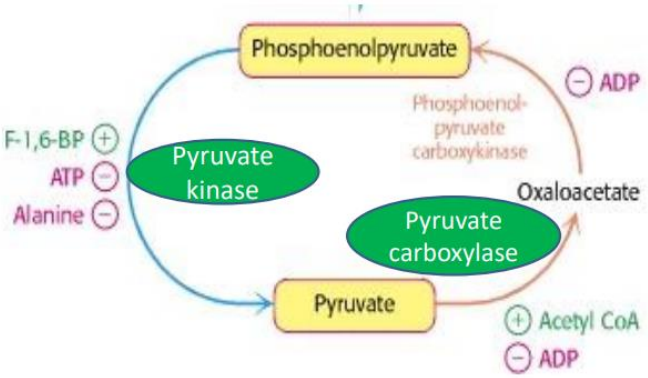
3. Induction of enzyme synthesis:
   increases the gene transcription for PEPCK enzyme via the transcription factor cAMP response element binding protein *(cortisol does the same action),* thus increasing the availability for this enzyme to produce PEP.

FINALLY, good news:
The doctor didn't say anything about point 3 so it is not important

A wise man once said: there are two kinds of people, those who study sheets and those who are lying.

Allosteric activation by acetyl CoA:

- Pyruvate carboxylase **(gluconeogenesis)** is activated by acetyl CoA, Pyruvate dehydrogenase **(glycolysis)** is inhibited by acetyl CoA.
- During fasting, fatty acids are converted to acetyl CoA in muscles so there is no need to dehydrate pyruvate, instead we need glucose for brain and RBCs.



Too many ADP means that the cell needs to produce ATP by glycolysis, so it inhibits Gluconeogenesis

- Alanine always increases in fasting, so it is an indicator for low blood sugar, thus inhibits glycolysis

Allosteric inhibition by AMP

- Gluconeogenesis can also be regulated by AMP/ATP ratio
- High ratio means that we need to form ATP, so it inhibits Fructose 1,6-bisphosphatase**,** thus inhibiting Gluconeogenesis.
- Low ratio means that there is high ATP so no need to glycolysis thus activating Gluconeogenesis.