صناعة glucose من
مشتقات غير كربوهيدراتية

Gluconeogenesis

(Production of glucose from non-carbohydrate precursors)

Dr. Diala Abu-Hassan

Textbook:

Lippincott's Illustrated reviews: Biochemistry

• العمليـة فـي صـورة .

_ عملية gluconeogenesis هي عكس عملية glycolysis

لكن زي ما بنعرف في glycolysis عنا 3 خطوات

irreversible ك يعني بدها other enzyme عشان يرجع

المركب من product ل substrate ، وهدول الثلاث

ح نحكي عنهم بالطريقة هاي .

_ pyruvate الي بنا نصنع منه glucose هون بكون جاي

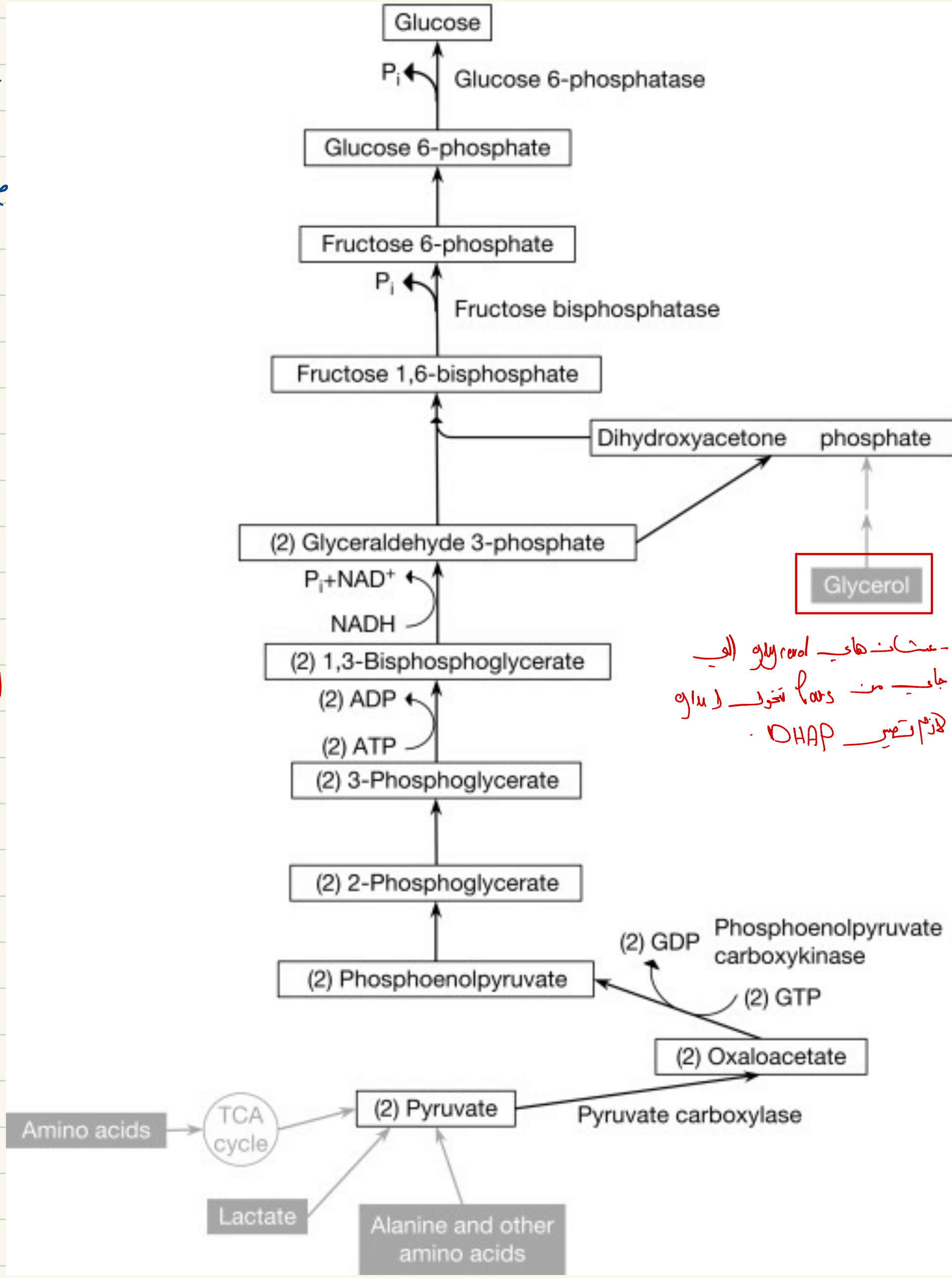
من sources غير glycolysis بنا تتذكروا انا بحالة

fasting هون والglycolysis بصير بـ well fed state

_ gluconeogenesis بيستهلك 6ATP ، وهي عملية

مستهلكة للطاقة . فالأولوية هون نصنع glucose

لتعويض ال brain cell and muscle cell



عشان هاي الglycerol الي
جاي من fats تتحول لـglu
لازم تصير DHAP .

لاتنسوا اخوتنا في غزة من الدعاء .

Lujain

شوفوا الشرح .

https://youtu.be/Cpbv6GS970A?si=alQXcssZD8HZc-Vs

Glucose Synthesis is Required for Survival

- Brain is dependent on glucose 120g/day
- Body glucose reserve is limited
  - ≈ 20 g (extra cellular fluid)
  - ≈ 75 g (liver glycogen); enough for 16 hours
  - ≈ 400 g (muscle glycogen); for muscle use only

    Main source of energy for resting muscle in post-absorptive state
- 70 Kg man has ≈ 15 Kg fat
  - Fatty acids can not be converted to glucose
  - Utilization of FA is increased 4-5 X in prolonged fasting
  - In prolonged fasting; FA → ketone bodies at high rate

the only source of energy.

glycogen amount.

