جامعة الملك سعود
King Saud University

بِسْمِ اللهِ الرَّحْمَنِ الرَّحِيمِ

MED437 KING SAUD UNIVERSITY

BIO TEAM

Gluconeogenesis

Biochemistry Team 437

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Notes and explanations
Extra information
Highlights

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

Gluconeogenesis is an **Anabolic** pathway; meaning we **use** ATP to get a complex molecule -glucose--
Don't confuse it with glycolysis where we generate ATP by metabolizing glucose

Gluconeogenesis

Gluconeogenesis: one of the essential pathways of energy metabolism

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

So, gluconeogenesis means the formation of new glucose.

But it is IMPORTANT to note that it is the formation from non saccharide substrates

Gluconeogenesis: An Overview

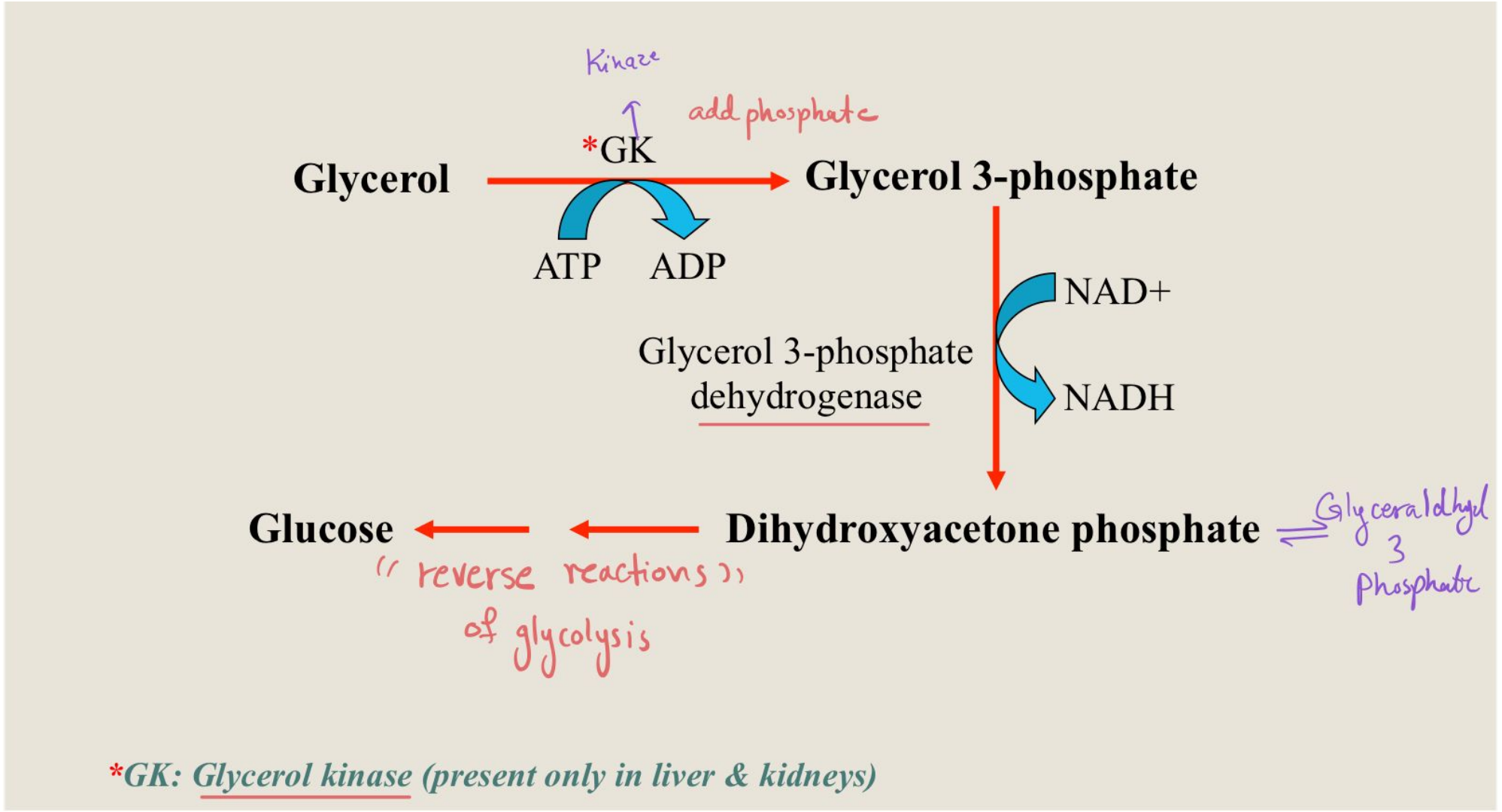
Site: **Liver (mainly) and Kidneys**

Both mitochondria and Cytosol are involved **Except**: if the substrate is Glycerol: only cytosol

