Glucose metabolism

Metabolism

- Most pathways can be classified into:

كيف بكسره، بالهضم ← بيعطي طاقة

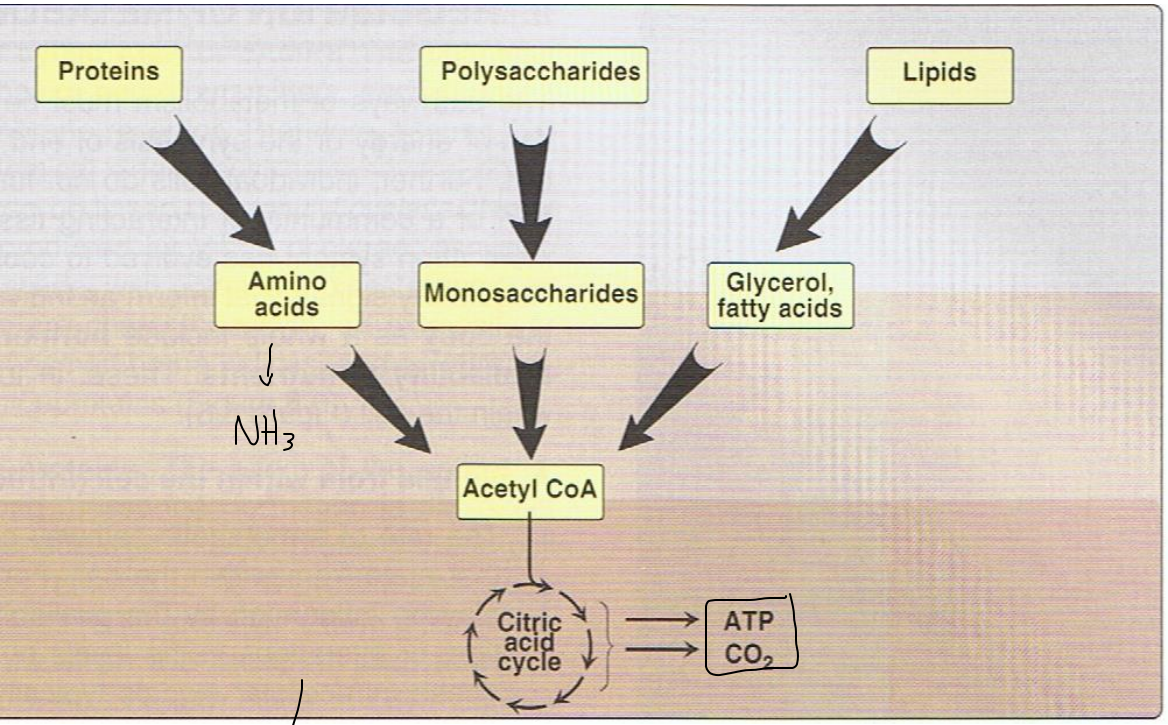
- **Catabolism**: degrade complex molecules (proteins, carbohydrate and triglycerides) to few simple products (CO_2, NH_3 and H_2O). Capture chemical energy to form ATP. Considered a **convergent** process (large no. of substances are degraded to few common end products).

كيف ببنيه، بتصنيع ← بده طاقة

- **Anabolism**: synthesize complex end products from simple precursors. Requires energy which is provided by the breakdown of ATP. Considered a **divergent** process (few starting precursors produce wide variety of complex substances)

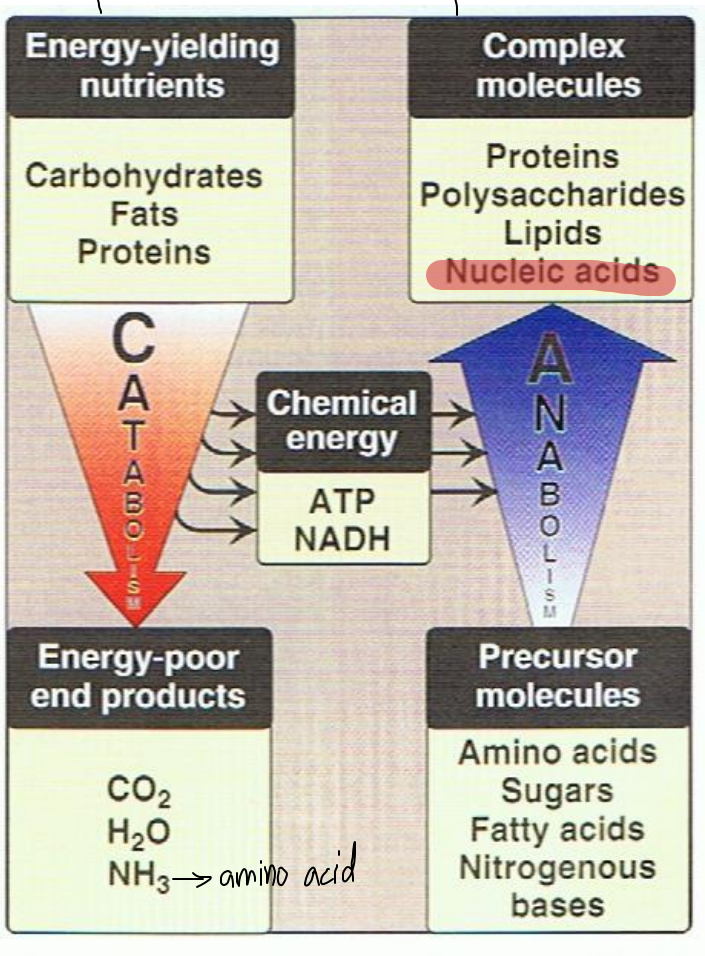
سلائف ←

Catabolism



→ catabolism from large molecules to small molecules

→ catabolism → anabolism



Regulation of metabolism

- Signals from within the cell (intracellular)

  The rate of a metabolic pathway may be influenced by the availability of substrates, product inhibition, or alterations in the levels of allosteric activators or inhibitors.

- Communication between cells (intercellular)

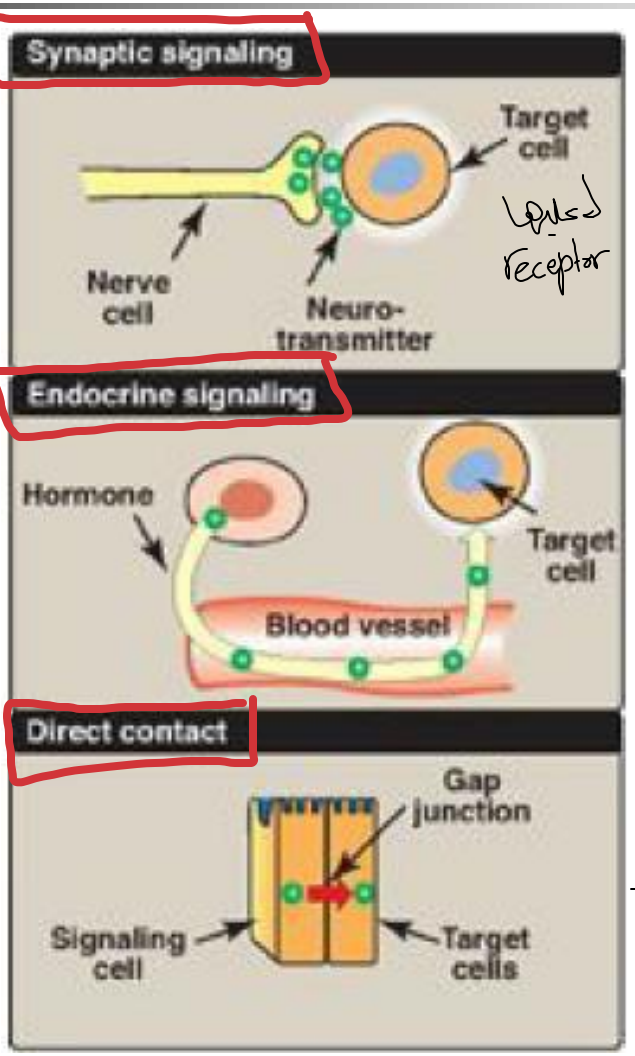
  Can be mediated by surface-to-surface contact, hormones and, in some tissues, by formation of gap junctions

- Second messenger systems

  Two of the most widely recognized second messenger systems are:

  - The calcium/phosphatidylinositol system
  - The adenylyl cyclase system

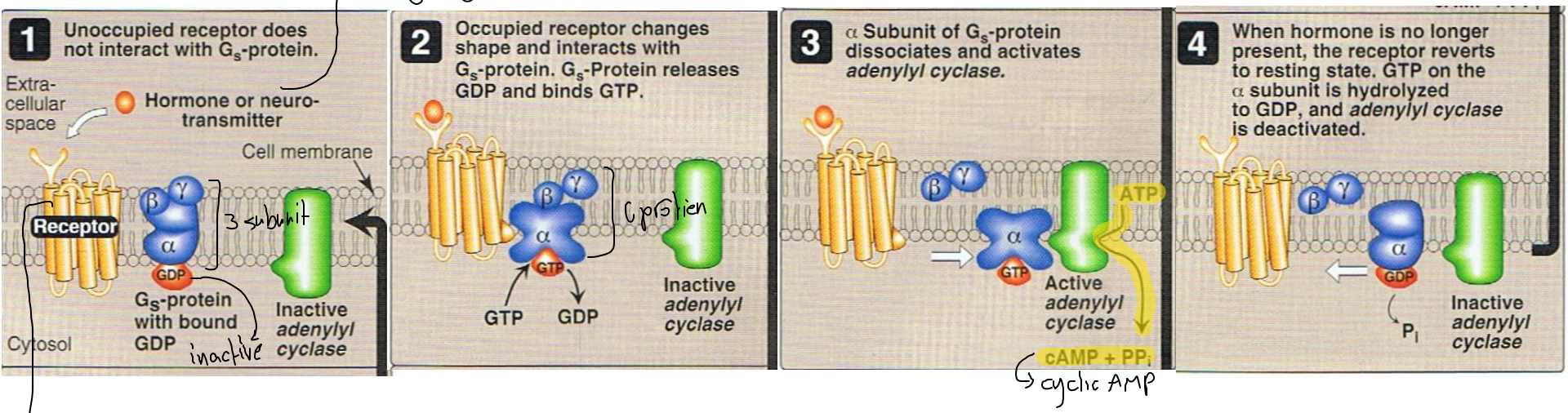
Communication between cells



→ by gap junction

Regulation of metabolism
Adenylyl cyclase

→ glucagon, insulin (adrenaline, Nor-adrenaline)



1. GTP-dependent regulatory proteins (Gs and Gi-proteins)
2. Protein kinases: phosphorylates different proteins and enzymes
3. Dephosphorylation of proteins: Phosphatases reverse the effect of kinases.

