Gluconeogenesis

Lecture 12

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Editing File

Biochemistry
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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 in general

Gluco- (Glucose) -Neo- (Meaning new)-Genesis (Formation) Team437

- The gluconeogenesis pathway shown as one of the essential pathways of energy metabolism
- It is an energy consuming anabolic pathway
- Occurs in Liver (mainly) and Kidneys
- The target of Gluconeogenesis is to result glucose from non-carbohydrate carbon substrates (Gluconeogenic substrates)
- Both mitochondria and Cytosol are involved
  Exception : if the substrate is Glycerol, only cytosol

Gluconeogenic substrates:	
Glycerol	**fatty acid**
Lactate and Pyruvate	**organic acids**
Glucogenic amino acids	**amino acid that can be converted into glucose through gluconeogenesis. - Not all amino acids can make glucose there are certain types**

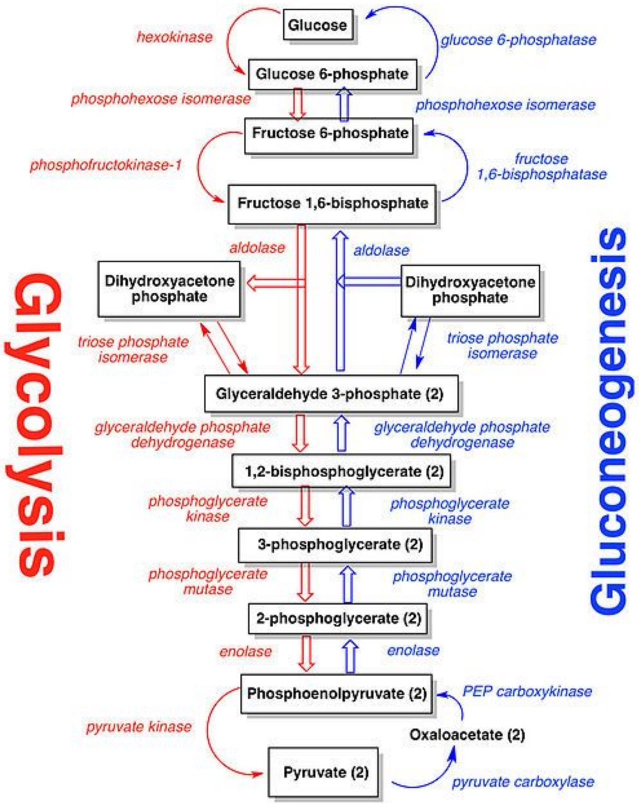
Gluconeogenesis pathway

- In Glycolysis there are 10 reactions from glucose to pyruvate,

  in gluconeogenesis there are 11 reactions.

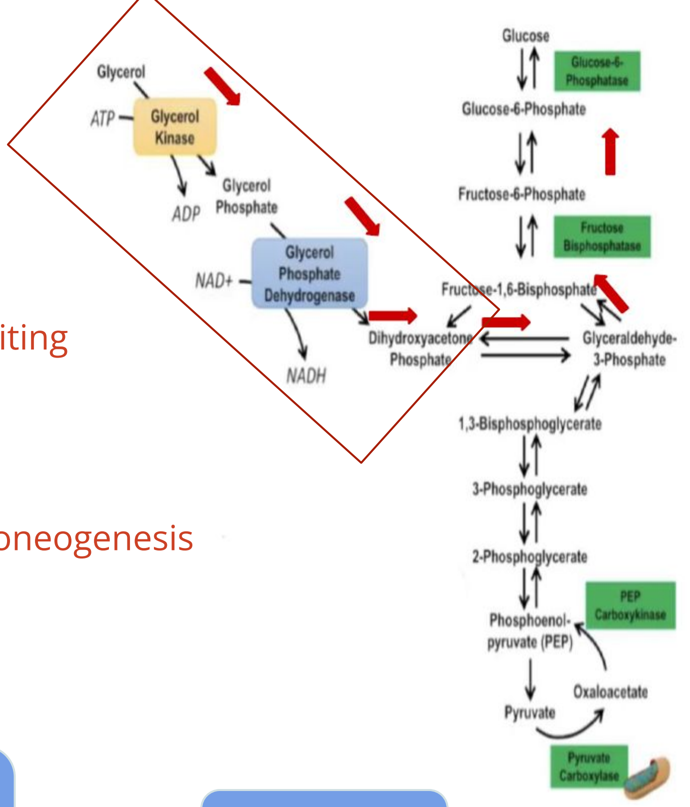
- 7 of the reactions in glycolysis are the same in gluconeogenesis (reversible)