الدماغ يحتاج كمية سكر كبيرة، ما بقدر liver يوفرها
عن طريق تكسير glycogen، لهيك بيصير gluconeogenesis

طب ليش ما نخزن كمية glycogen اكتر بالكبد والعضلات مثلاً؟

1) We store energy in form of lipids not Carbs why? because the energy stored in lipid is much higher than Carbs for example the one g of lipid generate 9 Kcal of energy, while one gram of Carbs generate 4 Kcal.

2) when we store glucose molecules which they are hydrophilic molecules, they will attract water molecules which result in increase the volume of cell

بالتالي بيصير حجمنا كثير كبير مقارنة بأوزاننا.

- مثال ← الشخص اللي وزنه 70 كغ عنده 15 كغ من الدهون، فلو اجرينا حساباتنا 15000 x 9 / 4، راح نلاقي انه الطاقة المخزنة في 15 كغ من الدهون تعادل الطاقة المخزنة بـ 35 كغ من الكاربز. (طبعاً وما ننسى الماء اللي ع بيجي كمان ذي ما ذكرنا فوق، فالكمية كبيرة).

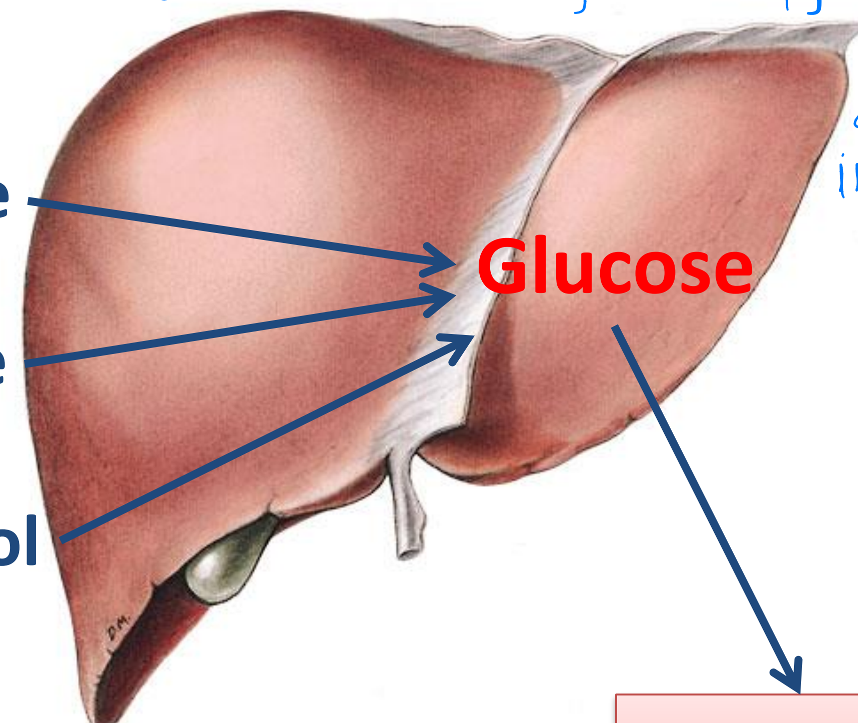
Gluconeogenesis occurs mainly in the liver

— glucogenic amino acid :- amino acids that generate glucose (Majority of them can generate glucose → which degraded into pyruvate or any of TCA intermediate

Tissues that do not oxidize glc. completely e.g RBCs Exercising muscle → **Lactate** → **Glucose**