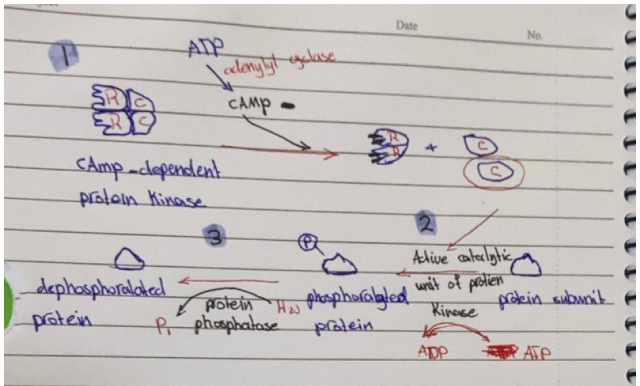
→ G protein coupled receptor (seven α helix receptor)

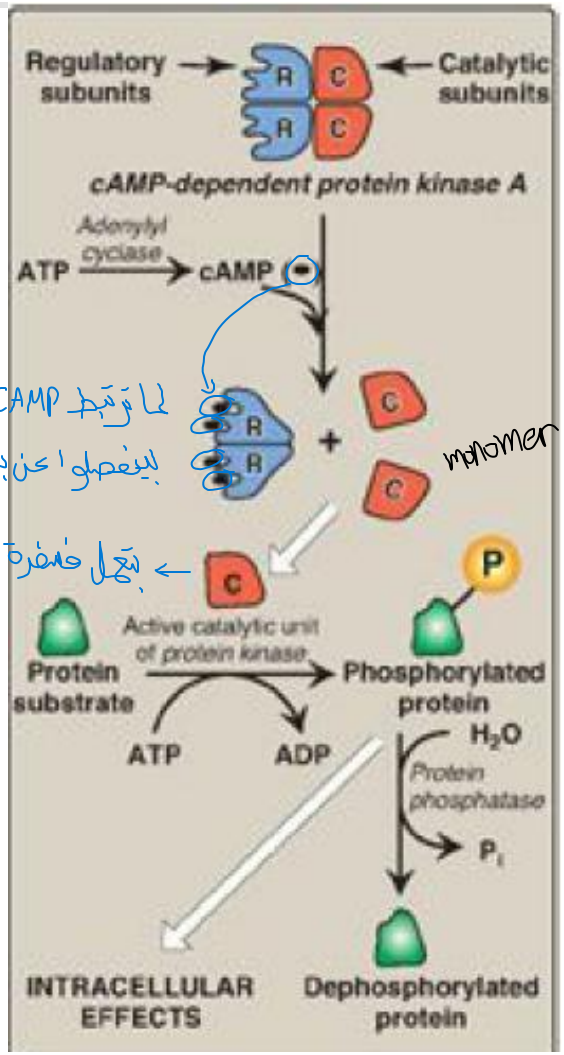
stimulatory inhibitory → in glucagon stimulatory

glycogen synthase ⟶ تصنيع الغلايكوجين

glycogen phosphorolation ⟶ فسفرة الغلايكوجين

phosphotase activation by insulin





Transport of glucose to cells

→ absorption by activation transporter in small intestine.

- Glucose cannot diffuse directly into cells, but enters by one of two transport mechanisms:
- ① Na-independent, ② facilitated diffusion transport system

طرق دخول الغلوكوز إلى الخلايا

fructose doesn't need to ATP
glucose and galactose need ATP

  - In facilitated diffusion, glucose movement follows a concentration gradient
  - Tissue specificity of GLUT gene expression: → by facilaited diffusion

↳ 14 → glucose transporter

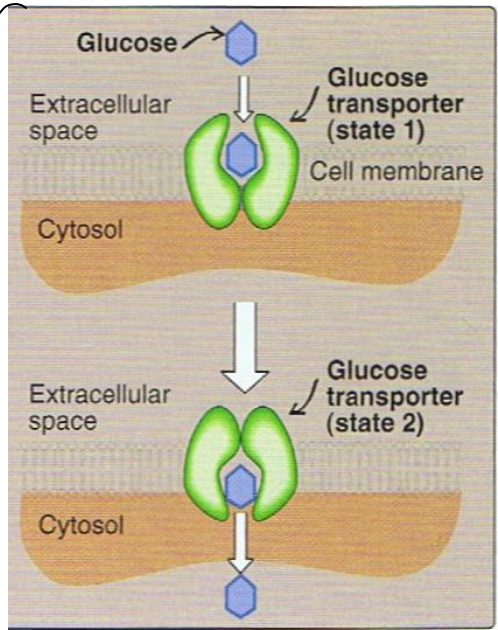
1. GLUT-3 is the primary glucose transporter in neurons
2. GLUT-1 is abundant in erythrocytes and brain, but is low in adult muscle
3. GLUT-4 (in adipose tissue and skeletal muscle). Their number is increased by insulin

expression depend on insulin ←

إذا في انسولين عطلت رح تاخذ جلوكوز إذا فاضي فش جلوكوز

4. GLUT-2 (in the liver, kidney, and β cells of the pancreas) can either transport glucose into these cells or from it depending on blood glucose levels

↳ two pathway for transport



Transport of glucose to cells

في الامتحان

- GLUT-5 is the primary transporter for fructose in the small intestine and the testes → sperm depend on fructose
- GLUT-7 (in the liver and other gluconeogenic tissues) mediates glucose flux across the endoplasmic reticular membrane.

موجود بالأغشاء التي يتم تصنيع الغلوكوز فيها

glucose-6-phosphate → glucose in endoplasmic reticulum and then trans by GLUT-7

Na-monosaccharide cotransporter system: is an energy-requiring process that transports glucose against a conc. gradient

→ active process (need ATP)

- This system is a carrier-mediated process in which the movement of glucose is coupled to the conc. gradient of Na, which is trasported into the cell at the same time.
- It occurs in the epithelial cells of the intestine, renal tubules, and Choroid plexus.
- This system is mediated by a family of fourteen glucose transporters in cell membranes (GLUT-1 to GLUT-14)
- They exist in the membrane in two conformational states. Extracellular glucose binds to the transporter, which then alters its conformation, transporting glucose across the cell membrane.

تتحمل ←

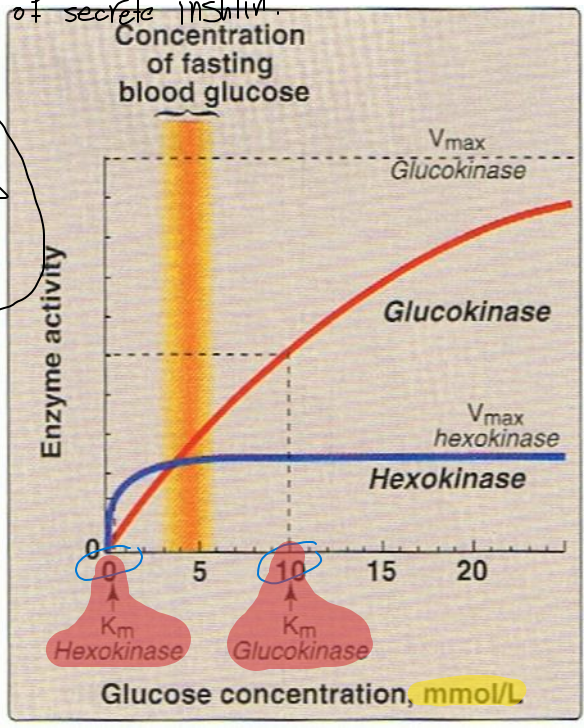
→ change in shape

Glycolysis

- Glycolysis occurs in the cytosol of all tissues and cells
- Defined as oxidation of glucose to pyruvic acid (in the presence of O_2, Aerobic) and to lactic acid (in the absence of O_2, anaerobic)
- The catabolism of 1 mol of glucose (6 C) produces 2 moles of pyruvate or lactate (3 C)
- Lactate is produced only in:
  - RBC: as there is no mitochondria → liver (converted to pirtuvic)
  - Exercising muscles: lack of O_2