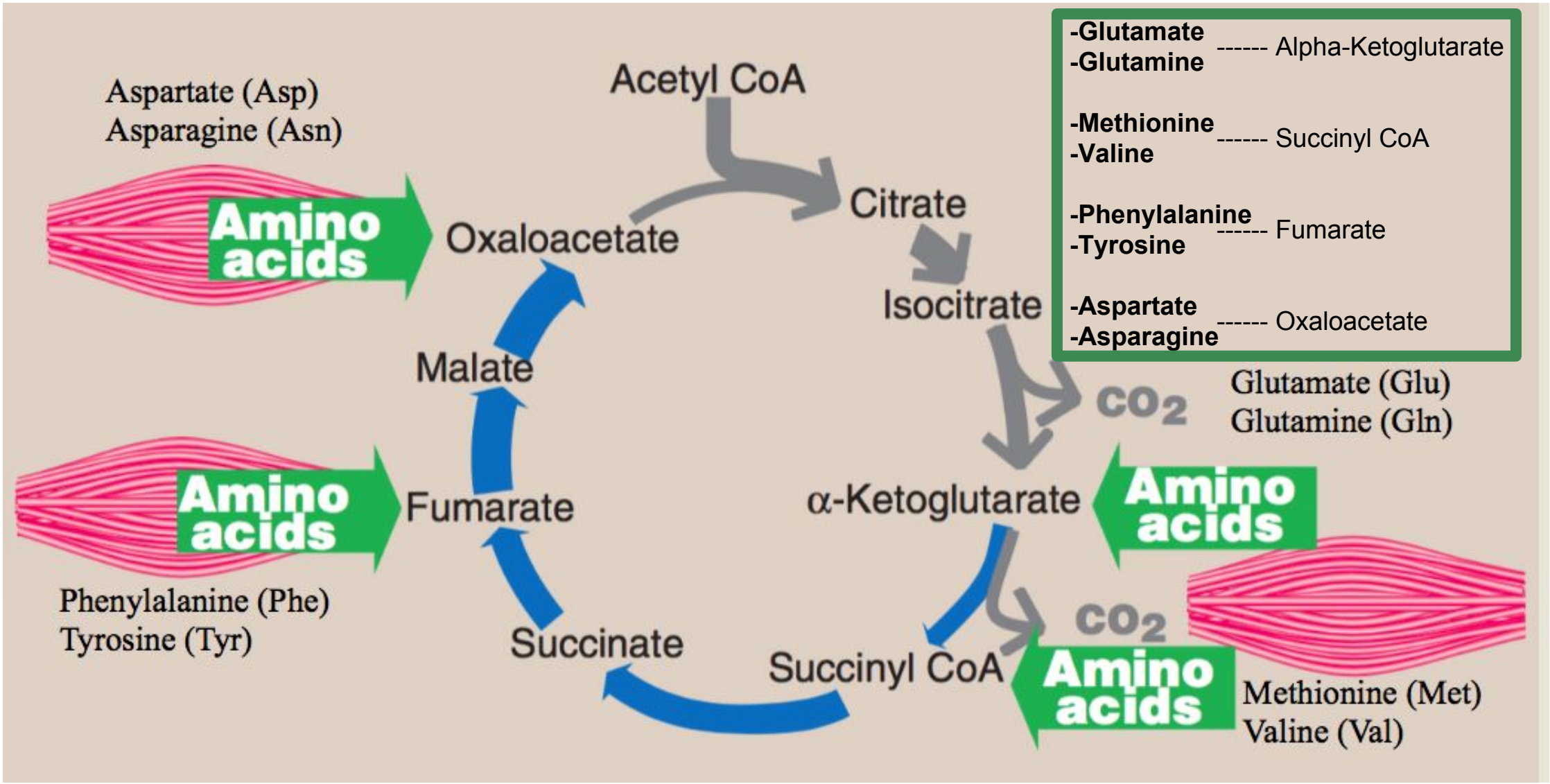
Gluconeogenic substrates:

1. **Glycerol** (Site: only in cytosol) (Glycerol rhymes with Cytosol)
2. **Glucogenic Amino Acids**
3. **Pyruvate and Lactate**

Gluconeogenesis Substrate: 1-Glycerol

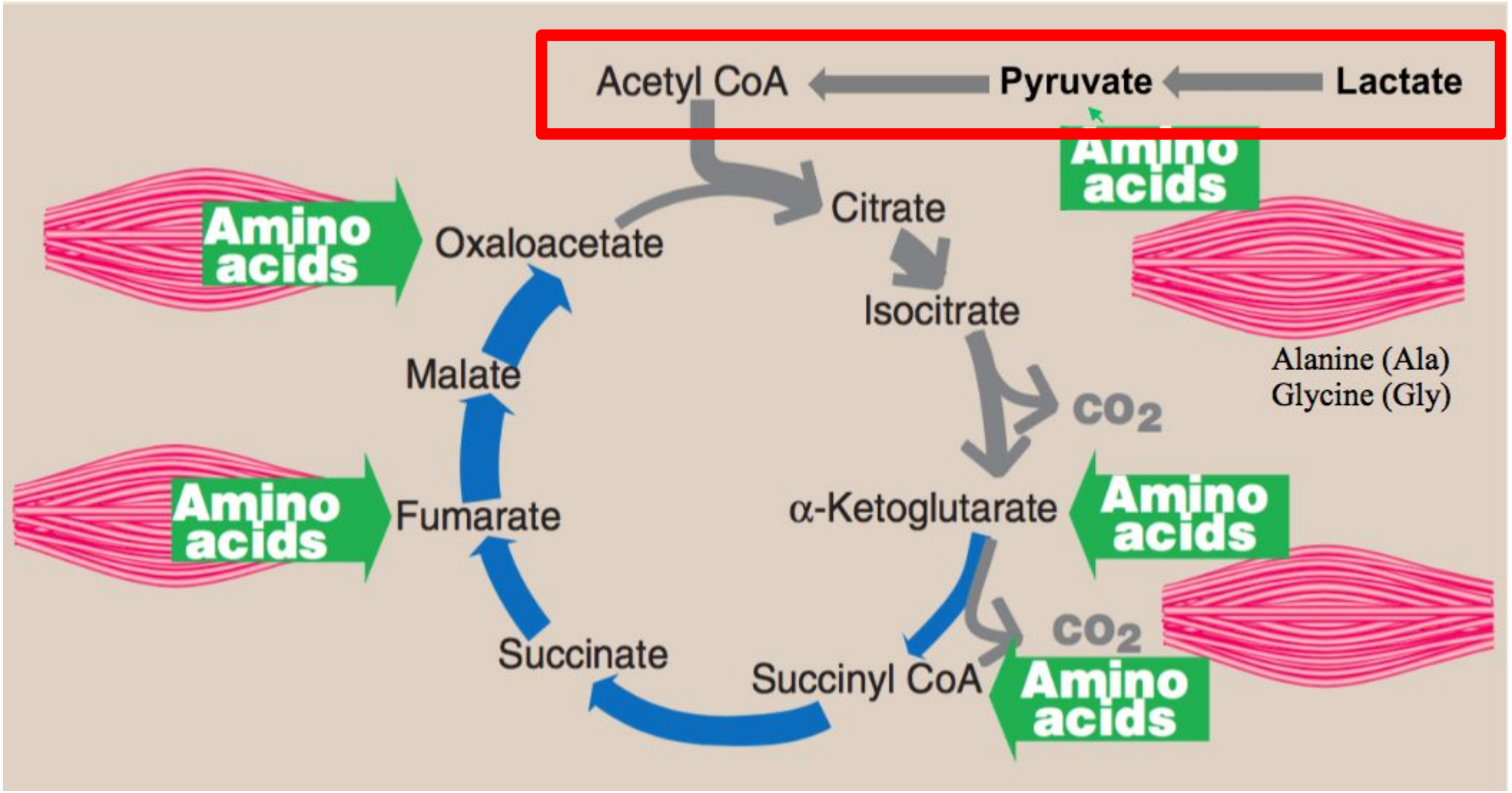


Gluconeogenesis substrates: 2-Amino acids



Gluconeogenesis Substrates:

3- Pyruvate and Lactate

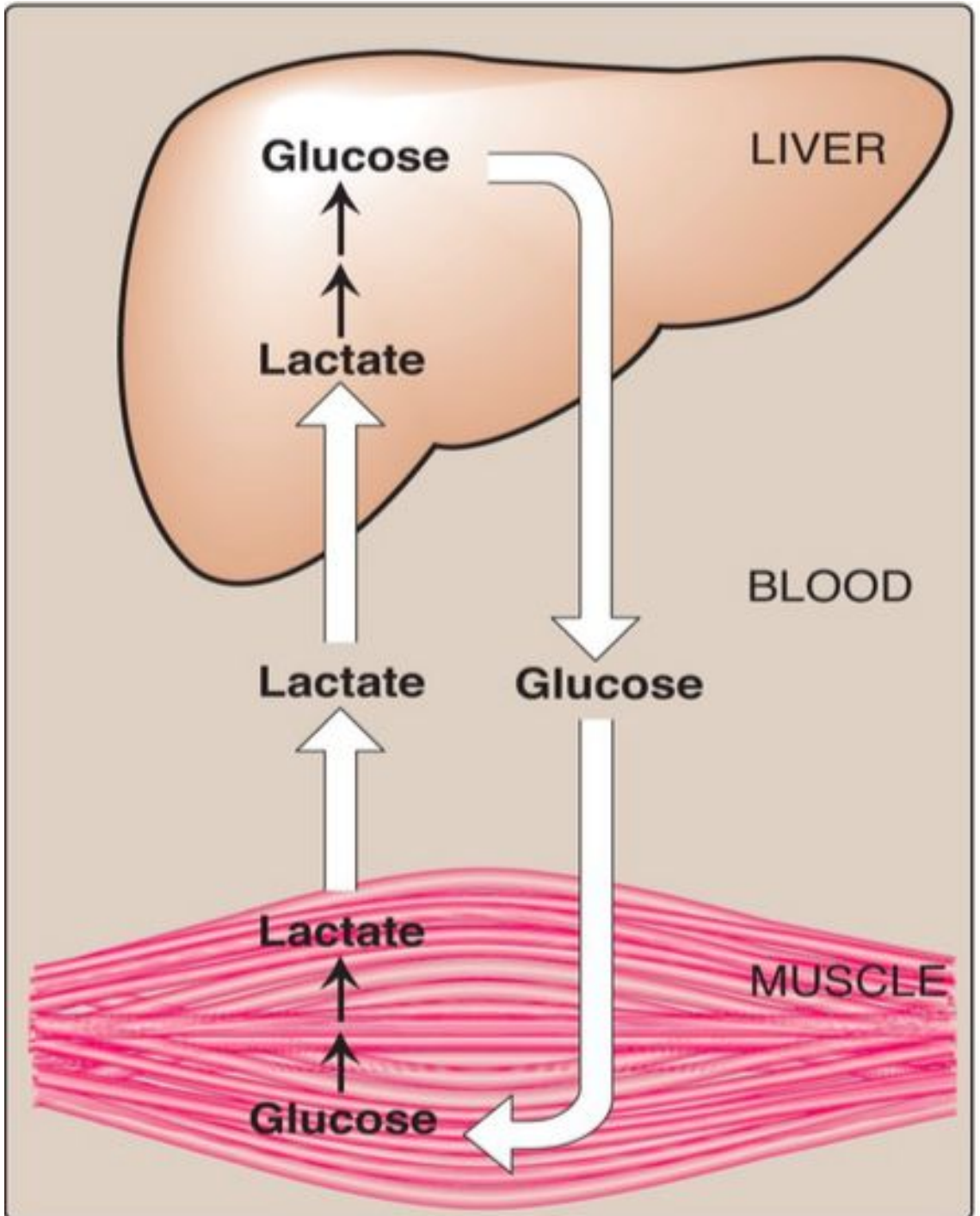


Gluconeogenic Substrates:
3- Lactate (Cori Cycle)

-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

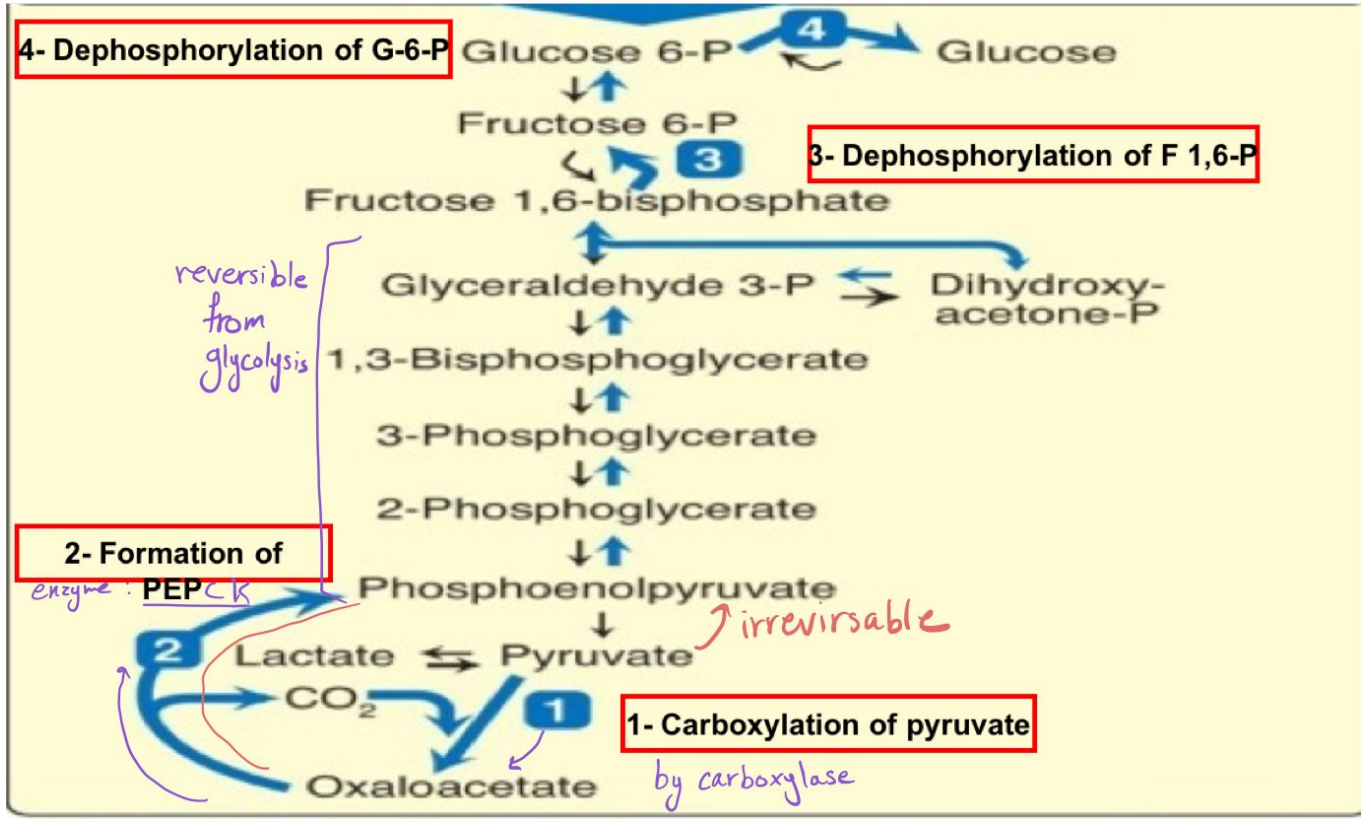
The Cori cycle (also known as the **Lactic acid** cycle), refers to the metabolic pathway in which **Lactate** produced by anaerobic glycolysis in the muscles moves to the liver and is **converted** to **glucose**