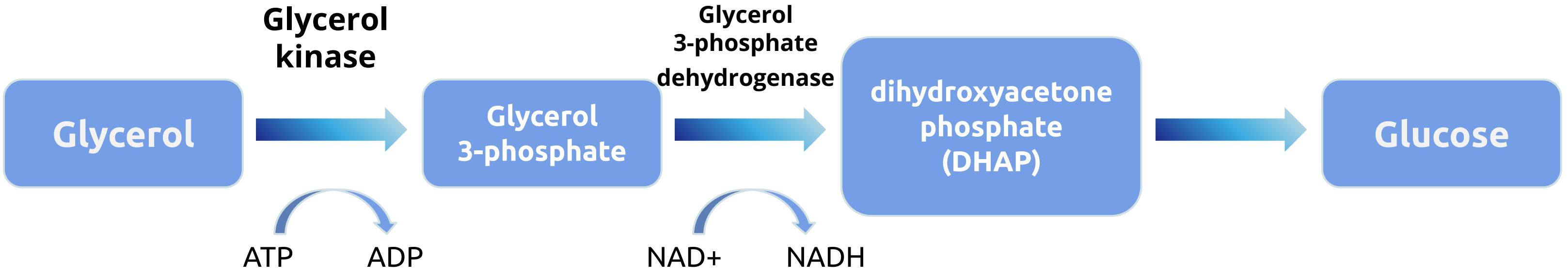
Glycolysis enzyme	Gluconeogenesis enzyme
Pyruvate kinase	- Pyruvate carboxylase - PEP-CK (PEP-carboxykinase)
PFK-1	- Fructose 1,6 bisphosphatase
Glucokinase / Hexokinase	-Glucose 6-phosphatase



Gluconeogenic Substrates: Glycerol

- Glycerol are made from hydrolysis of triglyceride
- Glycerol kinase are found only in liver or kidneys, it is also a rate limiting enzyme
- dihydroxyacetone phosphate (DHAP) can used for glycolysis or gluconeogenesis





Glucogenic Amino Acids

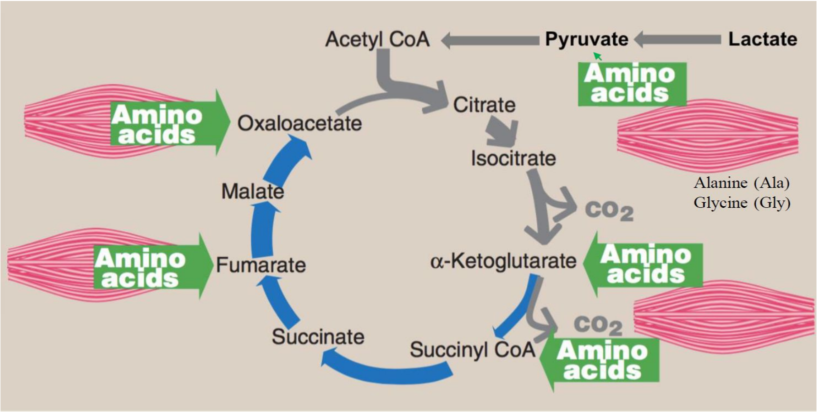
The catabolism of amino acids are either:

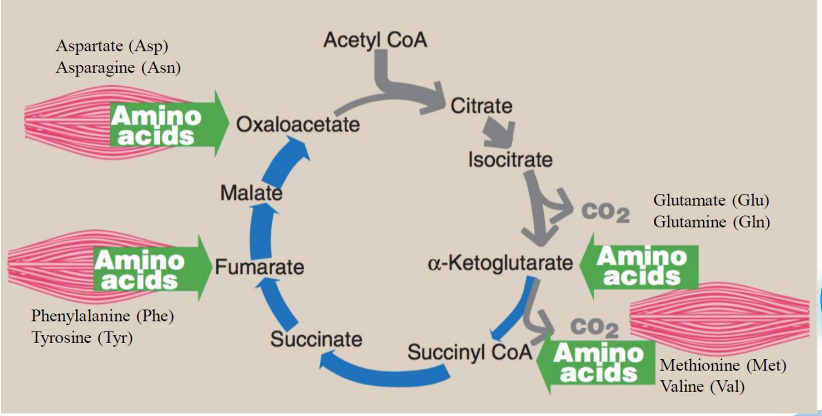
Alanine, Glycine	Pyruvate

krebs cycle (indirectly)

krebs cycle (directly)