Phosphorylation of glucose → the first step in glycolysis

- Phosphorylated sugar molecules do not readily penetrate cell membranes (no carriers, too polar to cross)
  اختراق بسهولة
- Hexokinase has broad substrate specificity and it is inhibited by the reaction product, glucose 6-phosphate
  → in all cell → خلية فيها بيلزم يشتغل
- It has a low Km (high affinity) for glucose. And low Vmax
  عنده قوة ارتباط عالية حتى لو كان التركيز منخفض
- Glucokinase (similar broad specificity): In liver parenchymal cells and islet cells of the pancreas
  → high Km, low affinity, high Vmax
  irreversible differ in Km and place
  → in pancreas
  يشتغل لما يدخل على الجسم كميات كبيرة من الكربوهيدرات يتحول لـ glycogen
- In β cells, glucokinase functions as the glucose sensor, determining the threshold for insulin secretion. In the liver, the enzyme facilitates glucose phosphorylation during hyperglycemia.
  → glucokinase works to convert from glucose to 6p-glucose in B cell → ↑ energy inside cell → calcium channel flux → activation of secrete insulin.
- Glucokinase functions only when the intracellular concentration of glucose in the hepatocyte is elevated, such as during the brief period following consumption of a carbohydrate- rich meal
  استهلاك



Steps of glycolysis

- **Energy investing phase:** استثمار — استثمار الطاقة وليس استهلاك الطاقة
  - **Step 1:** glucose is phosphorylated to glucose-6-phosphate. The reaction is irreversible and is catalyzed by either glucokinase (GK) in liver cells and hexokinase (HK) in other tissues. → regulated
  - **Step 2:** glucose-6-phosphate is isomerized to fructose-6-phosphate by isomerase enzyme
  - **Step 3:** fructose-6-phosphate is phosphorylated to F-1,6-diphosphate. The reaction is catalyzed by phosphofructo-kinase (PFK).
  - **Step 4:** F-1,6-bP is split by aldolase into two trioses (1 Glyceraldehyde-3-P and 2 dehydroxyacetone phosphate)

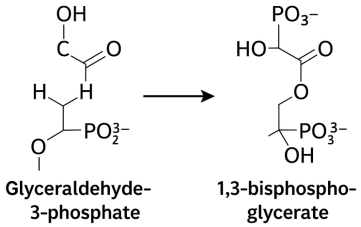
enzyme is irreversible and regulated are:
① glucokinase
② phosphofructokinase
③ pyruvatekinase

the most important step (slow pathway)

F-1,6 diphosphate يتقسم بالنص

Steps of glycolysis

step 6



- Step 5: DHAP is isomerized to G-3-P which is catalyzed by isomerase

II- Energy generating phase: step number six

- G-3-P is oxidized phosphorylated forming 1,3-biphosphoglycerate (1,3-BPG) and NADH which is catalyzed by glyceraldehyde 3-P dehydrogenase. NADH produces 2.5 ATP in ETC.

Kinase → phosphorylate

Oxidase → dehydrogen peroxide. (H_2O_2)

في هذه الخطوة NADH تكوّن

→ oxidation, reduction

- Step7: 1,3-BPG gives its high energy phosphate to ADP to form ATP converting to 3-PG. This is catalyzed by phosphoglycerate kinase. → energy produce from break linkage between molecule and phosphate + ADP → ATP
- Step 8: 3-PG is converted to 2-phosphoglycerate by mutase

→ 3- phosphoglycerate

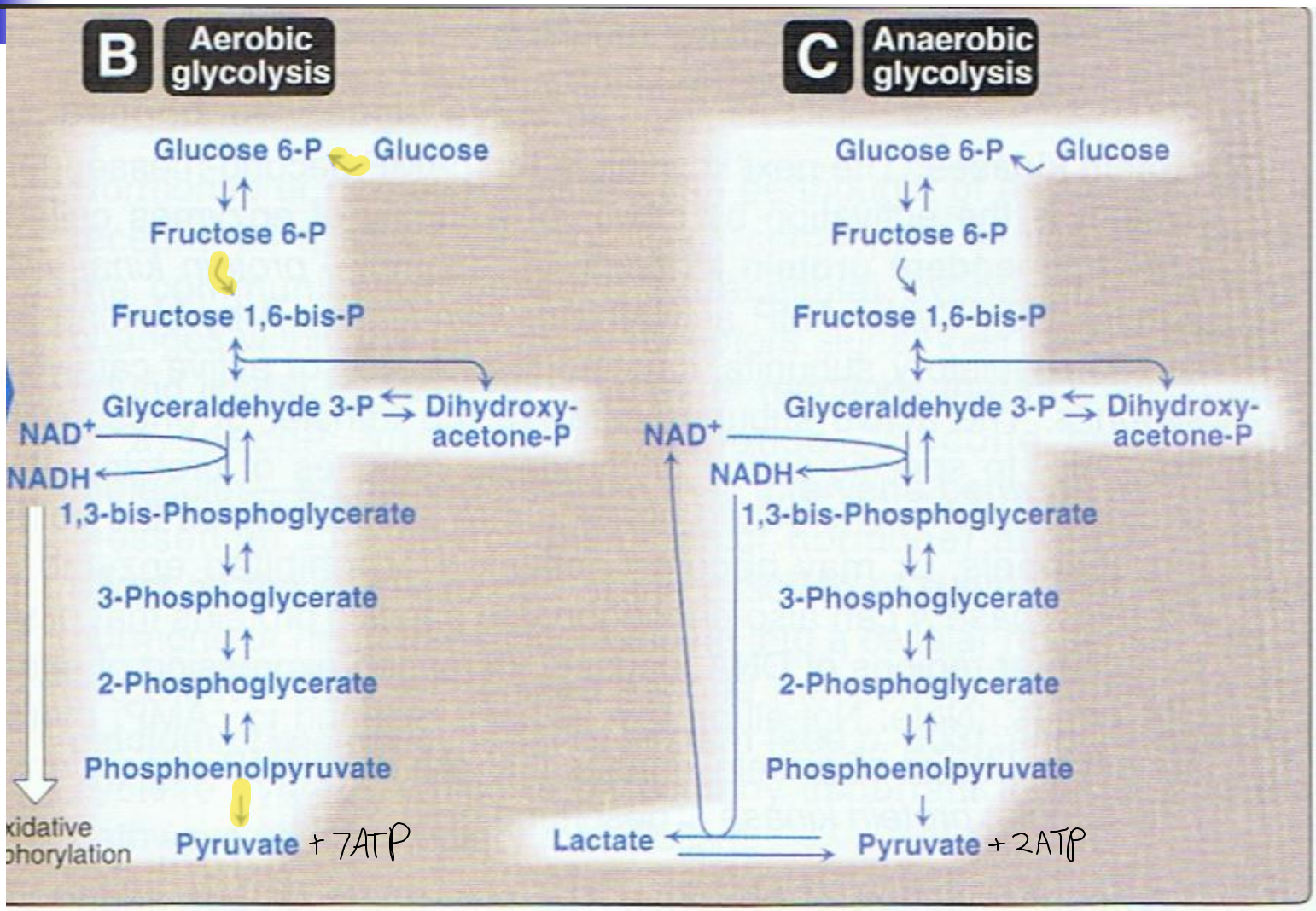
Steps of glycolysis

- Step 9: Enolase enzyme dehydrates 2-PG forming 2-phosphoenol pyruvate (PEP)
- Step 10: PEP is dephosphorylated giving its P to ADP to form ATP and converted to pyruvate. Rxn is irreversible and catalyzed by pyruvate kinase.
- Step 11: in RBC's and under anaerobic conditions NADH formed in step 6 is oxidized to give hydrogen and pyruvate which converts into lactate by lactate dehydrogenase