Muscle Glucogenic A.As → **Alanine** → **Glucose**

Adipose tissue → **Glycerol** → **Glucose**



Glucose → Peripheral tissues

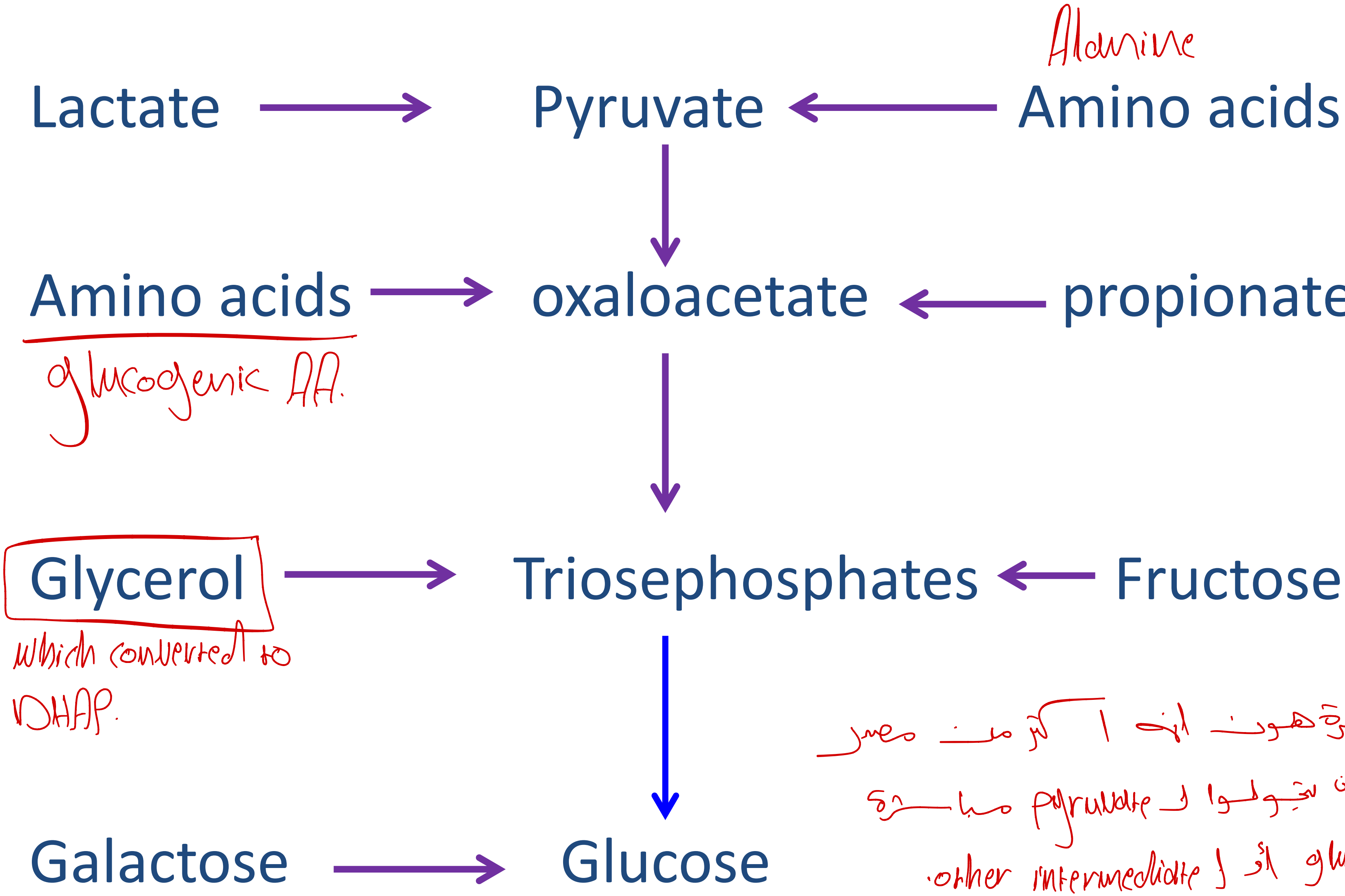
— 18 of Amino acid are glucogenic which mean all of them except the leucine and lysine.

Where and when does gluconeogenesis occur?

-gluconeogenesis differ from glycolysis in term of where it occur, as we say glycolysis occurs in all cells, However gluconeogenesis take place in specific sites.

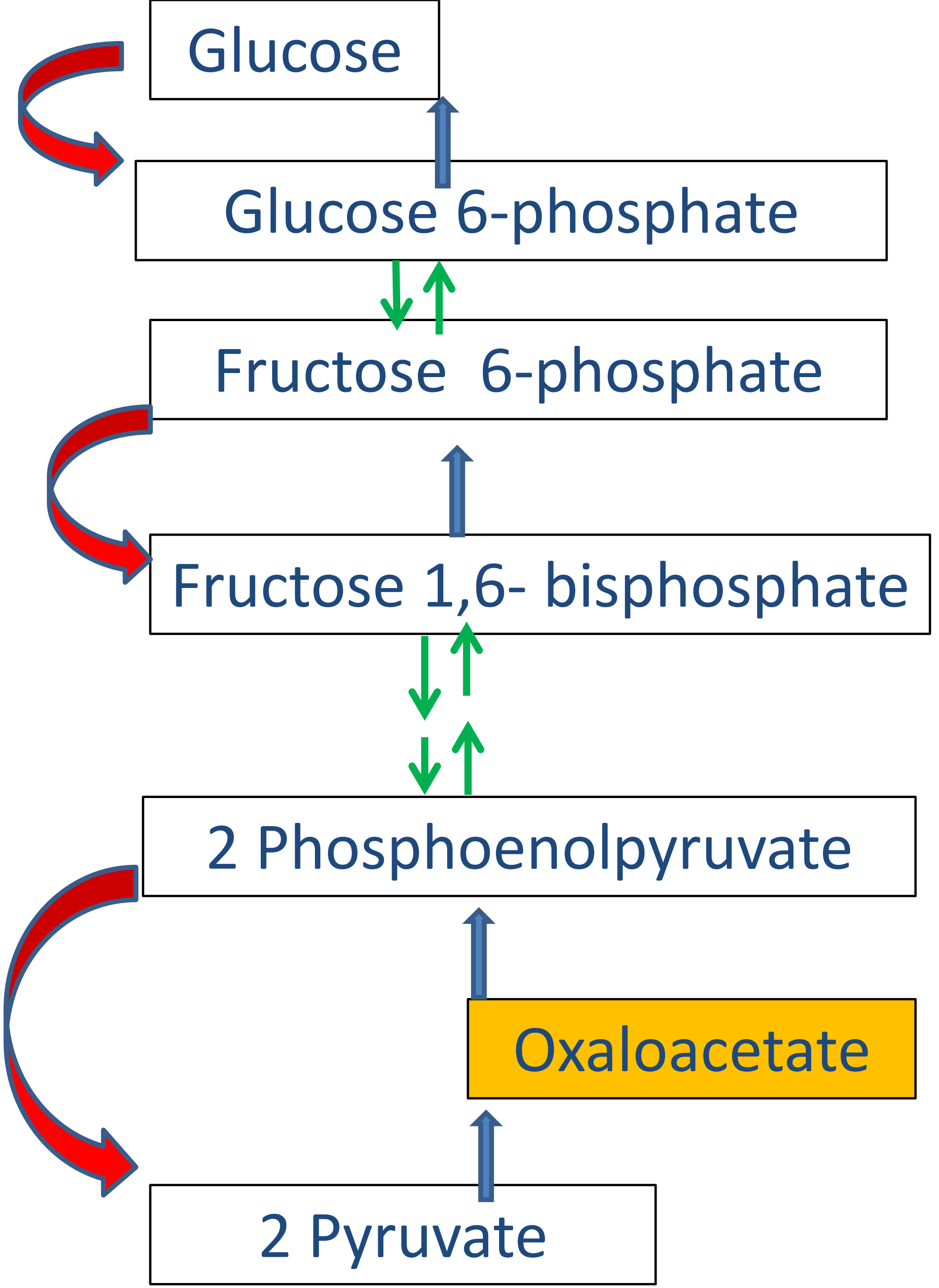
- During an overnight fast, ~ 90% of gluconeogenesis occurs in the liver and 10% by the kidneys
- During prolonged fasting kidneys become major glucose-producing organs (40% of total glucose production)

