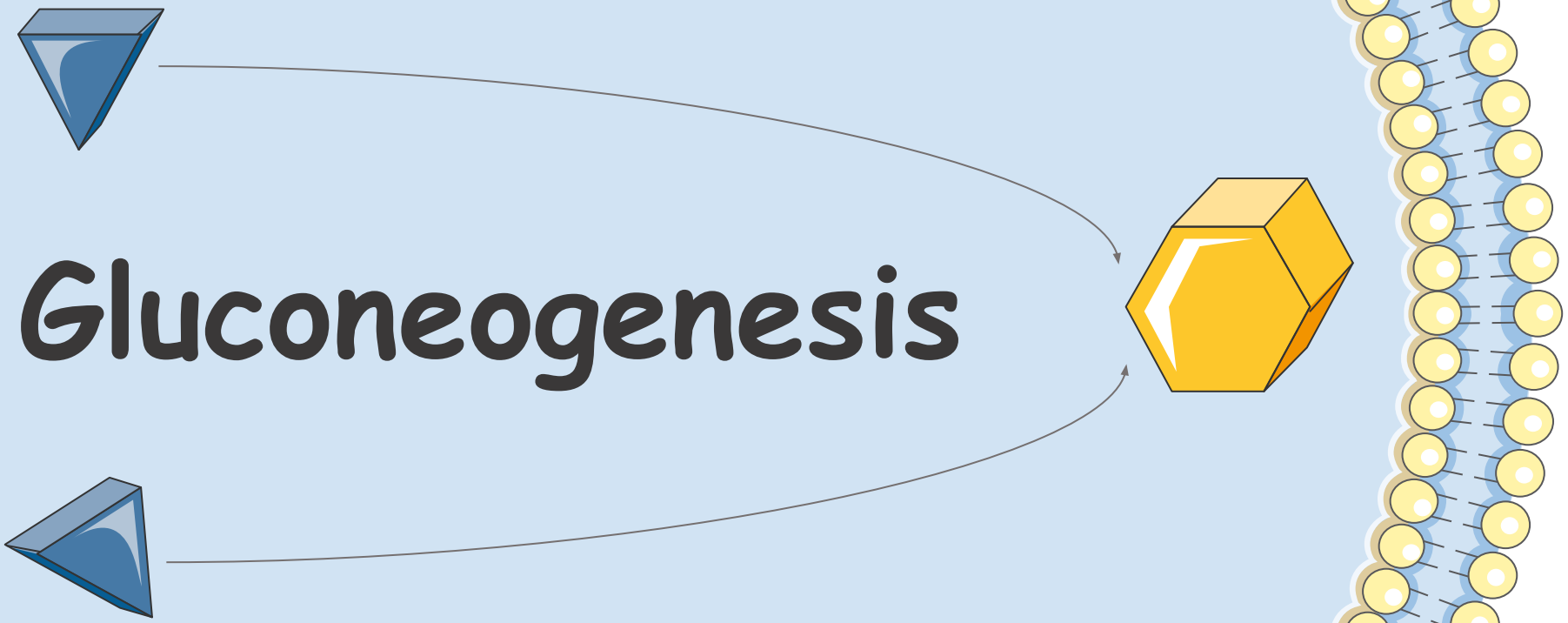
Gluconeogenesis



MED441
KING SAUD UNIVERSITY

Revised & Reviewed by:
Abdulaziz & Bahammam
Faye Wael Sendi

12
V1

Foundation Block - KSU

Color Index:

- Main text
- Important
- Notes
- Boys slides'
- Girls slides'
- Extra

Editing File

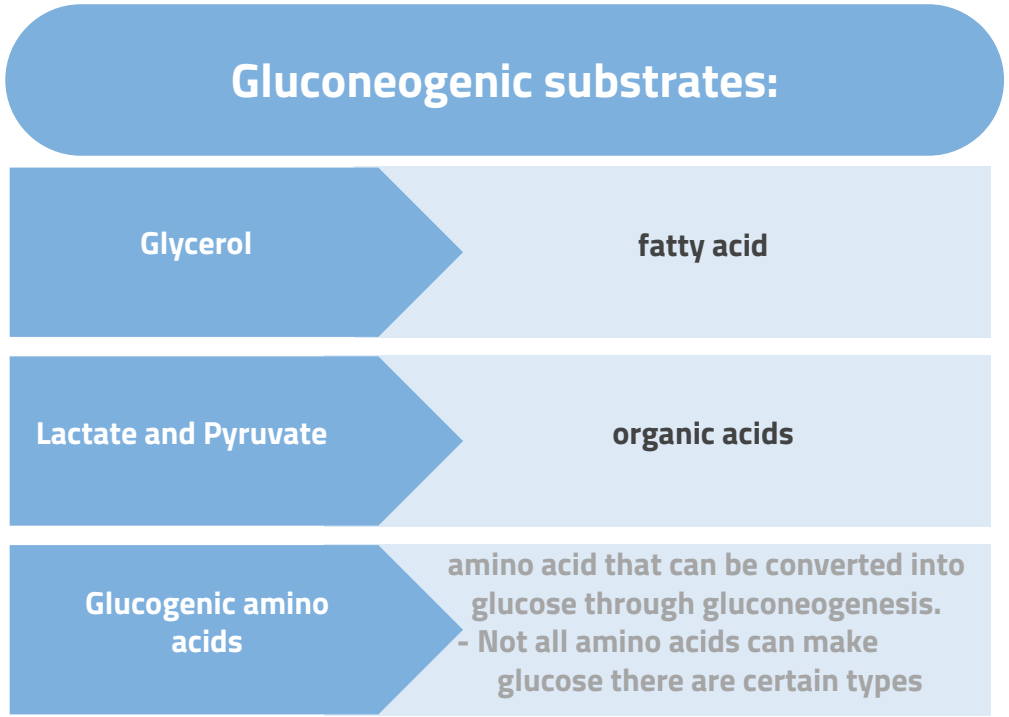
Objectives

- 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

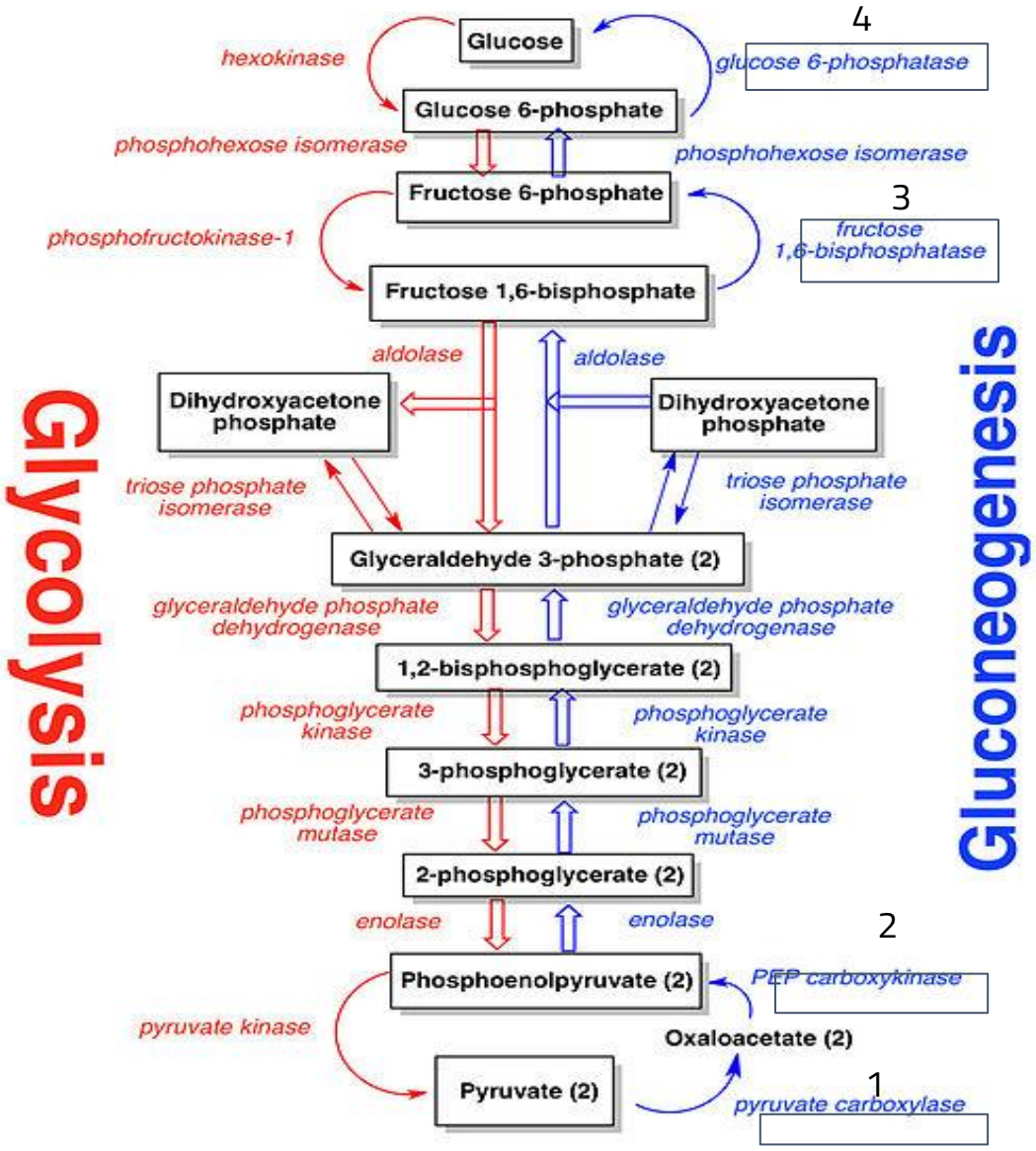
- The gluconeogenesis pathway shown as one of the essential pathways of energy metabolism
- It is an energy consuming anabolic pathway
- Occurs in Liver (mainly) and Kidneys
- The target of Gluconeogenesis is to result glucose from non-carbohydrate carbon substrates (Gluconeogenic substrates)
- Both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