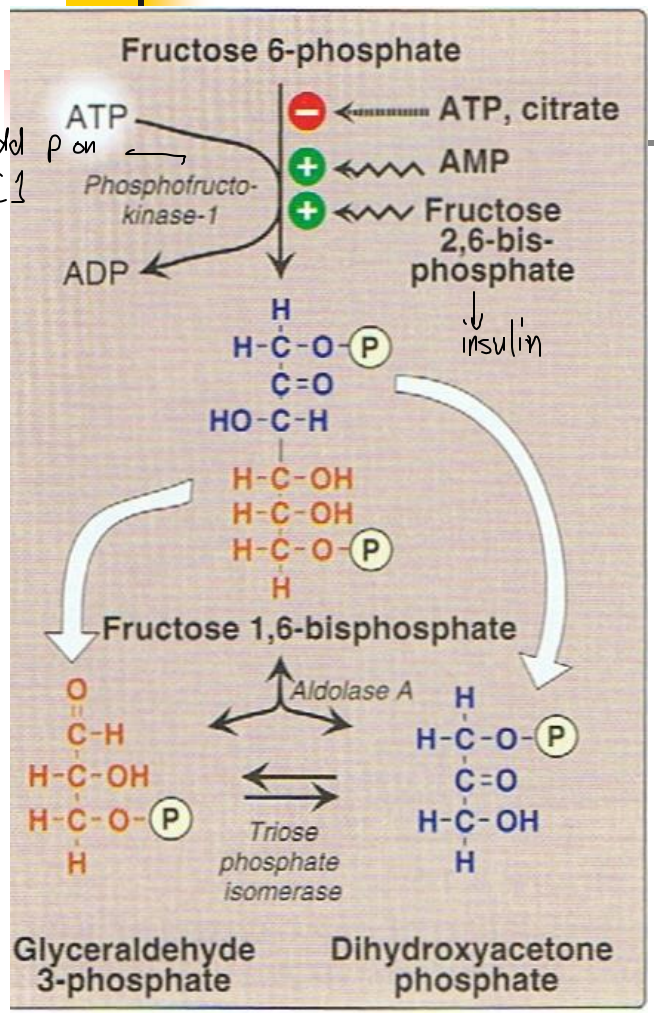
in aerobic glycolysis produce 7 ATP

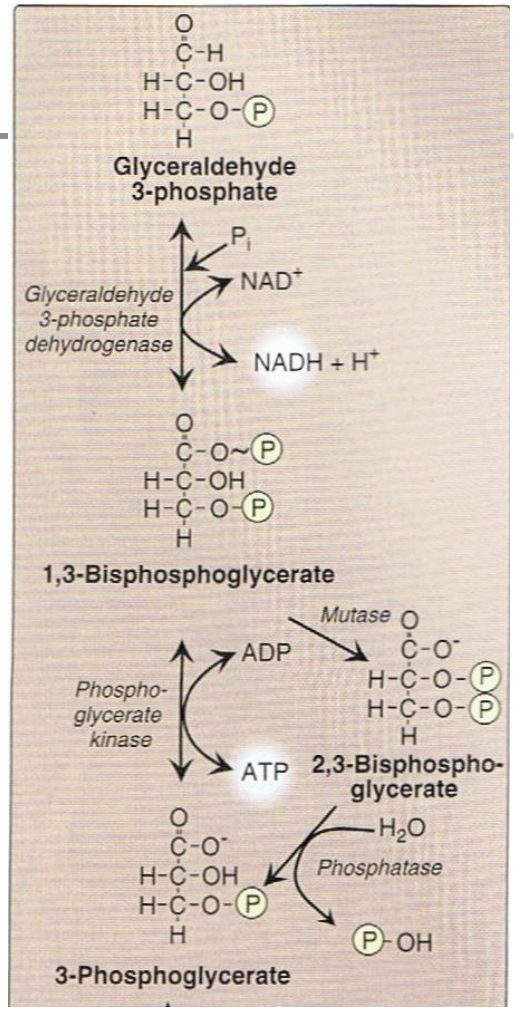
in anaerobic glycolysis produce 2 ATP

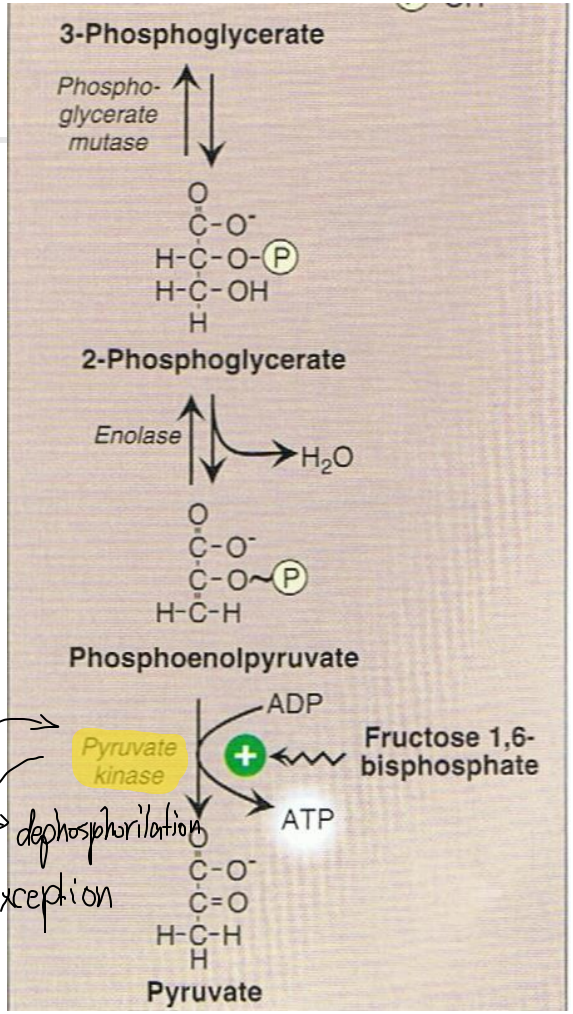
Schematic representation



↑ NADH → not need ATP → ↑ citrate → inhibition







Energy gain in aerobic glcolysis

Step 1	Glucokinase (GK)	- 1 ATP
Step 3	Phosphofructokinase (PFK)	- 1 ATP
Step 7	Phosphoglycerate kinase	+ 2 ATP
Step 10	Pyruvate kinase (PK)	+ 2 ATP
Step 6	2 NADH	+ 5 ATP
Net gain		+ 7 ATP

full oxidation for glucose → 32 ATP

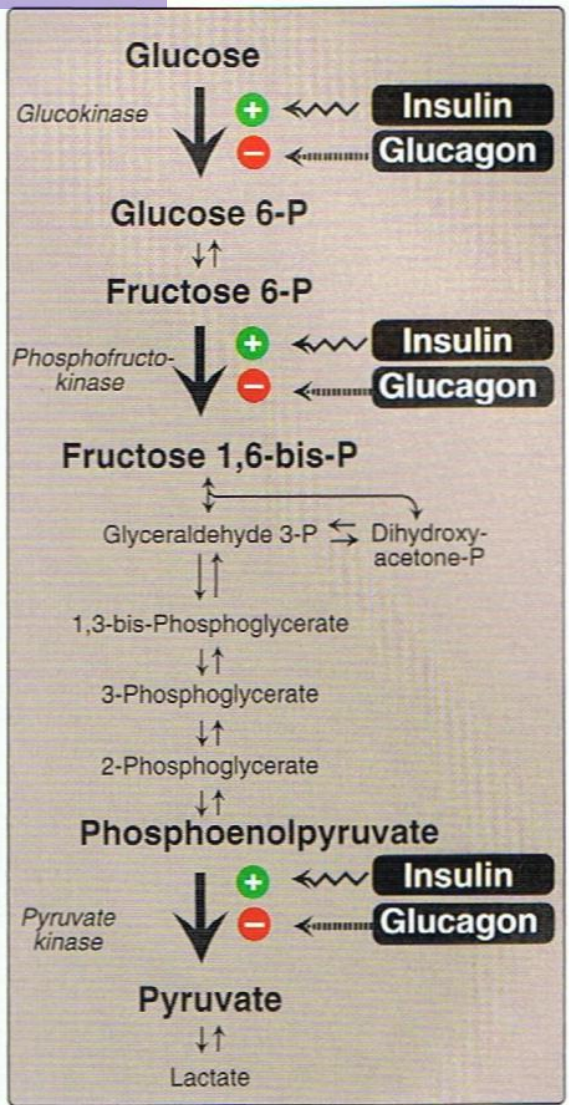
Anaerobic glycolysis → No NADH

Step 1	Glucokinase (GK)	- 1 ATP
Step 3	Phosphofructokinase (PFK)	- 1 ATP
Step 7	Phosphoglycerate kinase	+ 2 ATP
Step 10	Pyruvate kinase (PK)	+ 2 ATP
Net gain		+ 2 ATP

Hormonal regulation of Glycolysis

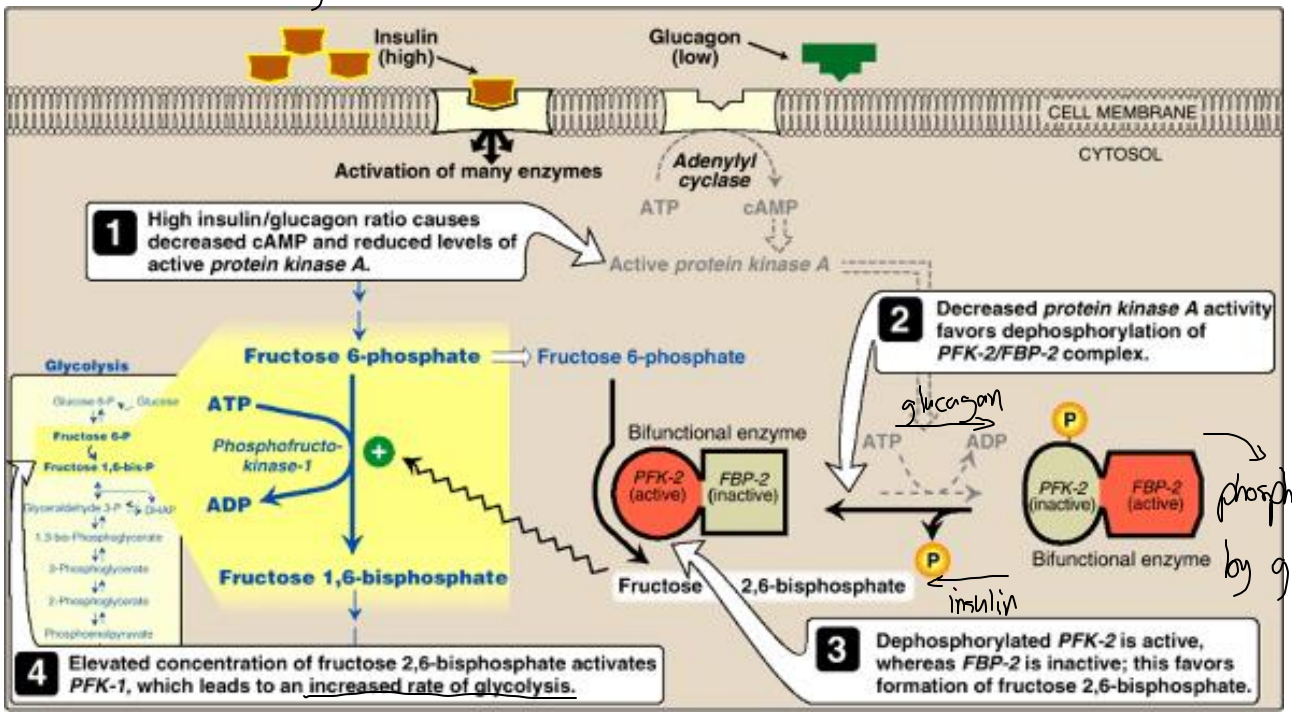
three hormone responsible for regulation glycolysis.