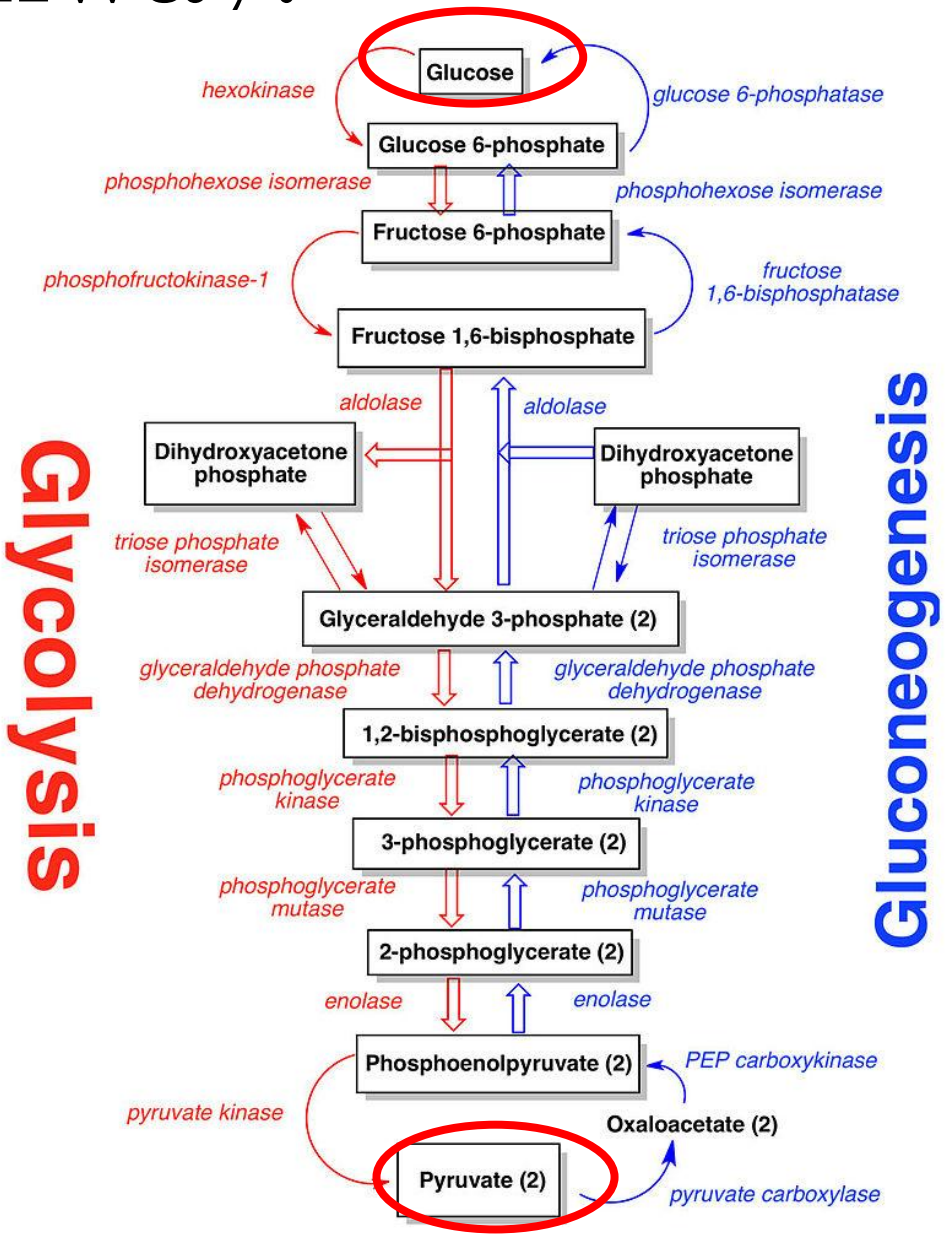
(The lactate is Re-transformed back into glucose in the LIVER)



Gluconeogenesis pathway:

We're working in reverse, (Backwards)
A reverse Glycolysis





Pyruvate Carboxylation

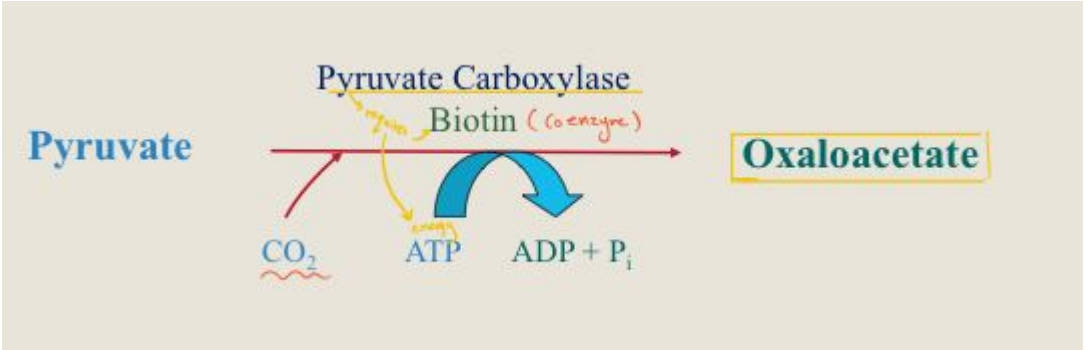
436note The carboxylation occurs in the liver and kidney, exactly in Mitochondria .
- So Pyruvate has to travel from cytoplasm to mitochondria why ?
- Because Pyruvate carboxylase is only found in matrix of mitochondria

Pyruvate carboxylase: is an enzyme that catalyzes the irreversible carboxylation of pyruvate to form oxaloacetate (OAA).