Entrance of substrates into gluconeogenesis



* الفكرة هون انه اكثر من مصدر ممكن يتحولوا لـ pyruvate مباشرة أو لـ glucose أو لـ other intermediate.

Gluconeogenesis is the opposite of glycolysis BUT

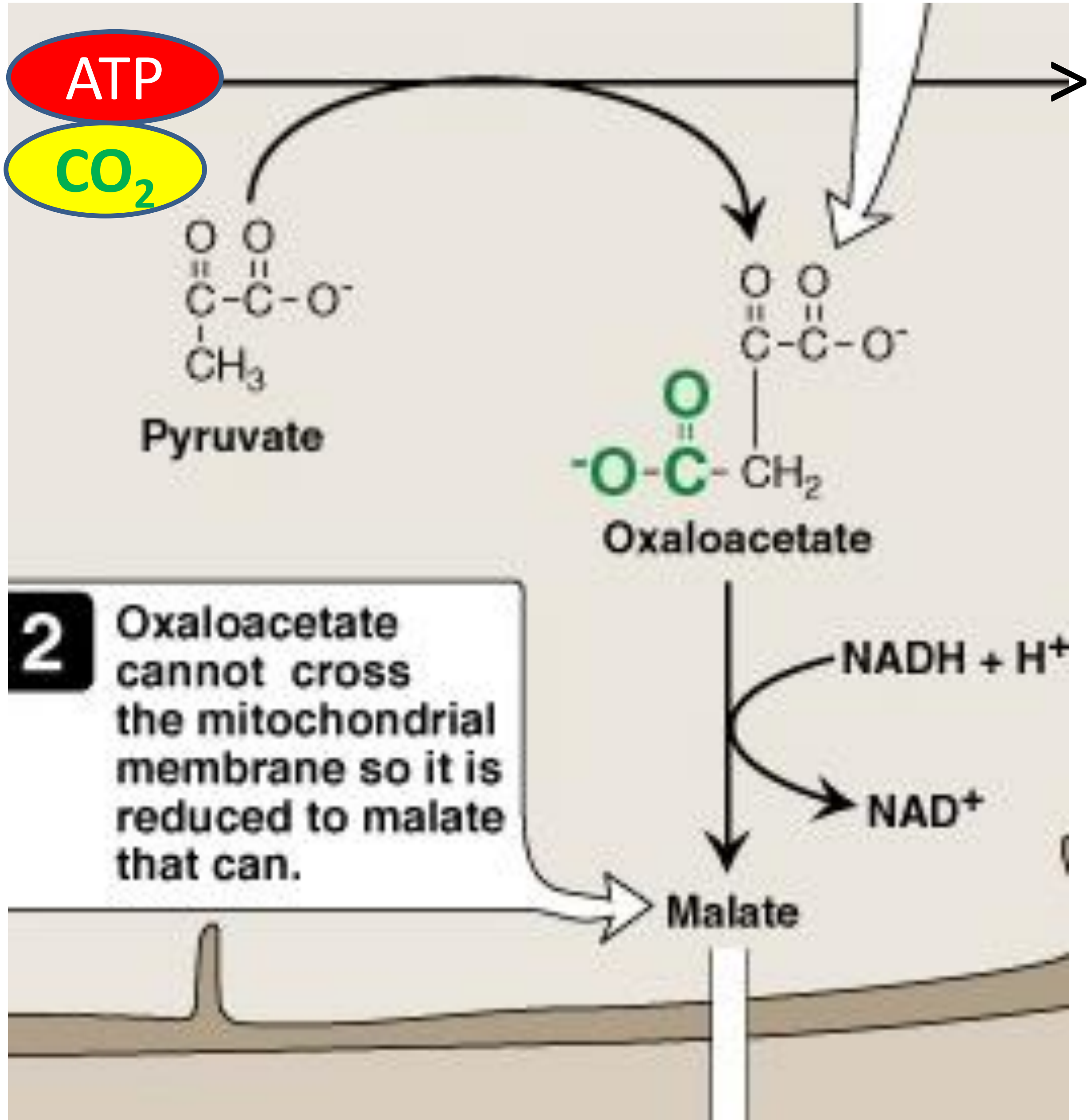


Reversing the irreversible steps

1. From pyruvate to phosphoenolpyruvate (PEP)

- Here we need two steps
- 2 molecules of pyruvate will convert to 2 molecules of oxaloacetate.