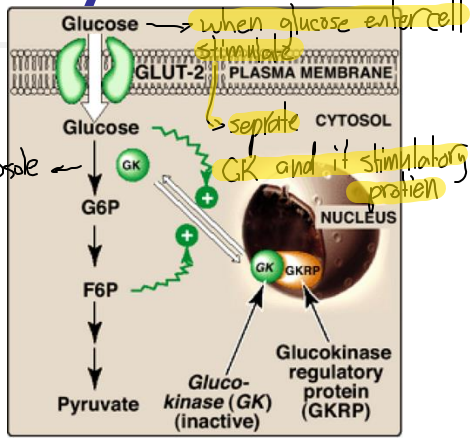
- GK (or HK), PFK and PK are the key enzymes of glycolysis. ← determination pathway
- PFK is the most important and considered the rate limiting enzyme.
- Hormones regulate glycolysis according to blood glucose level: ← بعدو جبة غنية بالكربوهيدرات
  - After CHO feeding: blood glucose increases, this stimulates insulin secretion, insulin stimulates glycolysis by increasing the synthesis of the three key enzymes: GK, PFK and PK.
  - During fasting: blood glucose level decreases, which inhibits insulin secretion and stimulates glucagon, adrenaline and corticosteroid which inhibit the synthesis of and activity of GK, PFK and PK. ← ما في إنسولين

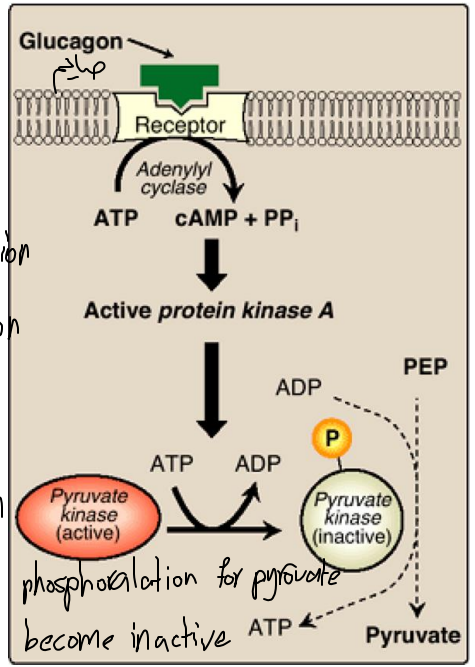


Hormonal regulation of Glycolysis

regulation the substance that affect to produce and activity for enzyme







phosphorylation by glucagon

↳ ATP ↑, sperate ↑ during hunger → glucagon hormone inhibition glycolysis in cell without brain and RBCs

⇒ glucagon increase phosphatase activity.

In-vitro inhibition of glycolysis

toxic

- Flouride inhibits enolase enzyme (step 8) → from 2-phosphoglycerate to 2-phosphophenol pyruvate

two importance for flouride ?!

  - It is used in toothpastes as it inhibits glycolysis in mouth bacterial flora.
  - It is also used as anticoagulant for blood samples to estimate its glucose content.

تقدير

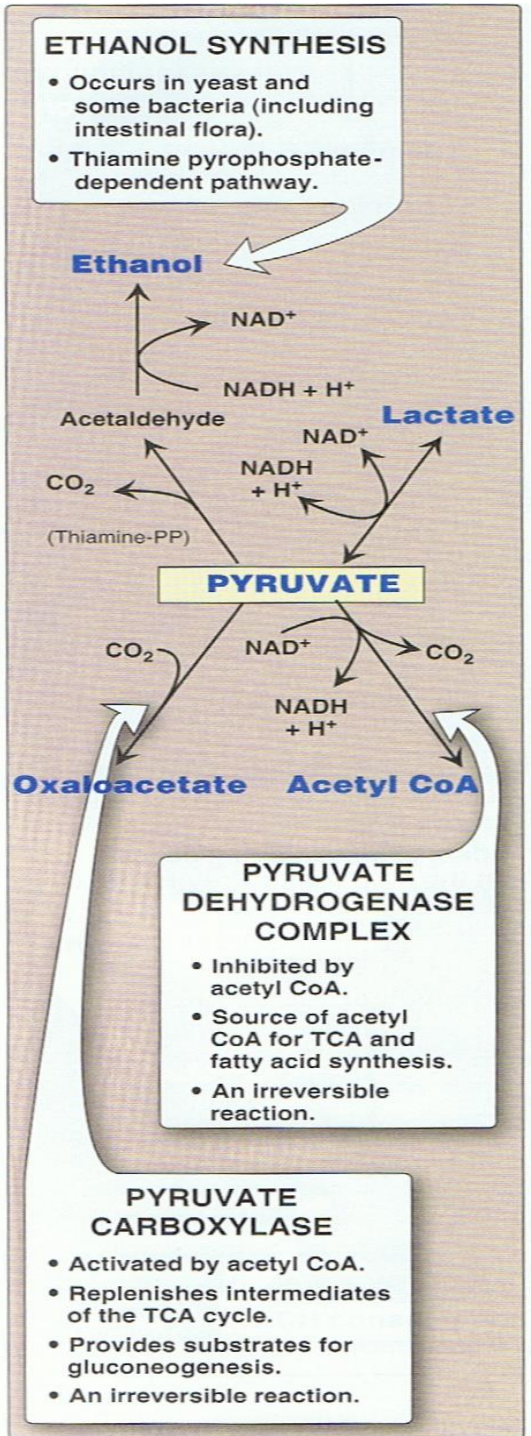
Fate of pyruvic acid

مصير البيروفيت

- Formation of acetyl CoA
- Formation of oxaloacetic acid
- Formation of lactate → in RBCs
- Formation of ethanol (in yeast and some M.O)

خميرة

→ مواد عضوية

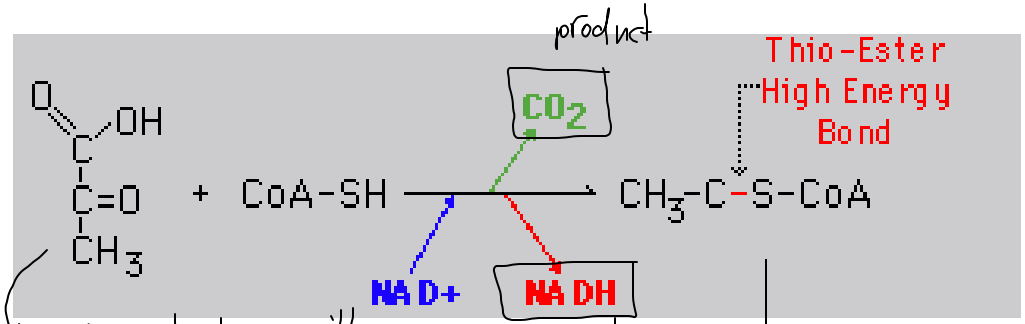


Aerobic phase of glucose oxidation

converted

glycolysis occur in cytosole → pyruvic acid enter mitochondria → from pyruvic to ACO

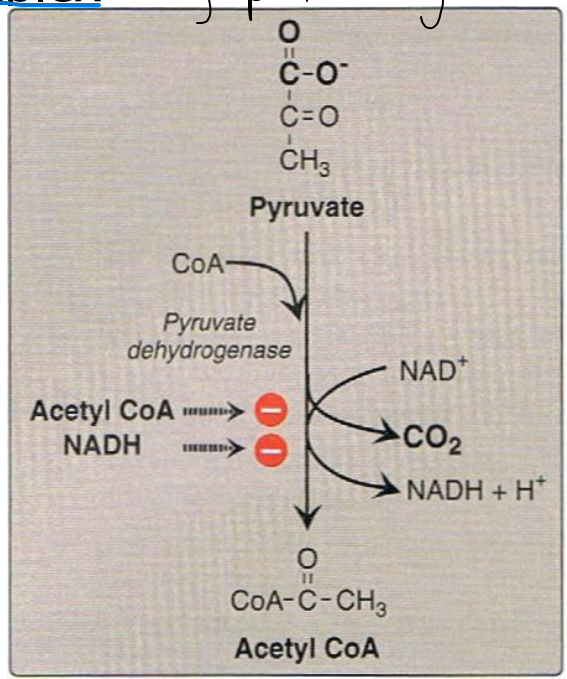
- Pyruvic acid formed by glycolysis enters the mitochondria where:
  - it will be metabolized to acetyl-CoA by oxidative decarboxylation
    remove COOH
  - then Acetyl-CoA is oxidized in Kreb's cycle