436note 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
1)Pyruvate carboxylase يحول Pyruvate الى Oxaloacetate
2)PEP-CK يحول Oxaloacetate الى PEP

436note Substrate: Pyruvate
Chemical Reaction: Carboxylation Enzyme: Pyruvate Carboxylase Co-Enzyme: Biotin
Product: Oxaloacetate



Summary of pyruvate carboxylation:

Puruvate carboxylation occurs in the mitochondria.
1-Pyruvate is first converted to oxaloacetate (OAA) by pyruvate carboxylase
2-oxaloacetate should be transferred to the cytoplasm to complete the gluconeogenesis; but OOA cannot cross the mitochondrial membrane, what do we do? We reduce it to malate by the enzyme malate dehydrogenase
3-malate crosses the membrane, then is oxidized to oxaloacetate again.
4- oxaloacetate is converted to PEP by the enzyme PEP carboxykinase.

Step(1) is shown in the picture above
Steps (2,3,4) are shown in the picture in the next slide

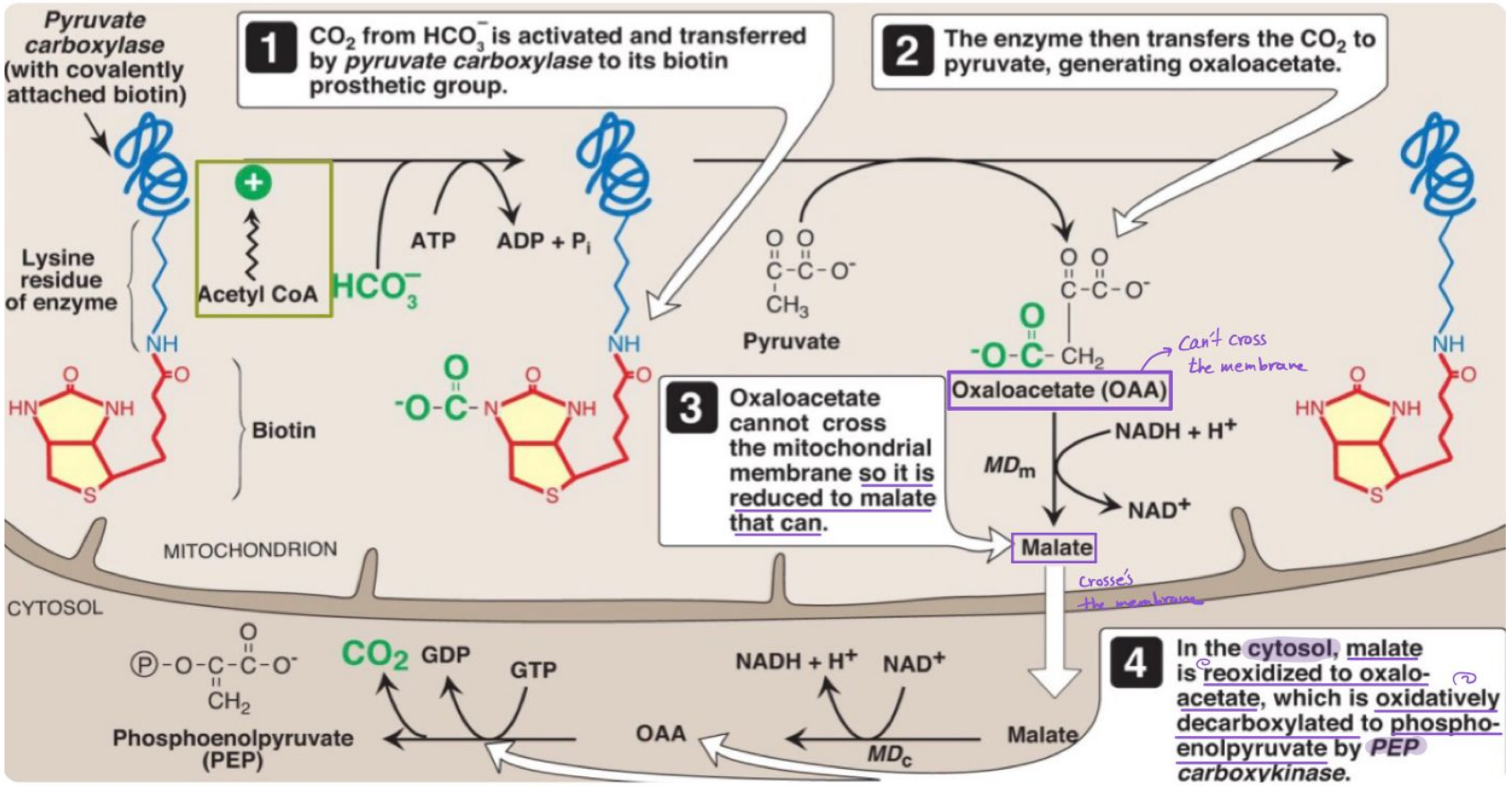
Pruvate Carboxylase and PEP-CK

Pyruvate carboxylase + PEP-CK ≠ Pyruvate kinase

Pyruvate Carboxylase is induced (activated) by Acetyl- CoA

- What happens during fasting?

- Acetyl-CoA is increased via fatty acid oxidation (FAO)