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



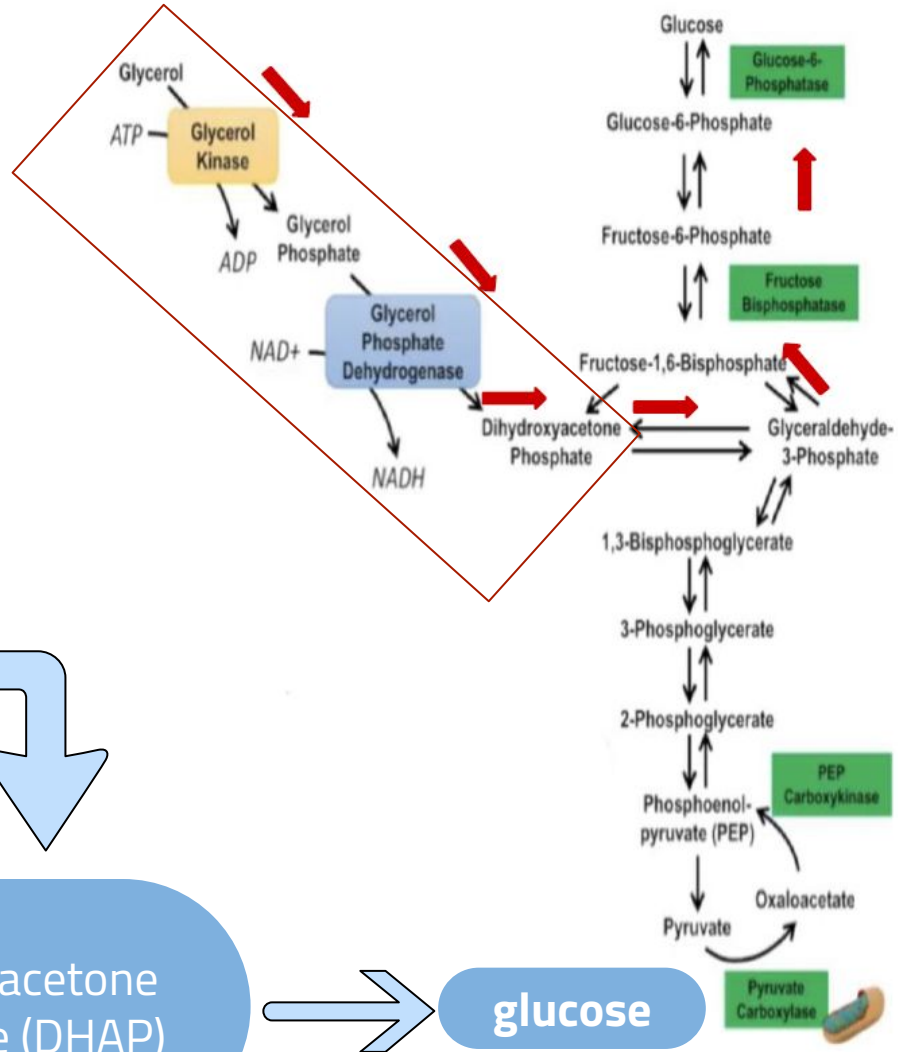
Gluconeogenic Substrates: Glycerol

Helpful video

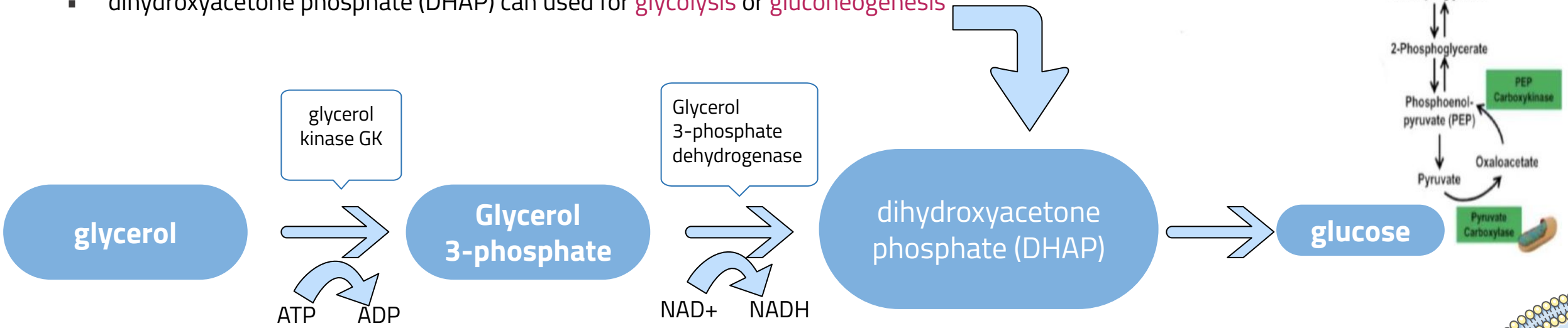
- Glycerol are made from hydrolysis of triglyceride

  triglyceride, Triacylglycerol and TAG are the same thing

- 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:

krebs cycle: directly

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

krebs cycle: indirectly

Alanine Glycine	Pyruvate

Alanine and glycine doesn't go to krebs cycle directly it has to be converted to pyruvate then it will enter krebs cycle