2 CO_2 + 10 ATP

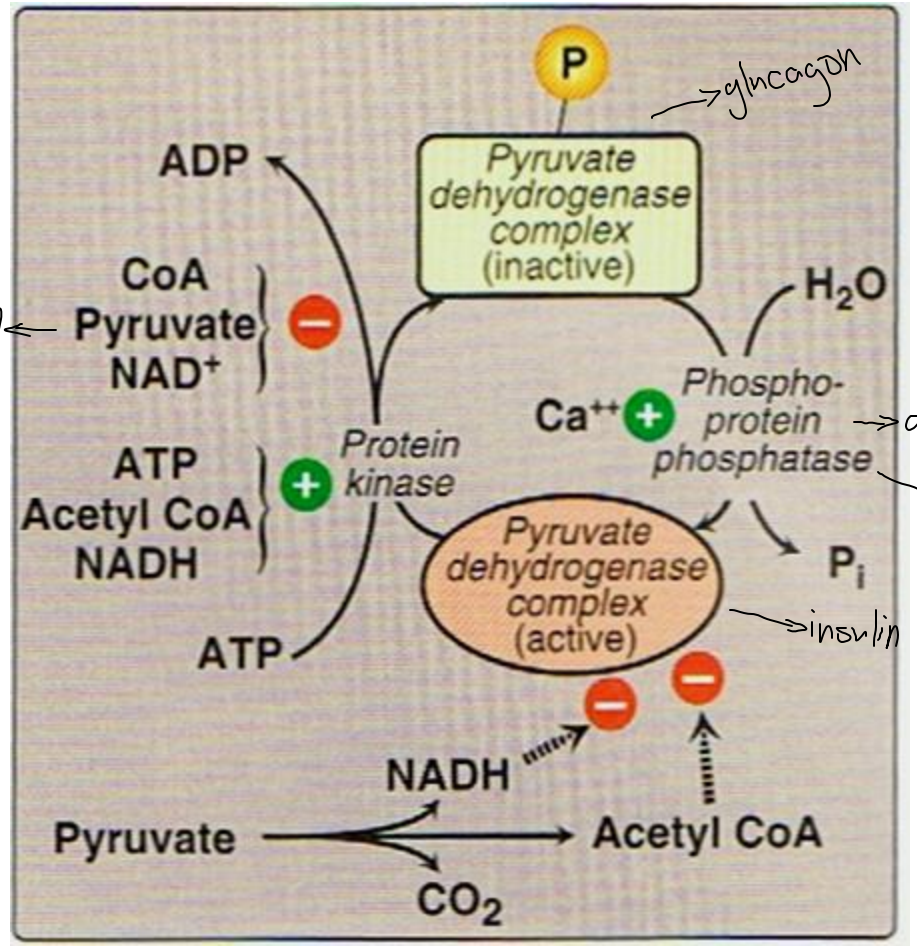
A-Oxidative decarboxylation of pyruvic acid

- Occurs in mitochondria
- Irreversible → in one direction → while lactate reversible (in two direction)
- Needs pyruvate dehydrogenase (PDH) complex → group from enzyme
- Requires 5 coenzymes
  - Thiamine pyrophosphate
  - 2-lipoic acid
  - CoA-SH
  - FAD
  - NAD^+



Regulation of pyruvate dehydrogenase

↳ by phosphoralated or dephosphoralated



calcium produce from excercise increase activity for this enzyme

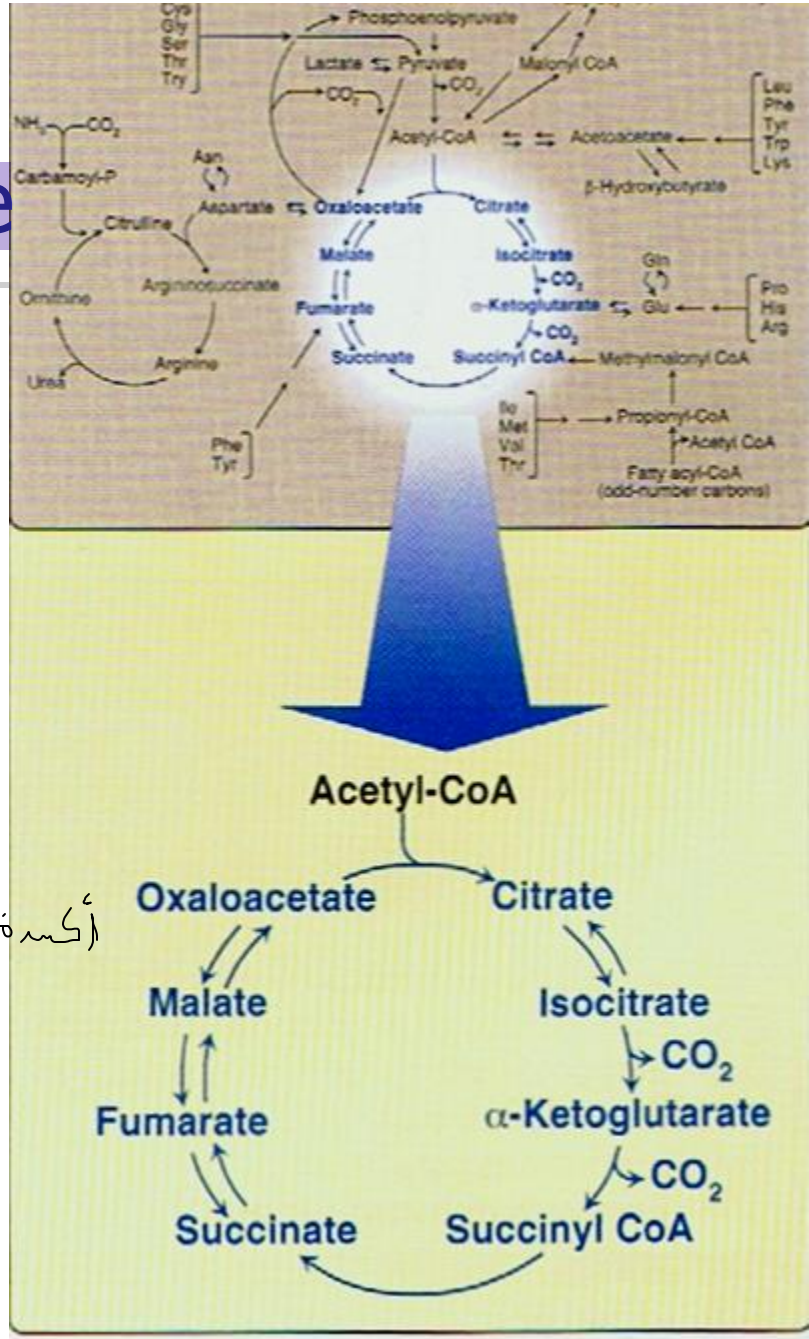
Tricarboxylic acid cycle

L> TCA

- Occurs in the mitochondria of each cell
- Does not occur in RBCs (no mitochondria)
- Considered the final common pathway for the complete oxidation of acetyl-CoA obtained from partial oxidation of CHO, lipids and proteins.

ناتج رئيسي ← أكسدة جزئية

final product CO_2 and H_2O



Steps of TCA → 2 A-CO A

(1 cycle) لكل وحدة بتعطي

- Step 1: condensation of acetyl-CoA and oxaloacetic acid to form citric acid. Catalyzed by citrate synthase.

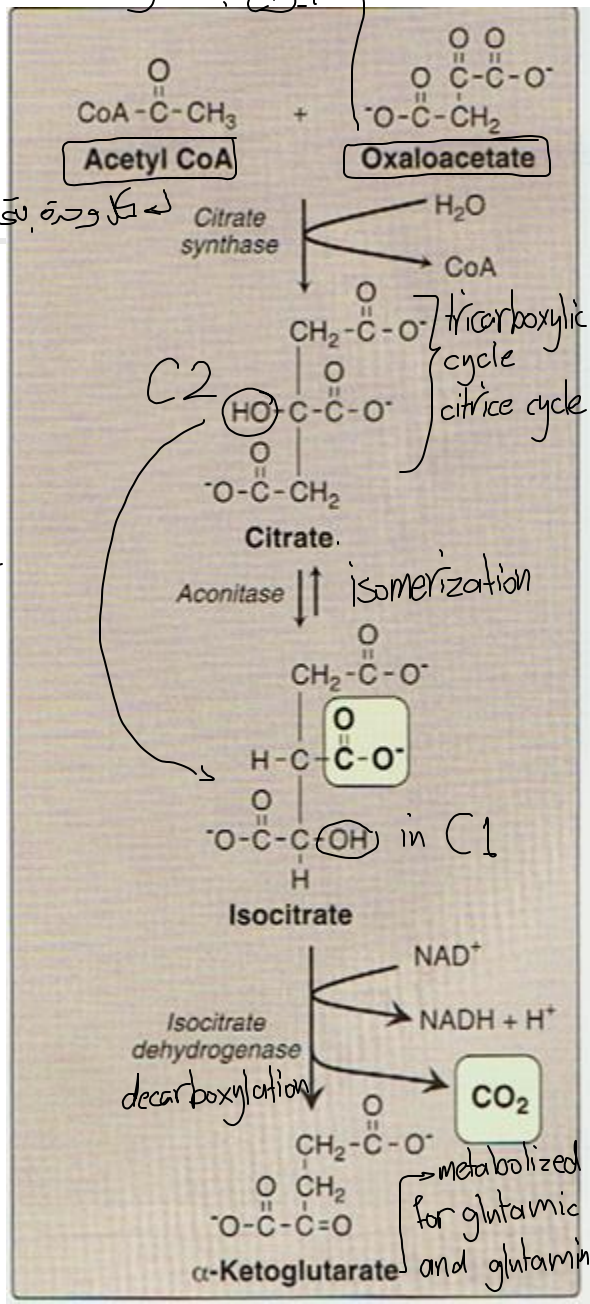
تكثيف

- Step 2: Citric acid is converted by isocitrate by aconitase.