Carboxylation of Pyruvate Produces Oxaloacetate (OAA)



- **By pyruvate carboxylase**
- **In mitochondria**
- **Allosterically activated by Acetyl Co A**

– The first step will occur is carboxylation of pyruvate to an oxaloacetate by adding CO_2 to oxaloacetate (you can notice that the number of carbon is increased from 3 to 4) and this step need ATP (occur in mitochondria)

– The first step done by enzyme pyruvate carboxylase and the Co-enzyme Biotin.

– This oxaloacetate can't cross the membrane of mitochondria to cytosol, so it will be reduced to Malate (oxidizing NADH to NAD^+).

– When the Malate reach the cytosol, we will oxidize it to be oxaloacetate where the NAD^+ will reduced to NADH.

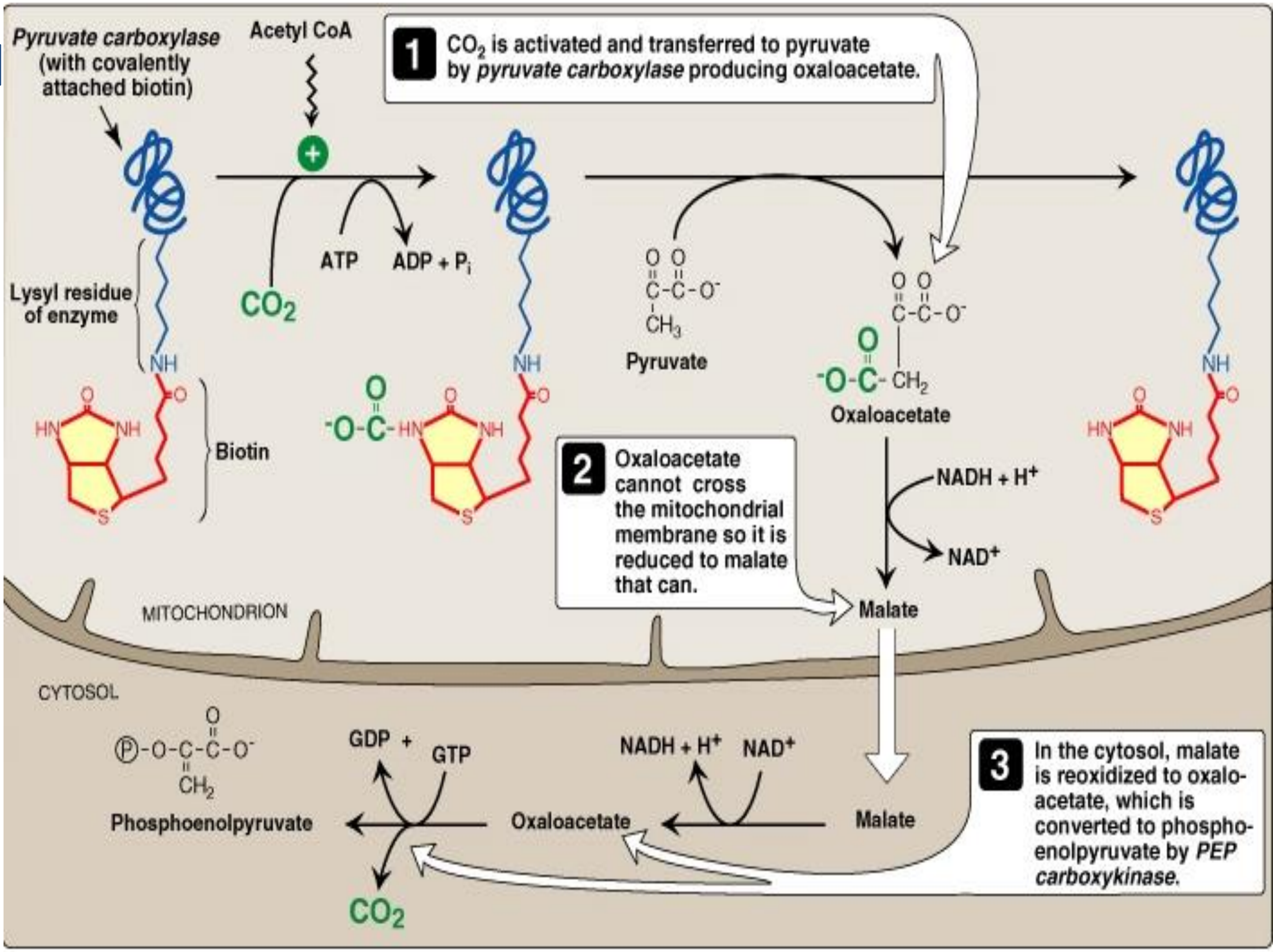
Now my oxaloacetate is ready to the next step of gluconeogenesis where we will convert it to PEP by Carboxy Kinase which will remove the Carboxyl group (the fourth carbon) and phosphorylate the molecule to become PEP (with 3C)

– Now, the PEP is ready for the next steps → اللي هي حكينا عكس عملية glycolysis لحد ما نوصل لـ fructose 1,6 bisphosphate عشان نغير الاتجاه.

From OAA to PEP

- Enzyme is found in both cytosol and mitochondria

- The generated PEP in the mitochondria is transported to the cytosol by a specific transporter



- The PEP that is generated in the cytosol requires the transport of OAA from the mitochondria to the cytosol

Reversing the irreversible steps

2. From fructose-1,6-bisphosphate to fructose-6-phosphate

– instead of fructose 1,6 bisphosphokinase we will use fructose 1,6 bisphosphatase.