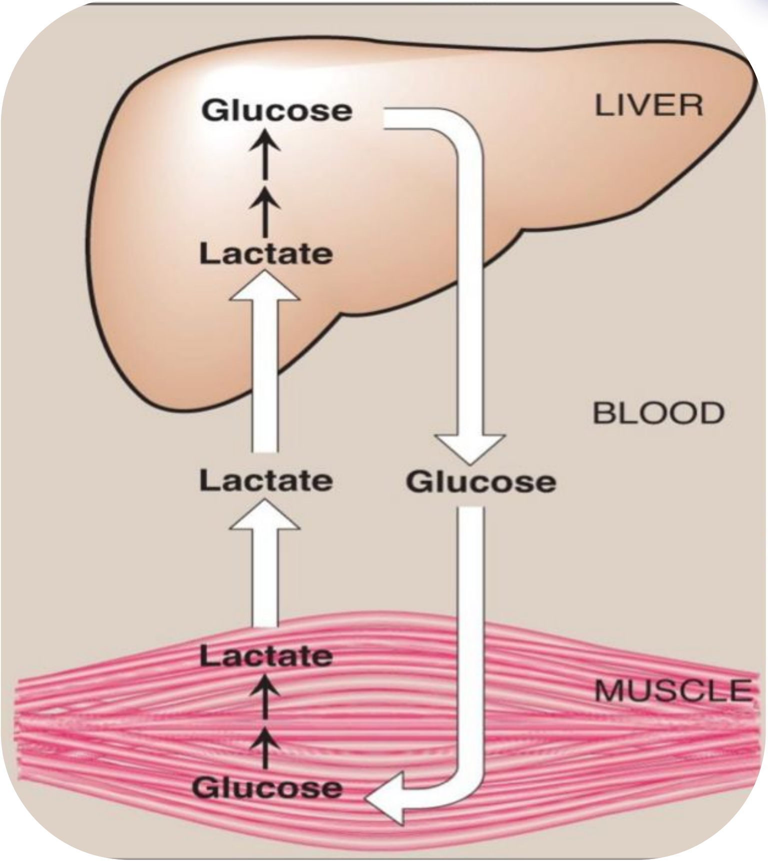
Glutamate, Glutamine	α-ketoglutarate
Methionine, Valine	Succinyl CoA
Phenylalanine, Tyrosine	Fumarate
Aspartate, Asparagine	Oxaloacetate





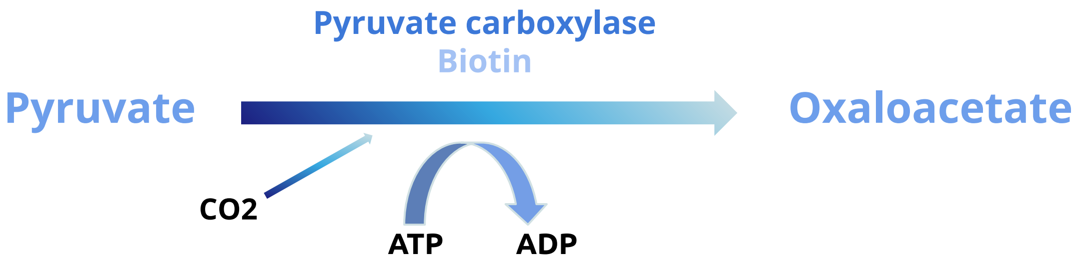
Gluconeogenic Substrates: Lactate (Cori cycle)

Glucose in the liver travels through the blood to the muscle where it is turned into lactate via anaerobic glycolysis then the lactate travels through the blood back into the liver where it is turned back into glucose then it can go back again to the muscle again or any tissues. this cycle is called (cori cycle)



436 Note: Lactate is released into the blood by exercising skeletal muscle and by cells that lack mitochondria such as RBCs.