Regulation of Pyruvate Carboxylase reaction

436team

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

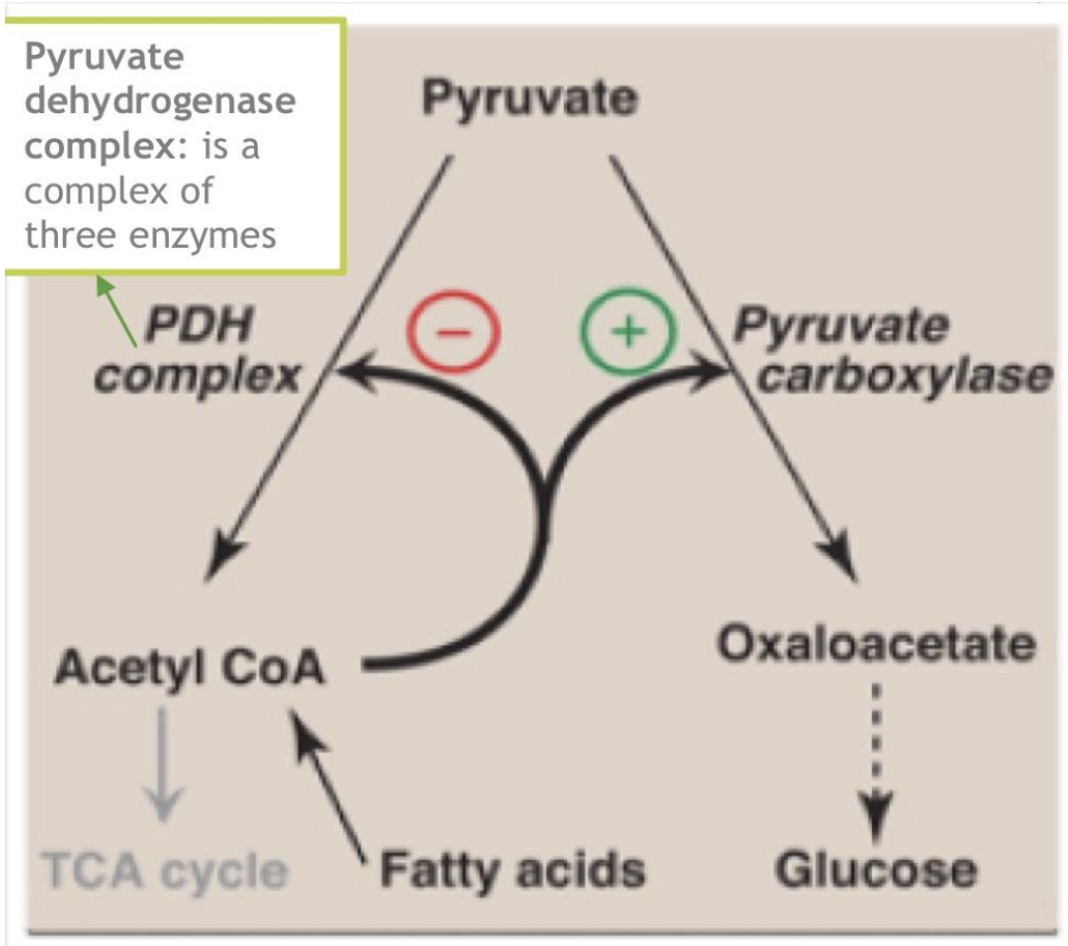
How? High level of Acetyl-CoA will inhibit PDH complex and stop or reduce the Glycolysi. And stimulate Pyruvate Carboxylase to start Gluconeogenesis.

+ positive regulation (activation)

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

-negative regulation (inhibation)

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

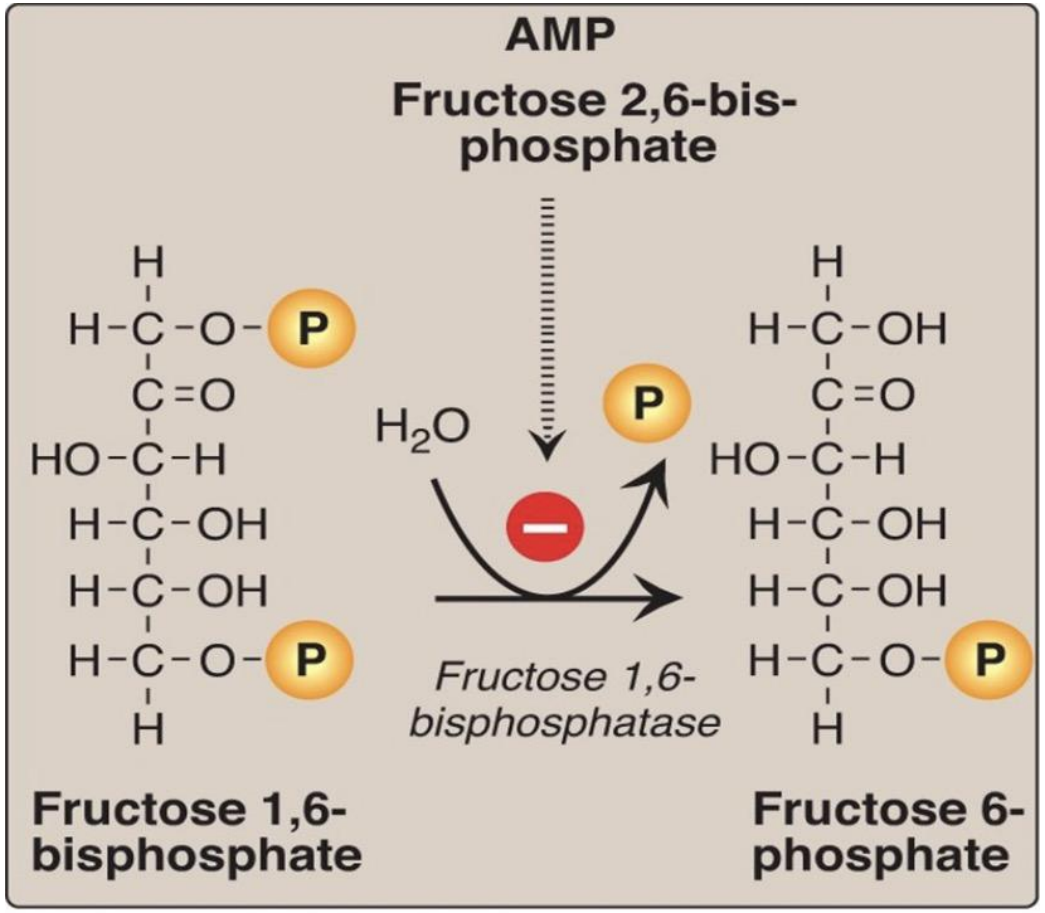


Fructose 1,6-Bisphosphatase

هو الأنزيم
ألي يحول
Fructose 1,6-Bisphosphate
الى
Fructose 6-Bisphosphate

Fructose 1,6-bisphosphatase ≠ PFK-1

436notes Fructose 1,6 bisphosphatase enzyme dephosphorylates (removes P group) Fructose 1,6 Bi-phosphate. Which turns it into Fructose 6-Phosphate. v (- negative regulation) What inhibits this process? v AMP and Fructose 2,6 bisphosphate