- تذكر ←

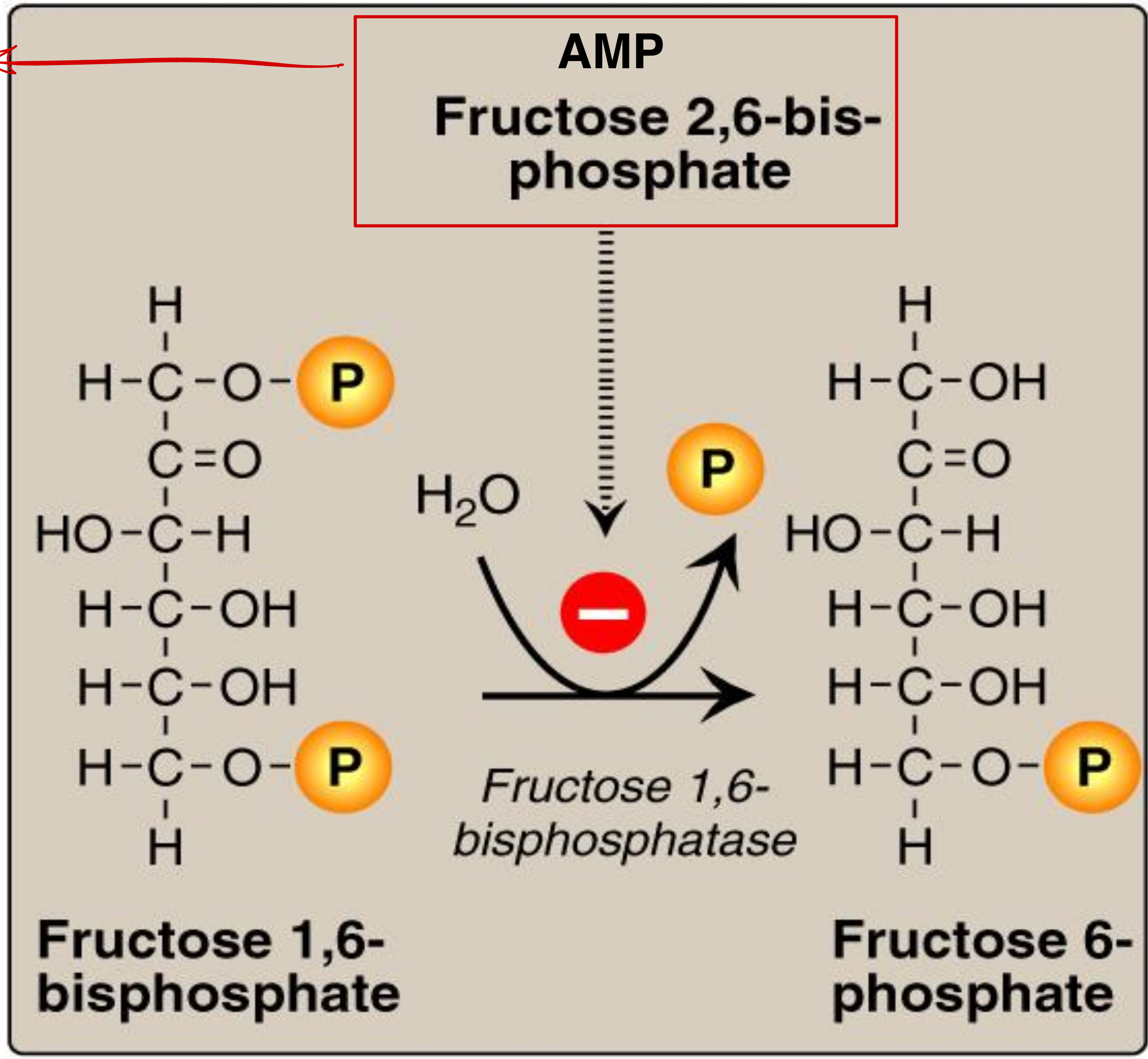
Kinase → إضافة phosphate

phosphatase → نزع phosphate

Dephosphorylation of fructose 1,6-bisphosphate

- Those molecules were activators to this step in glycolysis. Now they are inhibitors to this step in gluconeogenesis.