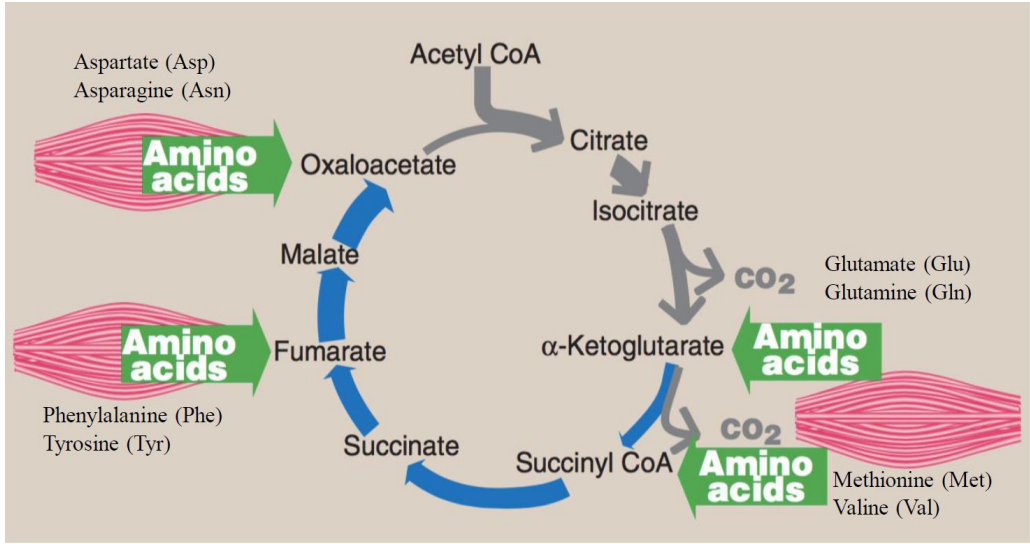
1

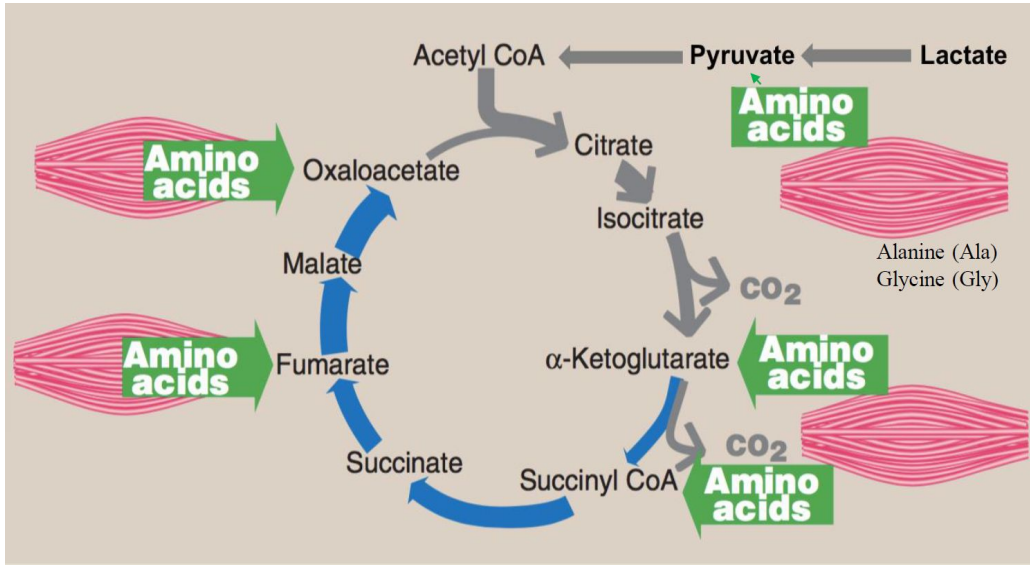
arginine can be converted to glutamate then to α-ketoglutarate (doesn't convert directly into a-ketoglutarate)

2

3

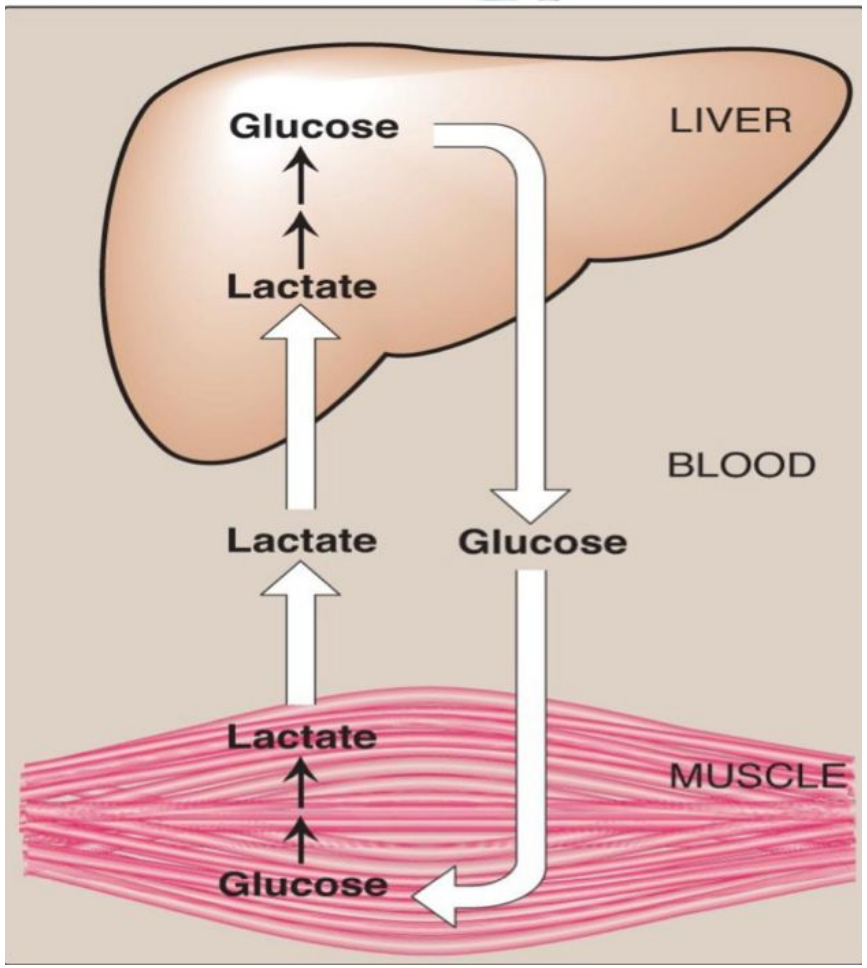
All amino acids are Glucogenic (make glucose) except: Leucine & Lysine