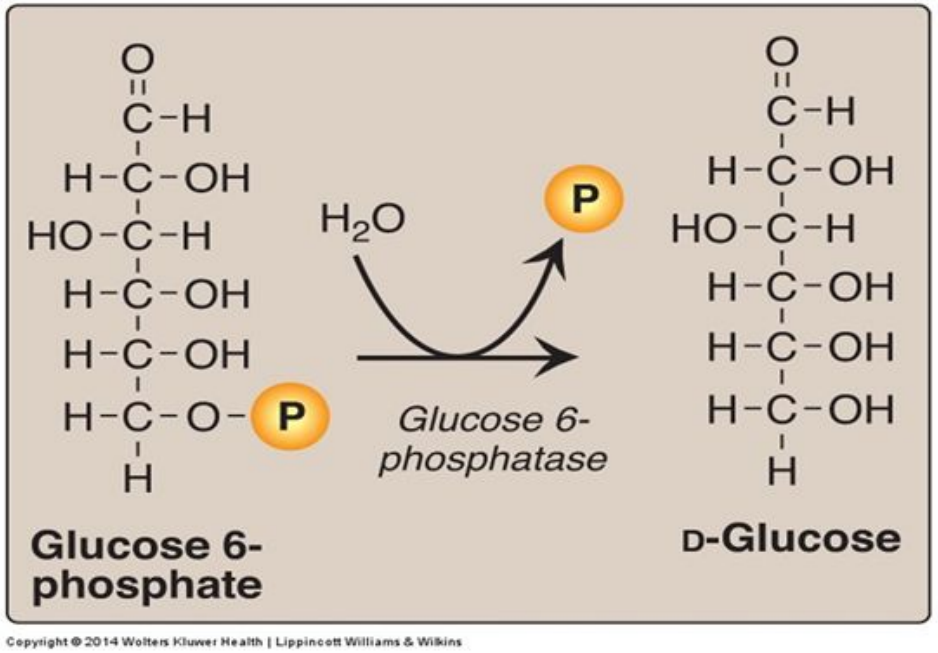


Glucose 6-Phosphatase

- Glucose 6- phosphate > D-Glucose
- Done by Glucose 6-phosphatase enzyme (removal of phosphate group)

- Dephosphorylationof glucose 6 phosphate allows release of free glucose from the liver and kidney into blood.

(when glucose is phosphorylated can not go outside the cell So. They need to Dephosphorylation To go from cell to circulation in blood to maintain blood sugar level)



Glucose 6-phosphatase ⇌ Glucokinase

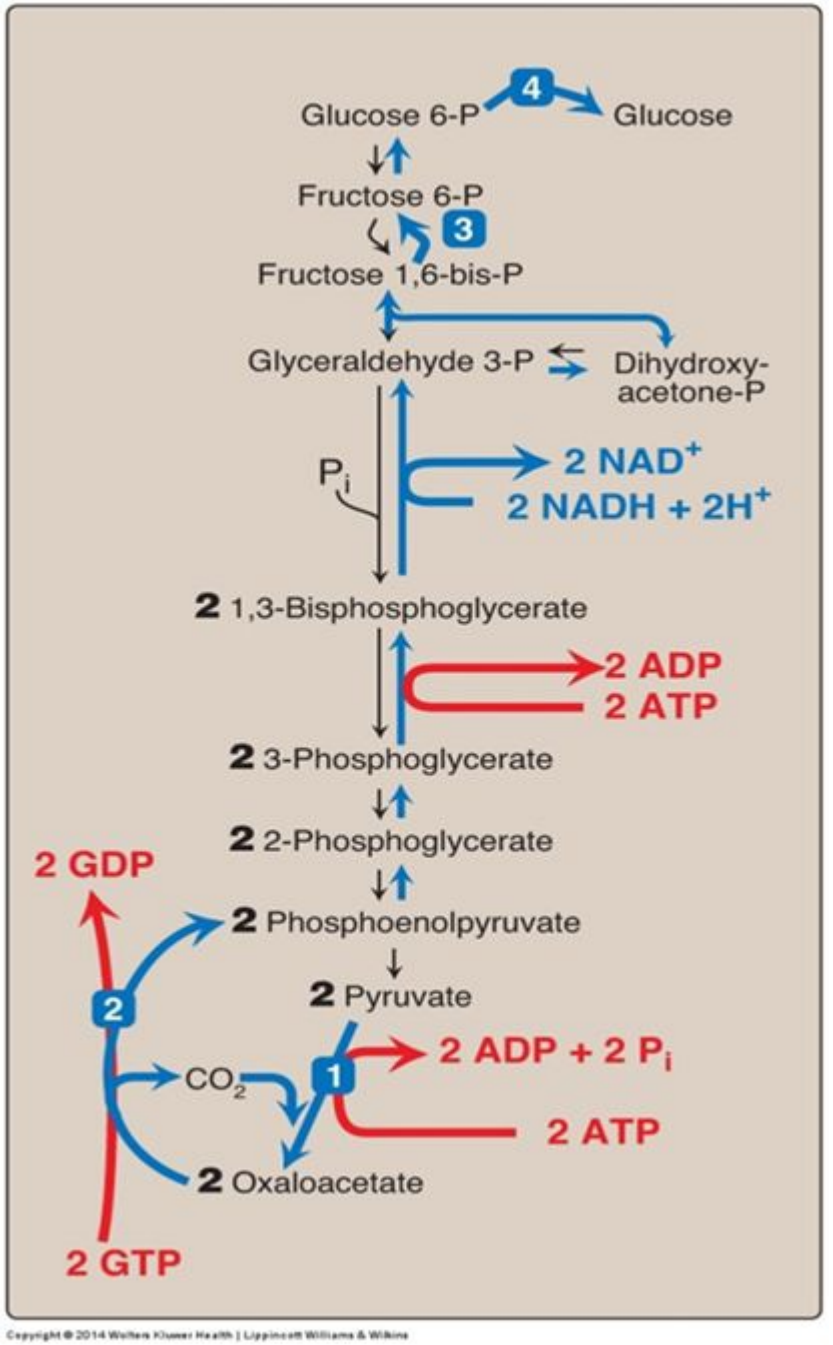
(Glucokinase is an enzyme that facilitates phosphorylation of glucose to glucose-6phosphate) 436 team

Gluconeogensis: Energy- Consumed

Six High-Energy Phosphate Bonds From Pyruvate to Glucose (From purvateto Glucose)

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

NET : 0 ATP



Gluconeogenesis: Regulation

- **Reciprocal control**
  Gluconeogenesis & Glycolysis

- **Allosteric:**
  Acetyl CoA (Pyruvate carboxylase)

AMP ⊖ or ATP ⊕
F 2,6-Bisphosphate ⊖ ⟩ F 1,6-bisphosphatase

- ⇧ **Glucagon** ⇩ **I/G ratio) stimulates gluconeogenesis**
  - Allosteric (⇩ F 2,6-Bisphosphate)
  - Induction (PEP-CK)

Important!!!
Pyruvate carboxylase is only found in matrix of mitochondria
Gluconeogenesis rate-limiting enzymes:
- ❖ Pyruvate carboxylase
- ❖ PEP-CK