Pyruvate Carboxylation



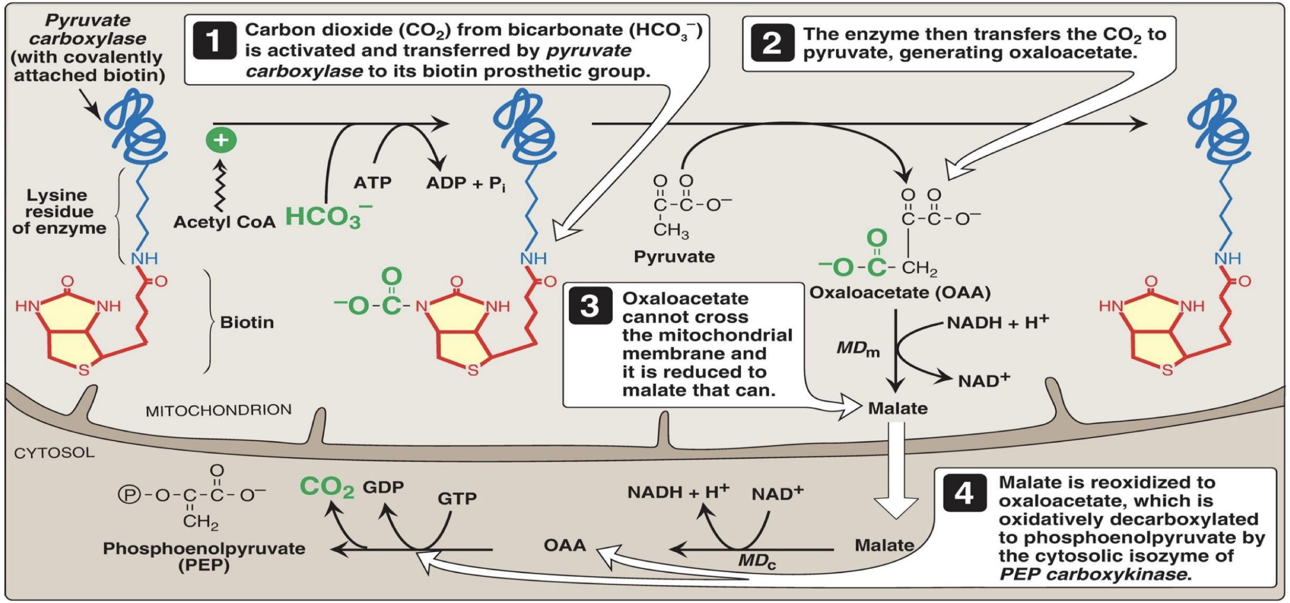
Pyruvate carboxylase, which converts pyruvate to oxaloacetate , is activated by Acetyl-CoA.

Acetyl-CoA is produced in the mitochondria from fatty acid oxidation. and it increases in fasting

Where does the carboxylation of pyruvate occur? In the mitochondria of liver kidney.

Why? Because the enzyme pyruvate Carboxylase is only found in the matrix of mitochondria.

Pyruvate Carboxylase and PEP CK



MD_m = malate dehydrogenase in Mitochondria

MD_c = Malate dehydrogenase in cytosol

so it's the same enzyme in different locations

Glycolysis

in glycolysis, the conversion of PEP to pyruvate, only one enzyme is needed which is Pyruvate kinase

Pyruvate carboxylase + PEP-CK = Pyruvate kinase

Gluconeogenesis

in gluconeogenesis the conversion of pyruvate to PEP must be in TWO steps and two enzymes

1. pyruvate carboxylase
2. PEP-CK (Phosphoenolpyruvate-carboxykinase)

Pyruvate Carboxylase and PEP CK

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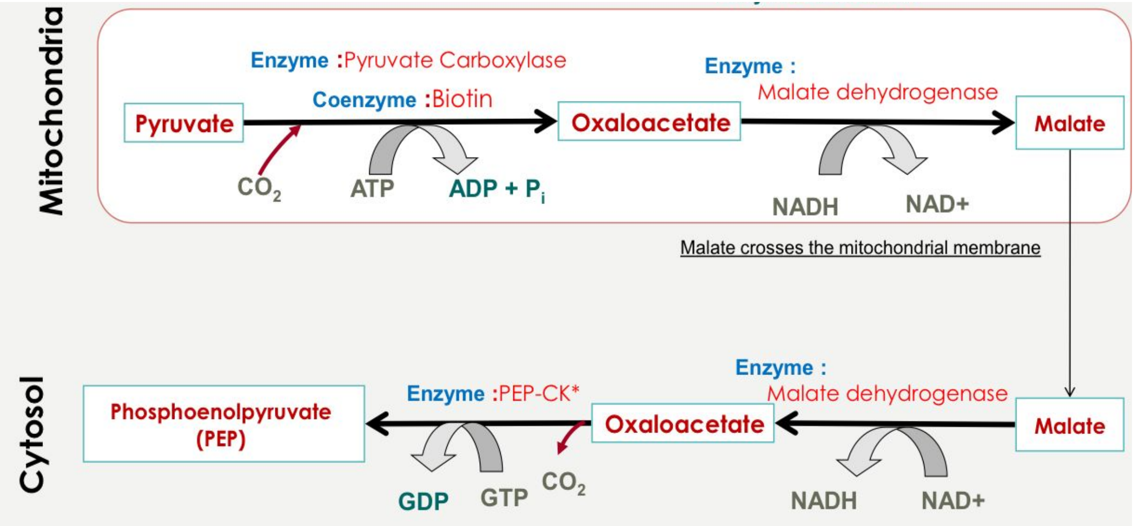