This reaction bypasses the irreversible phosphofructokinase -1 reaction

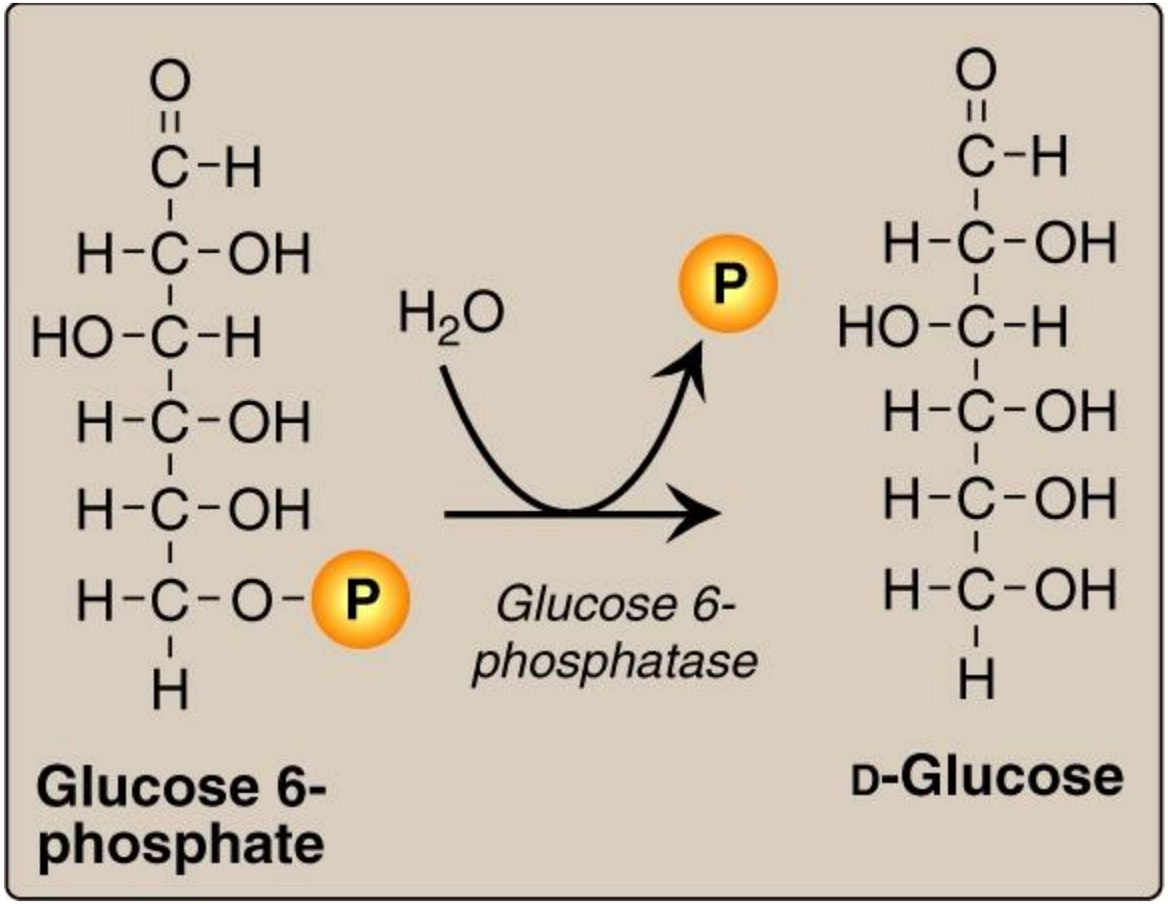


Reversing the irreversible steps

3. From glucose-6-phosphate to glucose

— This glucose 6 P. has to enter to the ER, because the enzym glucose 6 phosphatase which remove the phosphate is found on the ER. So we transport the phosphorylated glucose to ER by translocase. After removing phosphate, the glucose will leave the ER by Glut 7 (which only Glut found on ER)

Note ⇒ Gluts don't passage phosphorylated glu. through them.



Dephosphorylation of glucose 6-phosphate

- Bypasses the irreversible hexokinase reaction
- Only in liver and kidney
- Glucose 6-phosphate translocase is needed to transport G-6-P across the ER membrane

Glucose 6-phosphatase in Endoplasmic Reticulum (ER)

Hint: Muscle lacks glucose 6-phosphatase, and therefore muscle glycogen can not be used to maintain blood glucose levels.

.عشان هيك بس بنقدر نستخدم ال glycogen stored in liver

Formation vs. Hydrolysis of Glucose 6-phosphate

– we must hydrolyze the ATP to couple the two reactions together.

- Formation

$$Glc. + Pi \longrightarrow Glc.\ 6\text{-phosphate} + H_2O \qquad \Delta G = +ve$$

$$ATP + H_2O \longrightarrow ADP + P_i \qquad \Delta G = -ve$$

Hexokinase

$$Glc. + ATP \longrightarrow Glc.\ 6\text{-phosphate} + ADP \qquad \Delta G = -ve$$

- Hydrolysis

Phosphatase

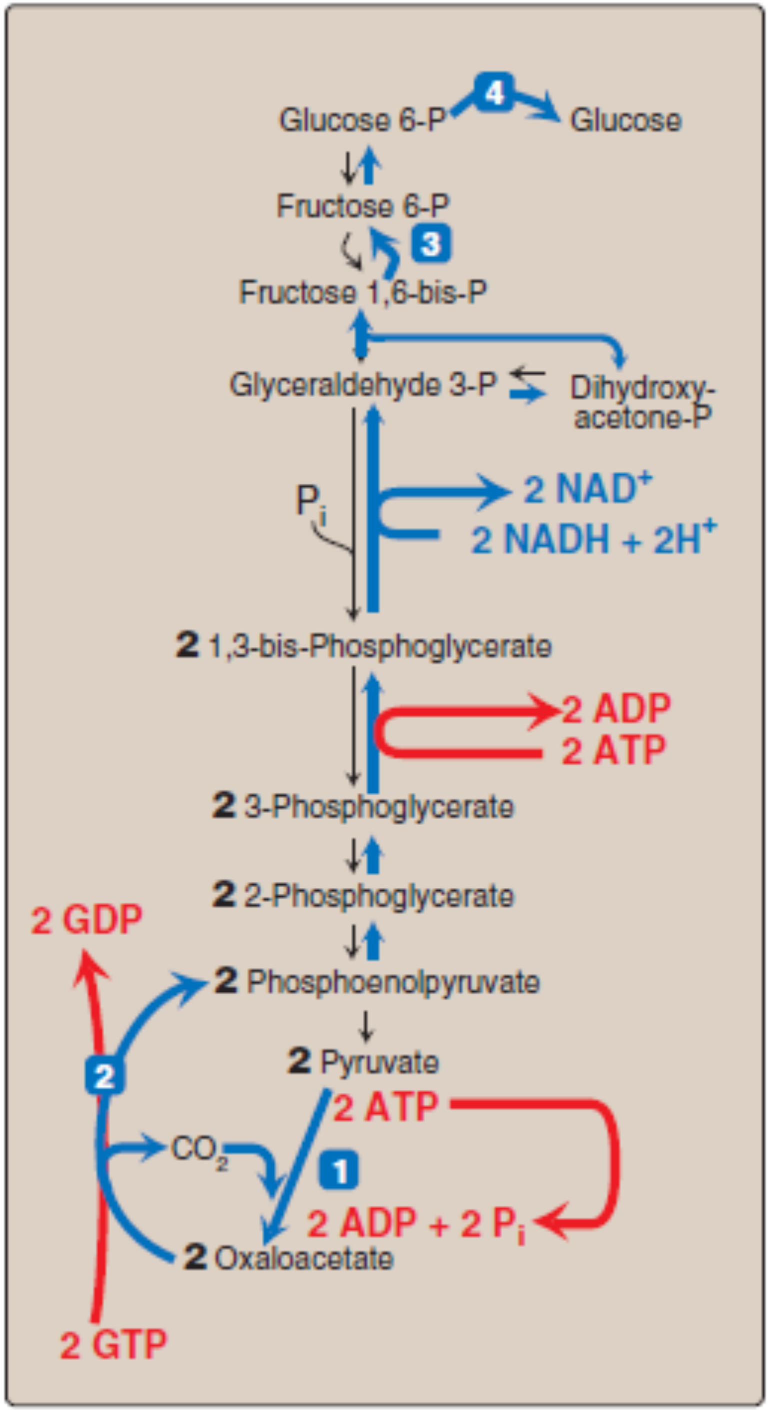
$$Glc.\ 6\text{-phosphate} + H_2O \longrightarrow Glc. + \boxed{P_i} \qquad \Delta G = -ve$$