- Step 3: Isocitrate is oxidized to α-ketoglutarate by isocitrate dehydrogenase. NADH is produced and CO2 is released.

decarboxylation

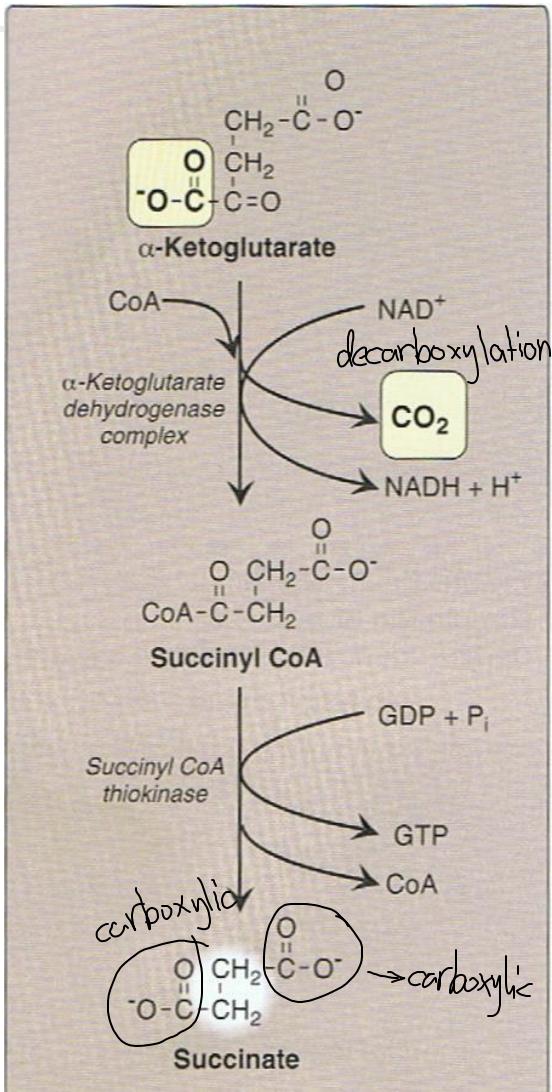
glutamine and glutamic can converted into energy



Steps of TCA

- Step 4: α-ketoglutarate is converted to succinyl CoA. CO_2 is released and NADH is produced. The reaction is catalyzed by α-ketoglutarate dehydrogenase complex. It also requires 5 coenzymes (thiamine pyrophosphate, lipoic acids, CoA-SH, FAD and NAD)

- Step 5: the high-energy, thioester bond of succinyl-CoA is cleaved providing energy for the synthesis of GTP fro GDP and Pi. Succinate is formed and the reaction is catalyzed succinate thiokinase.



Steps of TCA

single bond to double bond

- Step 6: succinate is oxidized to fumarate by succinate dehydrogenase. FAD is reduced to FADH2.

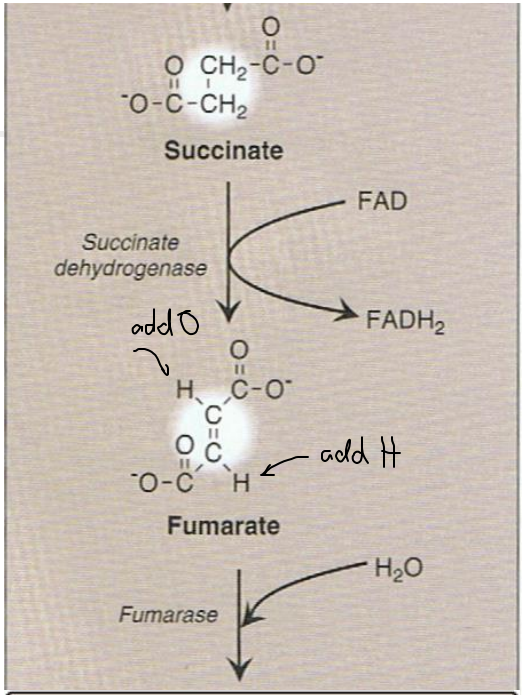
add H_2O

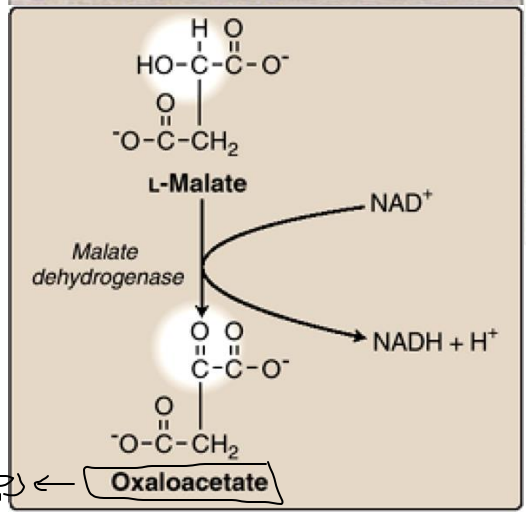
- Step 7: fumarate is hydrated to form malate by fumarase.

- Malate is oxidized to oxaloacetate by malate dehydrogenase. NAD is reduced to NADH.

- Oxaloacetate will reinitiate the cycle again.

produce 3NADH , 1 $FADH_2$, 1 GTP ,





رجعنا الأول ←

Energy gain in Kreb's cycle

Isocitrate DH	1 NADH	2.5 ATP
α-ketoglutarate	1 NADH	2.5 ATP
Succinate thiokinase	1 GTP	1 ATP
Succinate DH	1 FADH2	1.5 ATP
Malate DH	1 NADH	2.5 ATP
Net gain		**10** ATP

The overall energy gain of glucose oxidation one molecule

- Glycolysis --------- 7 ATP + 2 pyruvate
- 2 pyruvate -------- 2 acetyl-coA + 2 NADH ----- 5 ATP
- 2 acetyl CoA --------- 20 ATP
- The net ATP produced by the oxidation of 1 mol of glucose = 32 ATP

Defects in Glycolysis

- **Pyruvate dehydrogenase deficiency:** leads to congenital lactic acidosis.
  - → after glycolysis
  - → accumulate lactic acid in blood and tissue cause acidosis
- This enzyme deficiency results in an inability to convert pyruvate to acetyl CoA, causing pyruvate to be shunted to lactic acid via lactate dehydrogenase.
- This causes particular problems for the brain, which relies on the TCA cycle for most of its energy, and is particularly sensitive to acidosis.
  - يعتمد
  - بشكل خاص

this process comple with lipolysis

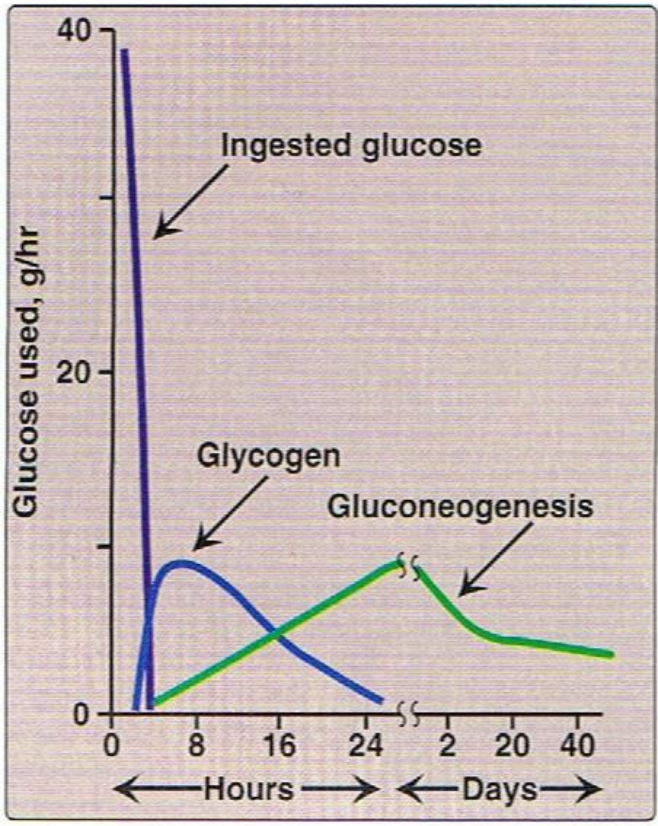
Gluconeogenesis → تخزين الغلوكوز

When and where does it occur

في بعض الأحيان — الستراف

→ in cytosole of liver and Kidney
oxaloacitate in mitochondria

- During prolonged fast and depletion of hepatic glycogen
- During overnight fast, liver is responsible for the majority of gluconeogenesis (90%) and the rest in the kidney (10%) → CIVT 2
- During prolonged fast, kidney produces about 40% of glucose production.
  60% in liver
- Glucose is formed from precursors as lactate, pyruvate, glycerol and ketoacids
  pyrovate → glucose
  oxaloacitate



Substrates for gluconeogenesis

- Those include all the intermediates of glycolysis and the citric acid cycle.

1. Glycerol: released during the hydrolysis of triglycerols in adipose tissue and delivered to the liver. Glycerol is phosphorylated by glycerol kinase to glycerol 3-phosphate, which is oxidized by glycerol 3-phosphate dehydrogenase to dihydroxyacetone phosphate which is an intermediate of glycolysis.