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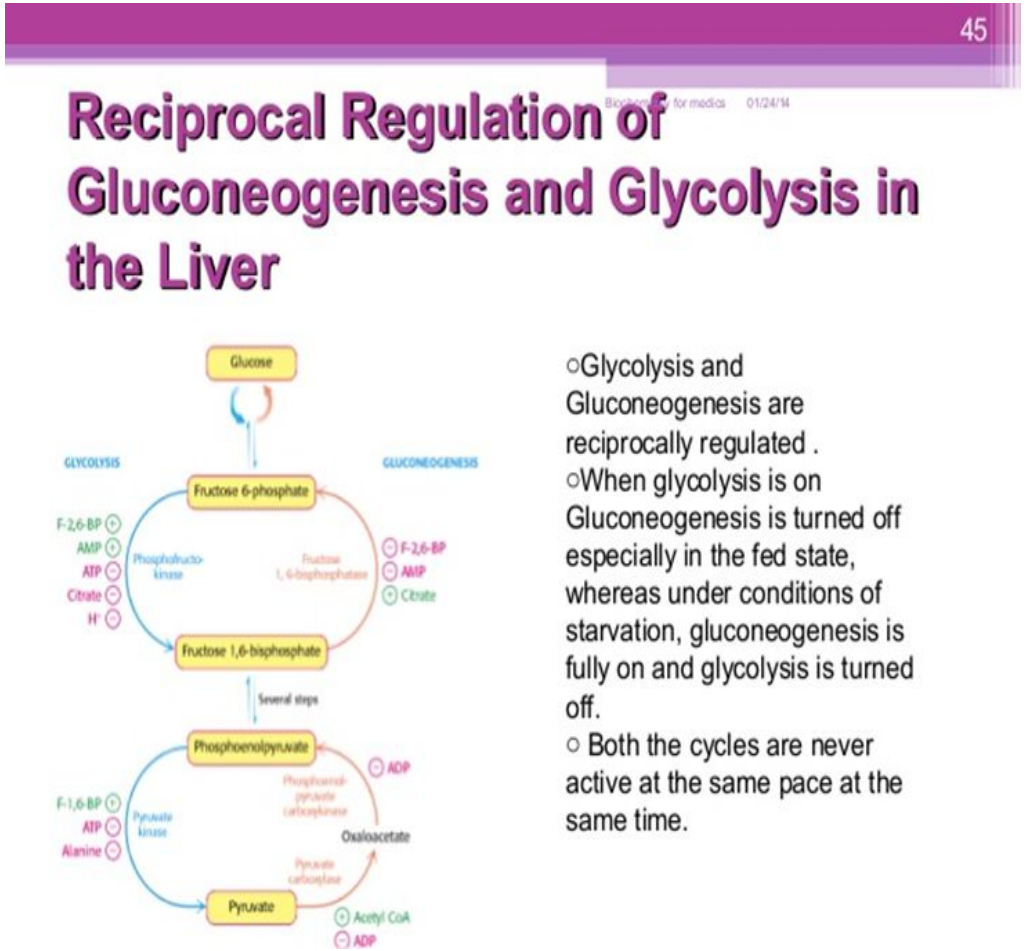


MCQ's

What are the substrates of Gluconeogenesis

A- Proteins, Fatty Acids, Steroids
B- Pyruvate, Saccharides, Amino acids.
C- Lactate and, Pyruvate, Amino Acids, Glycerol
D- Ethanol, Triglycerides, Lactate

When is Gluconeogenesis Stimulated

A- When Glucagon is low and insulin is high
B- When Thyroxine is high and insulin is high
C- When Glucagon is high and Insulin is low
D- When Thyroxine is high and glucagon is low

Where is the site of conversion of Lactate into Glucose

A- The Blood
B- Pancreas
C- Kidney
D- Liver

How much energy is consumed by Gluconeogenesis

A- 8 ATP
B- 6 ATP
C- 5 ATP
D- 3 ATP

What is the reciprocal pathway to Gluconeogenesis (opposite pathway)

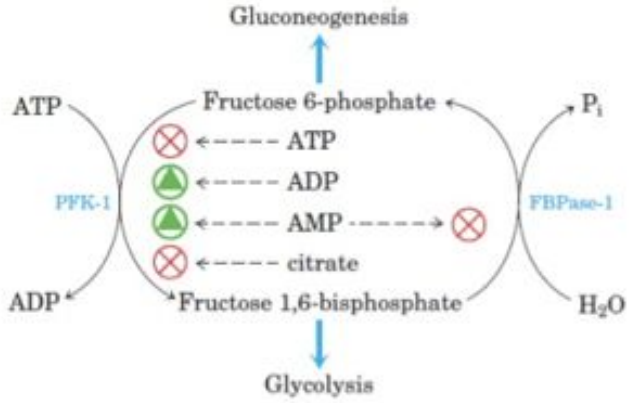
A- Glycogenolysis
B- Hexose Inversion
C- Glycolysis
D- Cori Cycle

C
D
C
C
B

Extra pictures for further understanding

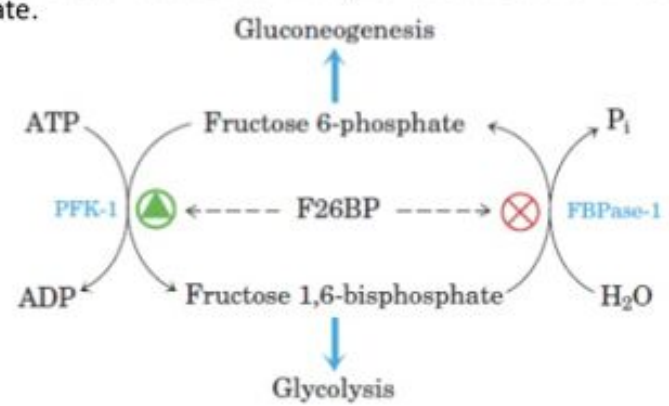
Allosteric regulation

- **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



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.

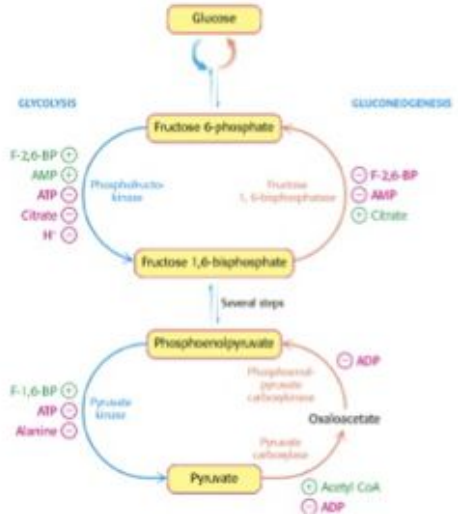


- PFK-1 is virtually inactive in the absence of F2,6-BP
- F2,6-BP *activates PFK-1 and stimulates* glycolysis in liver
- F2,6-BP *inhibits* FBPase-1 slowing gluconeogenesis.

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

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.

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