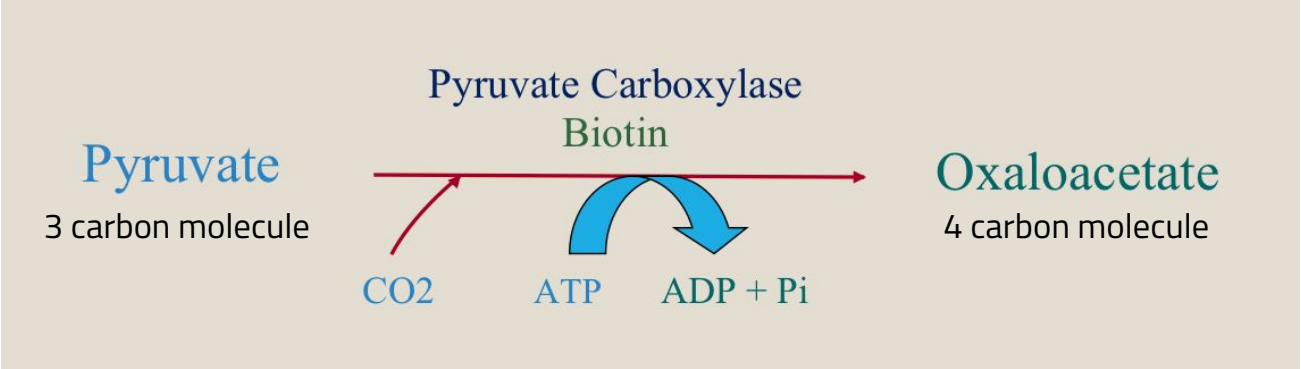
Gluconeogenic Substrates: Lactate (Cori cycle)

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



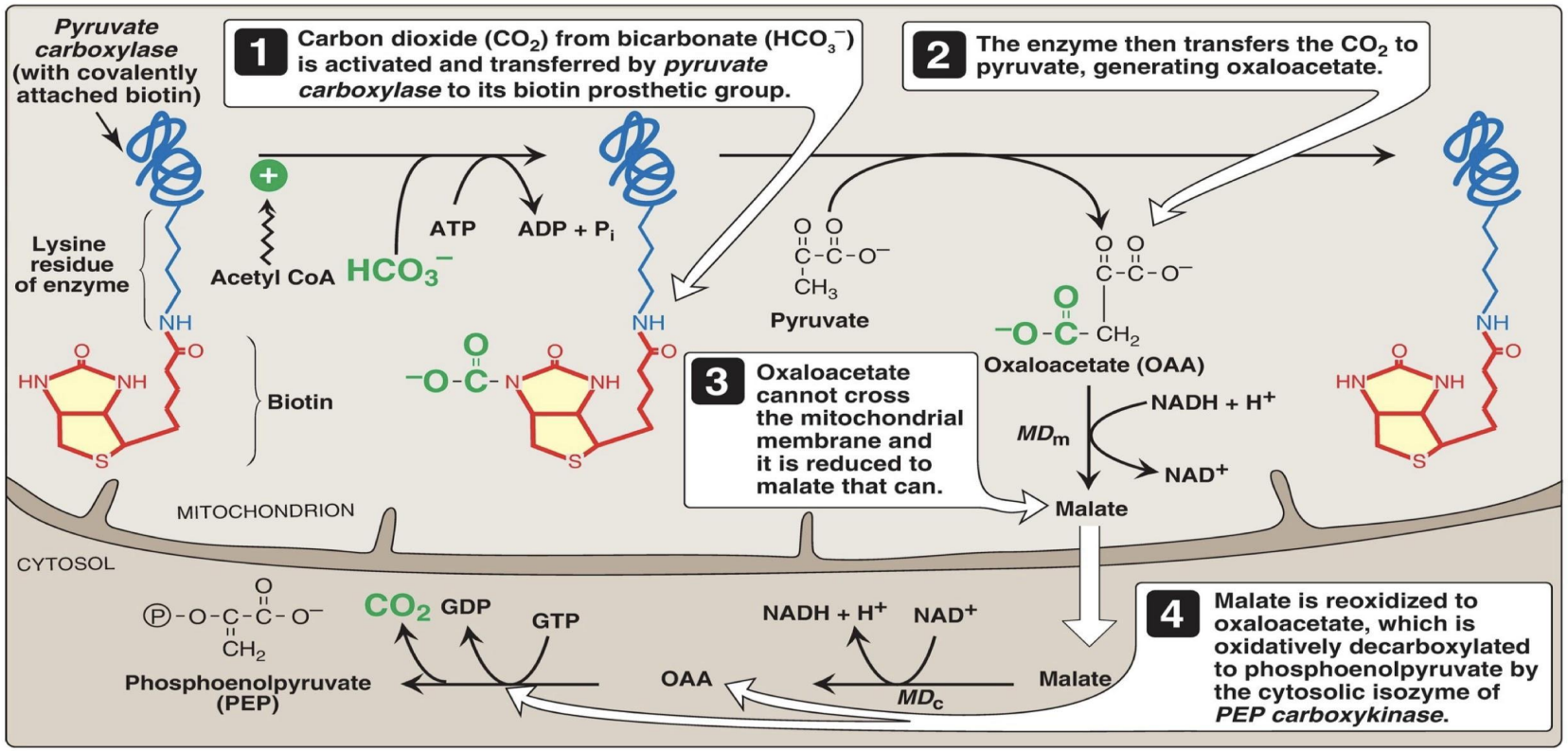
Pyruvate carboxylase, which converts pyruvate to oxaloacetate , is activated by Acetyl-CoA.