2. Lactate: released by exercising muscles and RBC's. This is transferred to the liver and reconverted to glucose.

3. Amino acids: hydrolysis of tissue proteins are the major source of glucose. α-ketoacids (oxaloacetate and α-ketoglutarate are derived from the metabolism of glucogenic aa which can enter the TCA

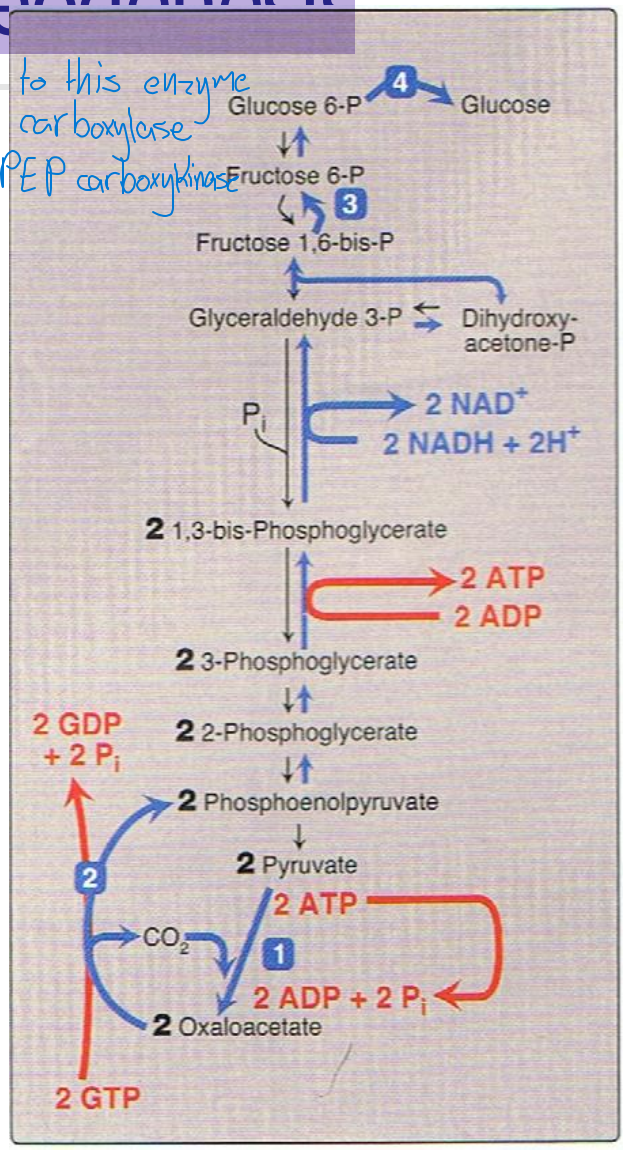
Reactions unique to gluconeogenesis

- Seven of the glycolysis reactions are reversible and are used for gluconeogensis while three of them are irreversible (Pyruvate kinase, phosphofructokinase and hexokinase)

alternative to this enzyme is pyruvate carboxylase and PEP carboxykinase

or glucokinase

1. Pyruvate carboxylase: Pyruvate is converted to phosphoenolpyruvate (PEP) by pyruvate carboxylase and PEP caboxykinase
   - Biotin: covalently bound to the N of lysine in the pyruvate carboxylase, requires CO_2 and ATP for the convertion of pyruvate to oxaloacetate. It occurs in mitochondria of liver and kidney. Muscles contain also pyruvate carboxylase for the use of OAA in TCA.
   - Allosteric regulation: it is allosterically activated by Acetyl coA.



Reactions unique to gluconeogenesis

2. Transport of oxaloacetate to the cytosol: oxaloacetate can't cross the mitochondrial membrane so it is reduced to malate by malate dehydrogenase that can cross. In cytosol malate is reoxidized to oxaloacetate by cytosolic malate dehydrogenase.

3. Oxaloacetate is decarboxylated and phosphorylated in the cytosol by PEP carboxykinase which utilize 1 GTP. PEP will continue in the reverse of glycolysis until reach fructose 1,6- biphosphate.

4. Dephosphorylation of frucose 1,6- biphosphate by frucose 1,6-biphosphatase to produce fructose 6-phosphate will bypass the irreversible PFK reaction. فش طاقة

The enzyme is inhibited by high levels of AMP and fructose 2,6-biphosphate, while high level of ATP and low AMP stimulate gluconeogenesis → inhibition phosphotase enzyme and activation to phosphofructokinase

Reactions unique to gluconeogenesis

5. Dephosphorylation of glucose 6-phosphate: occurs by glucose 6-phosphatase. This occurs only in liver and kidney. Two enzymes are required (glucose 6-phosphate translocase to transfer glucose 6-phosphate to ER and glucose 6-phosphatase) GLUT-7

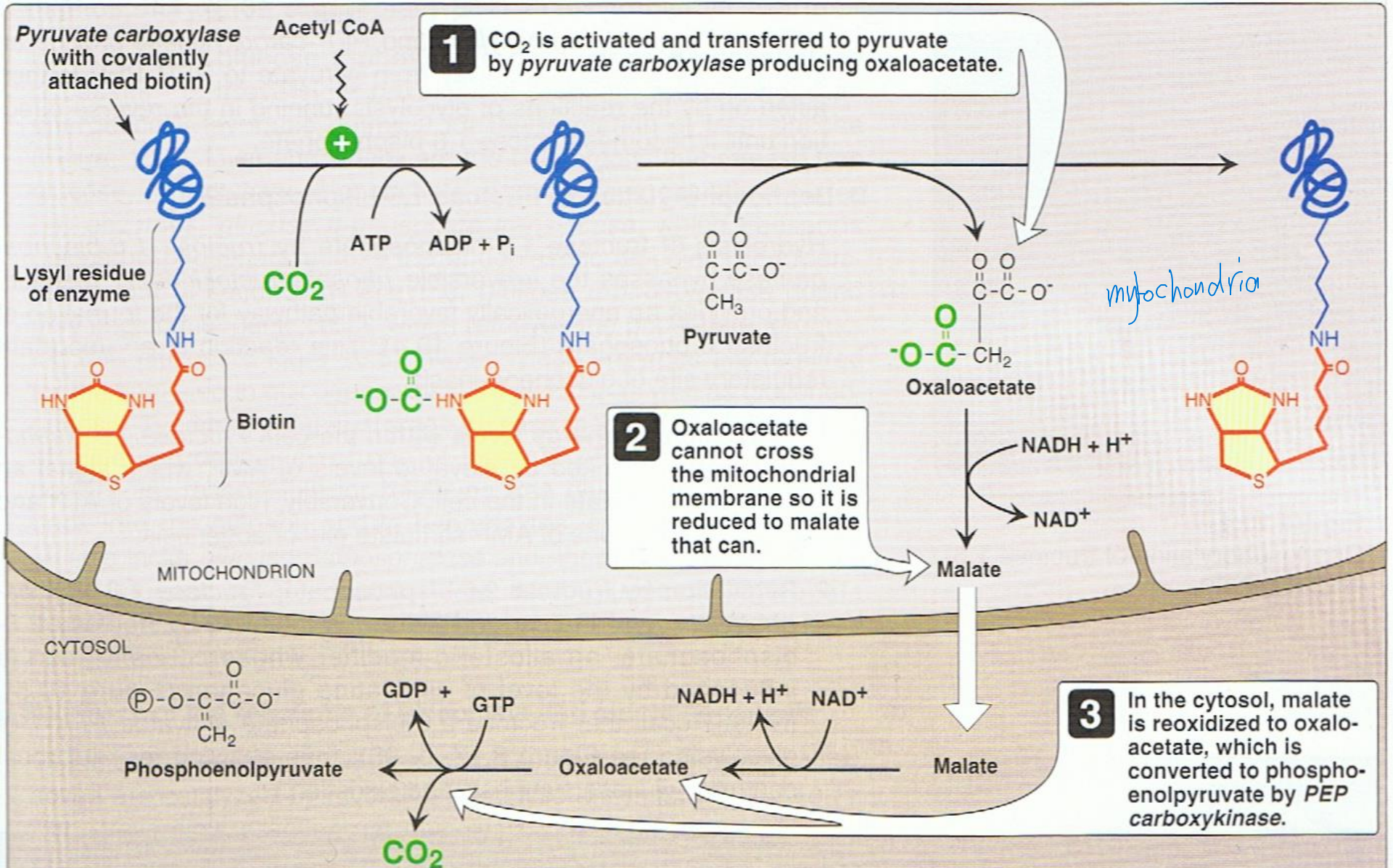
GLUT2 from cytosole to blood ← from ER to cytosole

Type 1a glycogen storage disease results from inherited diffeciency of one of them which has the following symptoms:

- Hypoglycemia
- Hepatomegaly and liver problems
- Lactic acidosis
- Growth failure

any deficiency in any enzyme causes accumilate sugar phosphate lead to hepatic damage

Pyruvate carboxylase



Regulation of gluconeogenesis

1. Glucagon: stimulates gluconeogenesis in three mechanisms:
    1. **Change in allosteric effectors:** it lowers level of fructose 2,6-biphosphate leading to activation of fructose 1,6-biphosphatase and inhibition of phosphofructokinase.
    2. **Covalent modification of enzyme activity:** it elevate cAMP leading to activation of cAMP-dependent protein kinase activity which will phosphorylate pyruvate kinase to its inactive form.
    3. **Induction of enzyme synthesis:** it increases the transcription of PEP carboxykinase gene.
2. Substrate availability: like glucogenic amino acids
3. Allosteric activation of pyruvate carboxylase by acetyl coA.
4. Allosteric inhibition of fructose 1,6-bisphosphatase by AMP

Note: ATP and NADH are produced in large quantities during fasts from fatty acid oxidation is required for gluconeogenesis.