– here the negative ΔG is enough for the reaction to take place, Not for generating ATP from p لذلك مش انتاج طاقة في عملية Hydrolysis

inorganic p isn't be used to form ATP.

- لازم تفهموا اشي ، مش كل الخطوات
الي بتستهلك طاقة في glycolysis بتصير تنتج
طاقة في gluconeogenesis.

Energy requirements of gluconeogenesis



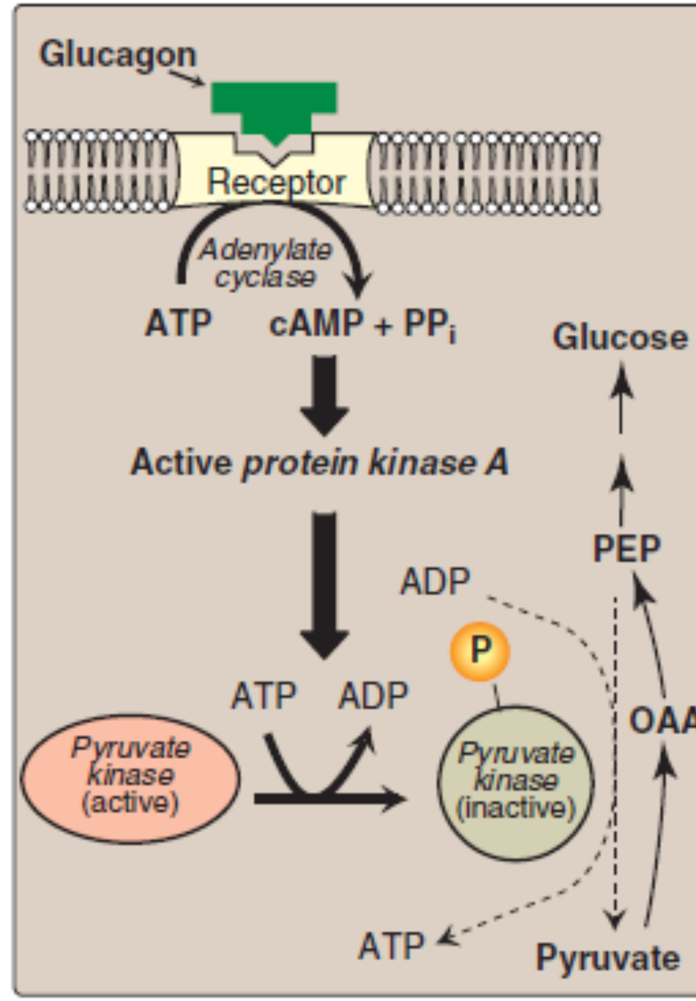
Regulation of gluconeogenesis

- Mainly by:

1. The circulating level of glucagon

- Glucagon lowers the level of fructose 2,6-bisphosphate, resulting in activation of fructose 1,6-bisphosphatase and inhibition of PFK-1
- Inhibition of pyruvate kinase
- Glucagon increases the transcription of the gene for PEP-carboxykinase

2. The availability of gluconeogenic substrates



3. Slow adaptive changes in enzyme activity due to an alteration in the rate of enzyme synthesis or degradation, or both

The low glucose Conc. will stimulate glucagon to bind to its receptor leading on cAMP activation, as well as protein Kinase A will be active and phospholyrate the pyruvate Kinase making it inactive and active the phosphatase which will remove the phosphate from fructose 2,6 bisphosphate make it fructose 6 phosphate so the Conc. of the glycolysis activator fructose 2,6 bp. is low which lead to stop glycolysis and turn on the gluconeogenesis.

- As any pathway the regulation occur at the amount and Conc. of enzyme and substrate avilibility.

Lujain Ahmad

ـ لا تنسونا من صالح الدعاء.