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

Gluconeogenesis

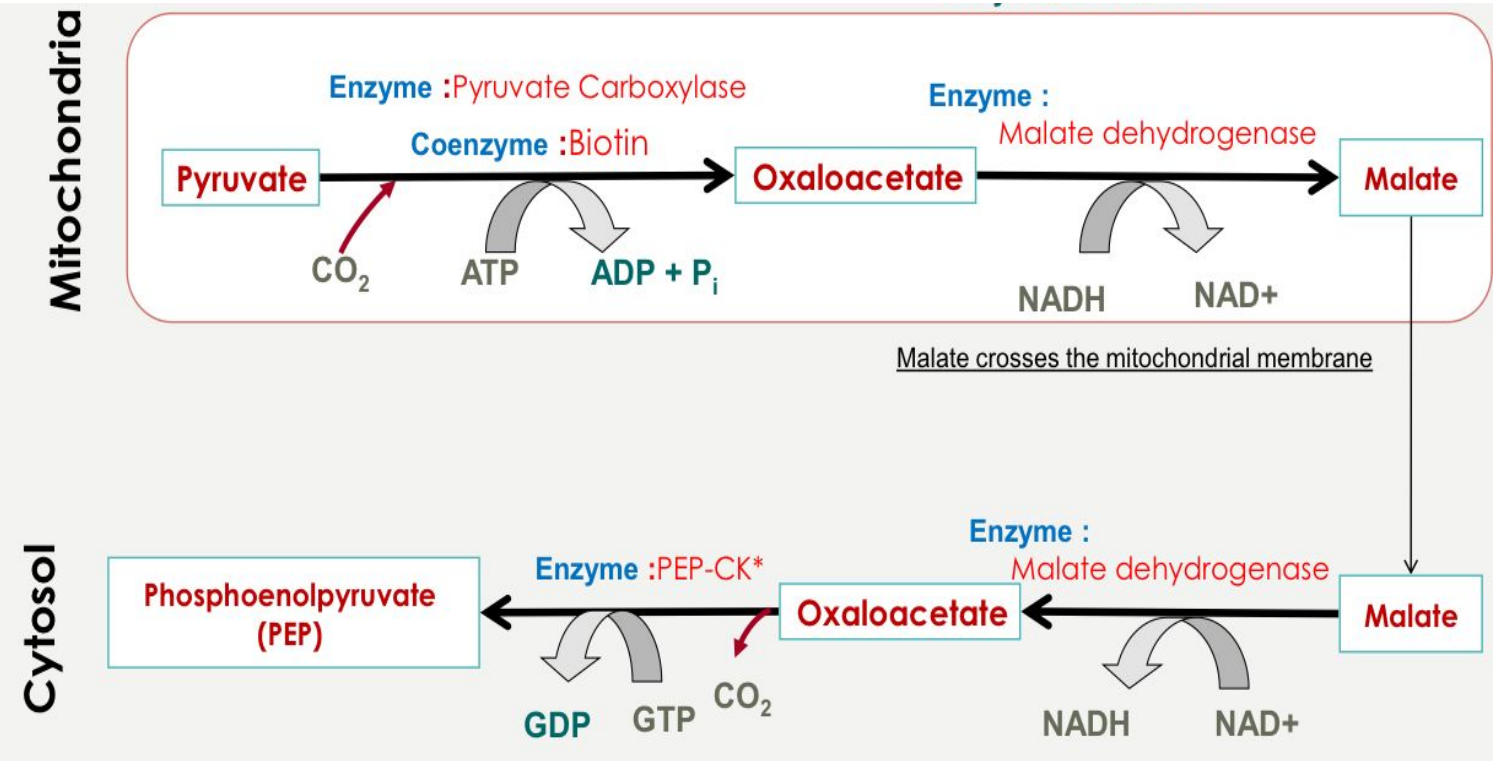
in gluconeogenesis the conversion of pyruvate to PEP must be in TWO steps and two enzymes

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

Pyruvate carboxylase + PEP-CK ≒ Pyruvate kinase

Pyruvate Carboxylase and PEP CK

Team 435



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.