step1:

a. we get CO2 from HCO3.
b. CO2 binds to the prosthetic group (biotin)
c. the enzyme (Pyruvate carboxylase) transfers CO2 from the biotin to the pyruvate forming oxaloacetate

step 2:

a. oxaloacetate cannot cross the mitochondrial membrane
b. the enzyme Malate dehydrogenase MDm reduces it to Maltate
c. Maltate leaves the mitochondria to cytosol

step 3:

in cytosol, malate is reoxidize to oxaloacetate by the enzyme malate dehydrogenase MDc.

step 4:

using the enzyme PEP-CK :

a. Oxaloacetate (OAA) is decarboxylated (it loses CO2) to phosphoenolpyruvate PEP
b. (OAA) gains a PO3 group

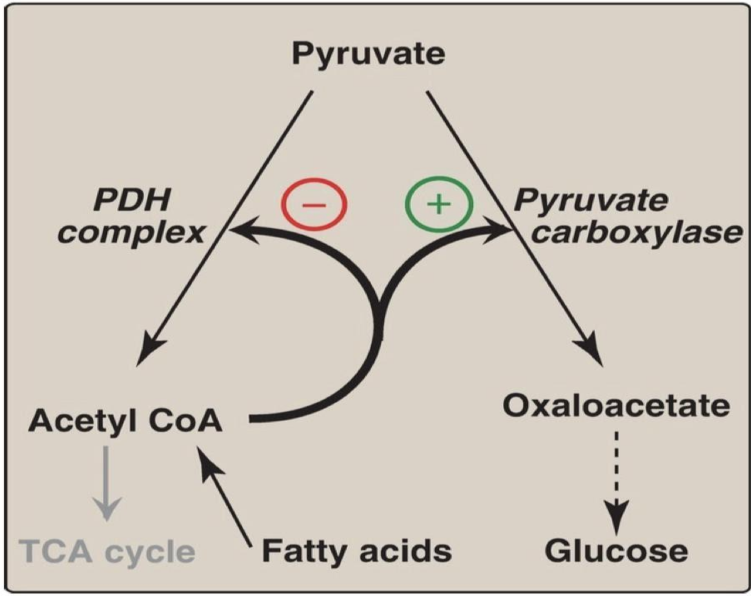
Note:
PEP-CK= Phosphoenolpyruvate carboxykinase
Notice ATP in mitochondria and GTP in cytosol

Regulation of Pyruvate Carboxylase reaction Acetyl

the acetyl CoA diverts pyruvate away from oxidation (PHD complex pathway) and pushes it towards the gluconeogenesis (Pyruvate carboxylase)

How?

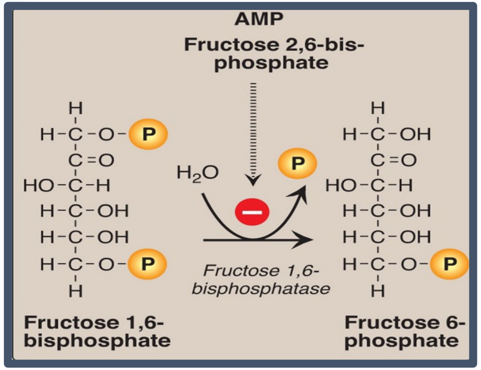
High level of Acetyl-CoA will inhibit PDH complex and stop or reduce the Glycolysis. And stimulate Pyruvate Carboxylase to start Gluconeogenesis.