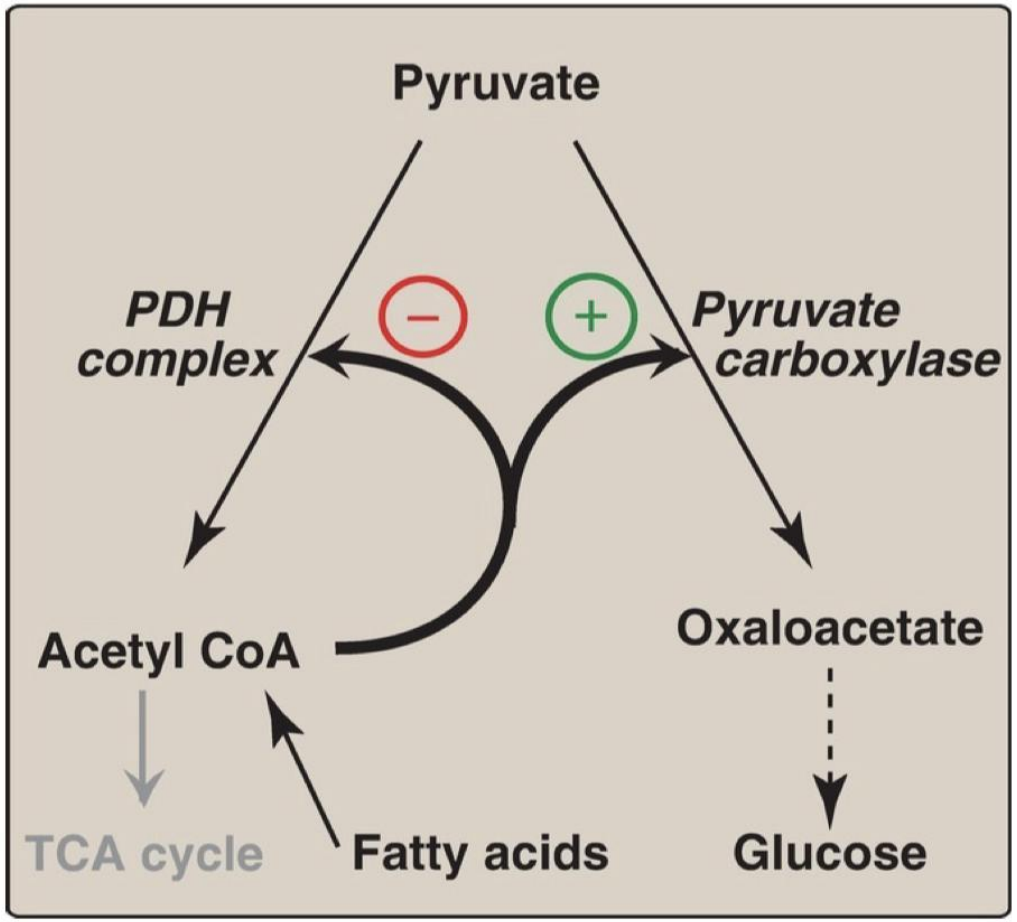
step 4:

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



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

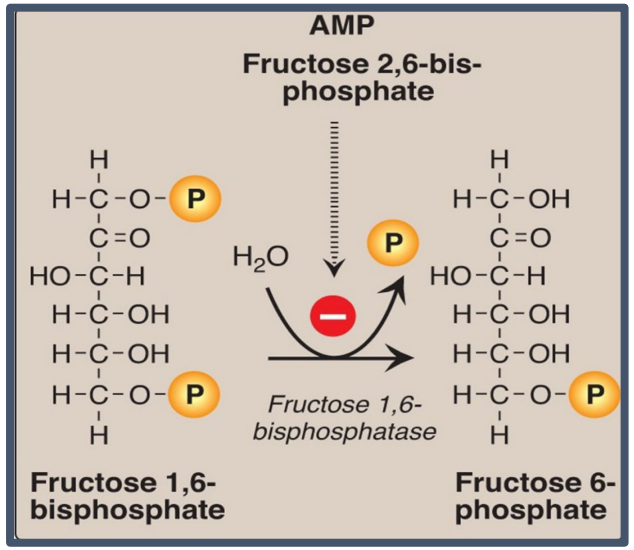
the acetyl CoA diverts pyruvate away from oxidation (PHD complex pathway) and pushes it towards the gluconeogenesis (Pyruvate carboxylase)

How?