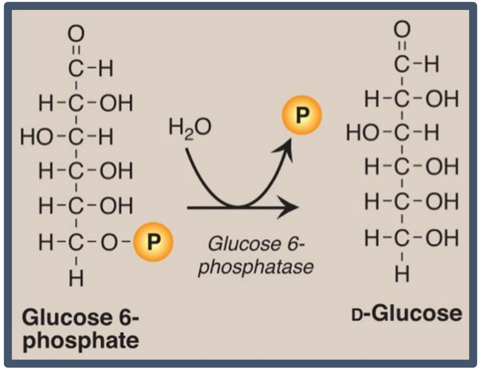
High level of Acetyl CoA can be due to PDH complex or fatty acid oxidation

positive regulation	negative regulation
- High Acetyl CoA will stimulate the enzyme pyruvate carboxylase Biotin to make more oxaloacetate Then, the oxaloacetate will proceed the pathway to produce more glucose	High level of Acetyl-coA inhibit PDH complex and stop or reduce the Glycolysis. - PDH function: converts pyruvate to Acetyl coA

Fructose 1,6 Bisphosphate



Glucose 6- Phosphatase



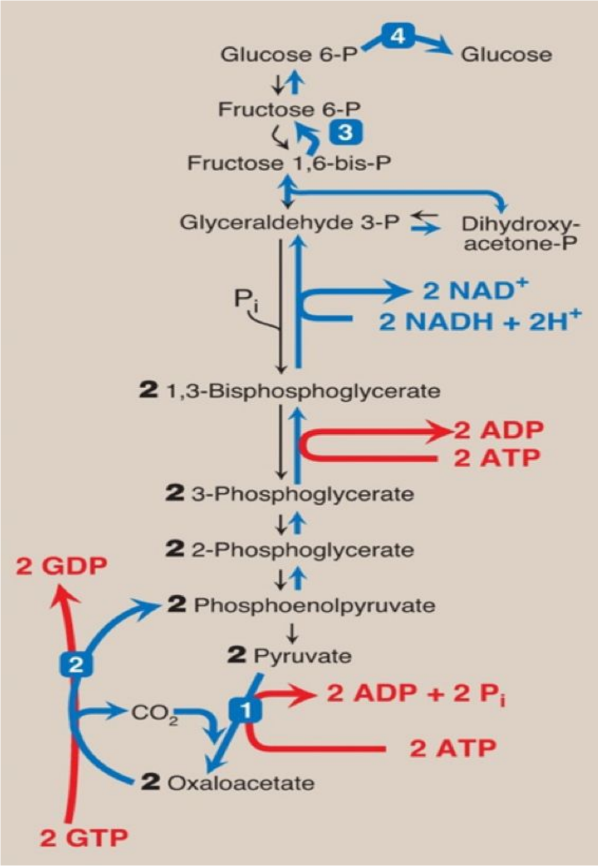
Dephosphorylation of fructose 1,6- bisphosphate

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

Dephosphorylation of glucose 6-phosphate

- Glucose 6-phosphatase = Glucokinase in liver or hexokinase in kidney
- Dephosphorylation of Glucose 6-phosphate allows release of free glucose from the liver and kidney into blood

Gluconeogenesis: Energy Consumed



Six High-Energy Phosphate Bonds From Pyruvate to Glucose

For every molecule of glucose synthesized from two molecules of pyruvate, **4 ATP**, 2 GTP, and 2 NADH are used, but when finally get glucose. The glycolysis will give us 38 ATP so it's worth it. Also, we can recycle the non-carbohydrate precursor into glucose.

Gluconeogenesis: Regulation

Gluconeogenesis: Regulation

Reciprocal control (عملية عكسية)

Gluconeogenesis
Glycolysis

Allosteric
↑ Acetyl CoA (pyruvate carboxylase)

F 1,6-bisphosphatase:
↑ATP
↓ AMP
↓ F 2,6-Bisphosphate

↑ Glucagon (↓ I/G ratio) stimulate gluconeogenesis

- Allosteric (↓ F 2,6-bisphosphate)
- induction (PEP-CK)

Take home massage

- 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

Quiz

Where does the gluconeogenesis mainly occur			
A- Muscles	B- Liver	C- Intestine	D- Kidney
Where does the carboxylation of pyruvate occur?			
A- Mitochondria	B- Cytoplasm	C- Smooth endoplasmic reticulum	D- Rough endoplasmic reticulum
How many enzymes are needed to convert pyruvate to PEP ?			
A- Two	B- one	C- Three	No need
The dephosphorylation of fructose 1,6- bisphosphate induced by :			
A- ADP	B- AMP & Fructose 2,6- bisphosphate	C- ATP	D- None of them

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

Thanks to the amazing team Bio441

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