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

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

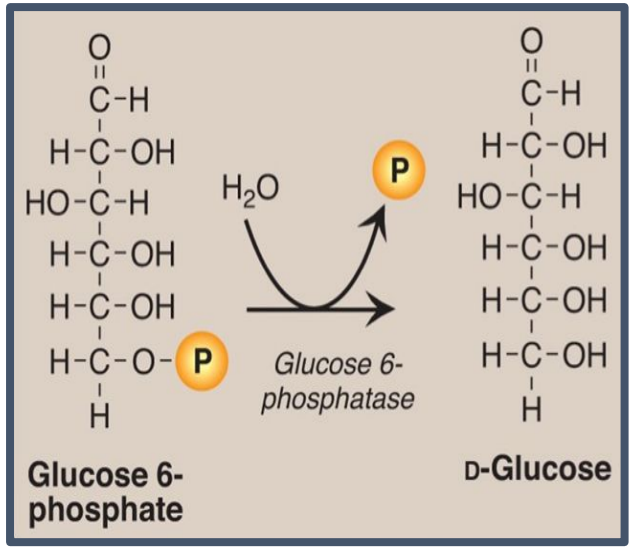
Fructose 1,6 Bisphosphate



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

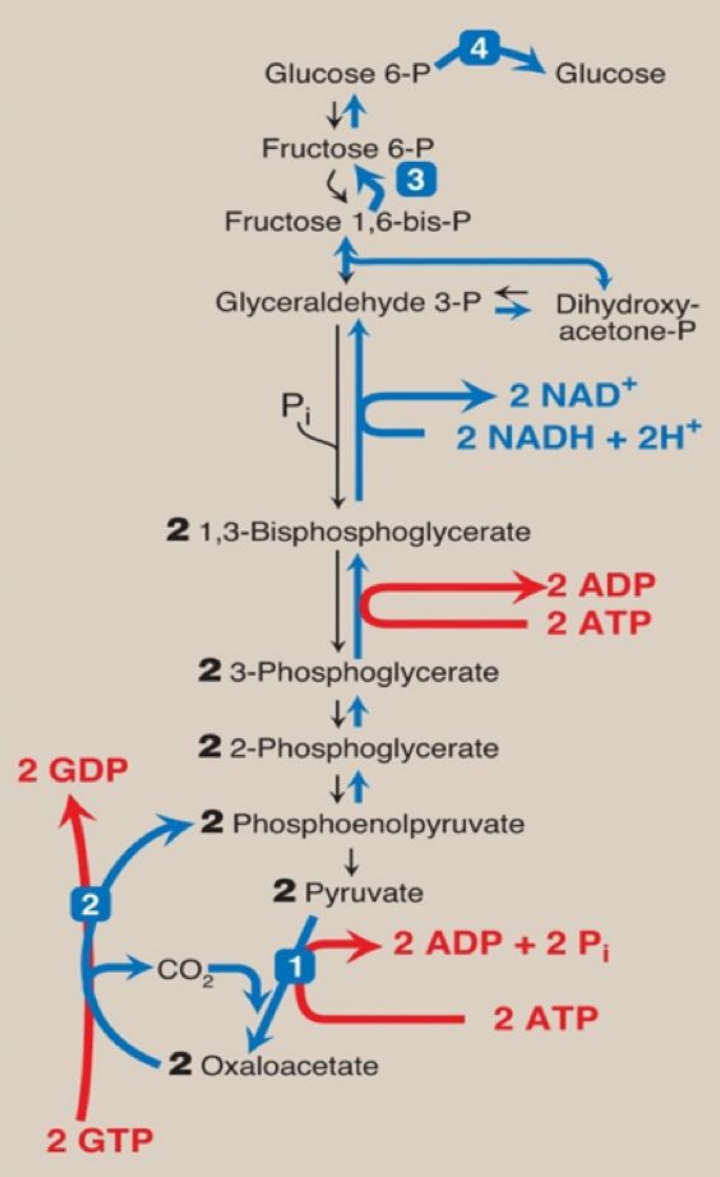
Glucose 6- Phosphatase



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 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 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

Q1: what is the amino acid that can be converted to Fumarate							
A	Alanine	**B**	Tyrosine	**C**	Leucine	**D**	Glycine
Q2: One of the unique enzyme of gluconeogenesis is							
A	Enolase	**B**	Phosphofructokinase-1 (PFK-1)	**C**	glucose-6-phosphatase	**D**	Pyruvate kinase
Q3: dihydroxyacetone phosphate can be used for							
A	Glycolysis	**B**	Gluconeogenesis	**C**	both A&B	**D**	none
Q4:In glycolysis fructose 6-phosphate is turned to fructose 1,6 bisphosphate by enzyme Phosphofructokinase-1, in gluconeogenesis this reversed step is done by the enzyme							
A	Phosphofructokinase-1 (PFK-1)	B	Pyruvate kinase	C	Fructose 1,6 bisphosphatase	D	Phosphohexose isomerase
Q5:oxaloacetate cannot cross the mitochondrial membrane so it must be converted to:							
A	phosphoenolpyruvate	B	fumarate	C	malate	D	Pyruvate

Answer Key: 1) B 2) C 3) C 4) C 5) C

Q6:What are the amino acids that are converted to Succinyl CoA to enter krebs cycle

Q7:What is the name of the coenzyme of pyruvate carboxylase

Q8:what are the major gluconeogenesis substrates?

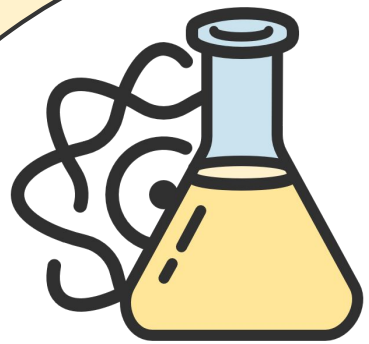
Q9:what are the amino acids that enter krebs cycle by transfer into pyruvate?

Q6: Methionine and valine

Q7: Bioten

Q8: lactate, glycerol, glucogenic amino acids

Q9: Answer: glycine & alanine



Biochemistry 441

Girls

Boys

Ghadah Alarify - Leader

Yara Almufleh
Reema Alrashedi
Wareef Almousa
Joud Alangari
Fay Alluhaidan
Sarah Alhamlan
Arwa Almobeirek
Jumana AL-qahtani
Latifa Alkhdiri
Alanoud Alhaider
Futoon Almotairi
Manal Aldhirgham
Raaoum Jabor
Norah alawlah
Shahad Helmi
Rand Aldajani

Khalid Alhamdi - Leader

Ahmed Alayban
Sultan Alosaimi
Abdullah Alomran
Bassam Alghizzi
Ibrahim Aljurayyan
Mohammed Almutairi
Turki Alkhalifa
Malik Alshaya
Faisal Alhmoud
Abdulrahman Alnoshan
Ahmed Alqahtani
Hamad Alshaalan
Anas Alharbi
Mohammed Alwahibi
Saad Alghadir

BiochemistryTeam441@gmail.com