Biochemistry

Title = Carbohydrate metabolism Glycolysis
Lec no = 10
Done By = Baraa Safi

وقل رب زدني علما

Carbohydrate metabolism
Glycolysis

Lecture number 10
Lecture 2/5 in CHO metabolism

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CHO metabolism	*1. Glycolysis* *a. First phase* *b. Second phase* *2.Pentosephosphate pathway* *3.Metabolism of non-glucose sugars* *a.metabolism of fructose.* *b.metabolism of galactose* *c.metabolism of glucuronic acid* *3. Glycogen metabolism* *a. Glycogen synthesis* *b. Glycogen breakdown*

Important definitions

- **Metabolism:** series of biochemical reactions that occur for biomolecules in living organisms
    - Classified as anabolism or catabolism

- **Anabolism:** synthesis of macromolecules from simple ones (usually *endergonic*)

- **Catabolism:** breakdown of macromolecules into simplest forms (usually *exergonic*)
    - 3 or 4 stages
        - **Stage 1:** hydrolysis of macromolecules in GI tract to nonomeric building blocks (digestion/ absorption)
        - **Stage 2:** building blocks degraded to **acetyl coA**
        - **Stage 3:** Krebs cycle oxidises **acetyl coA** to CO2 with release of energy stores
        - **Stage 4:** oxidative phosphorylation in which energy from NADH+H, FADH released via ETC

* رح نتكلم اليوم عن تكسير الكربوهيدرات/البلوكوز (Glycolysis)

رح نوخذ هاد بعدين مش بالسنة الأولى

* (Krebs cycle) مش محددة بس بـ (Glycolysis) ⇐ بتعمل مع أكثر من نوع تفاعل

1

- بعد الهضم والإمتصاص فضل عندنا بشكل أساسي هو الجلوكوز (Monosaccharides)

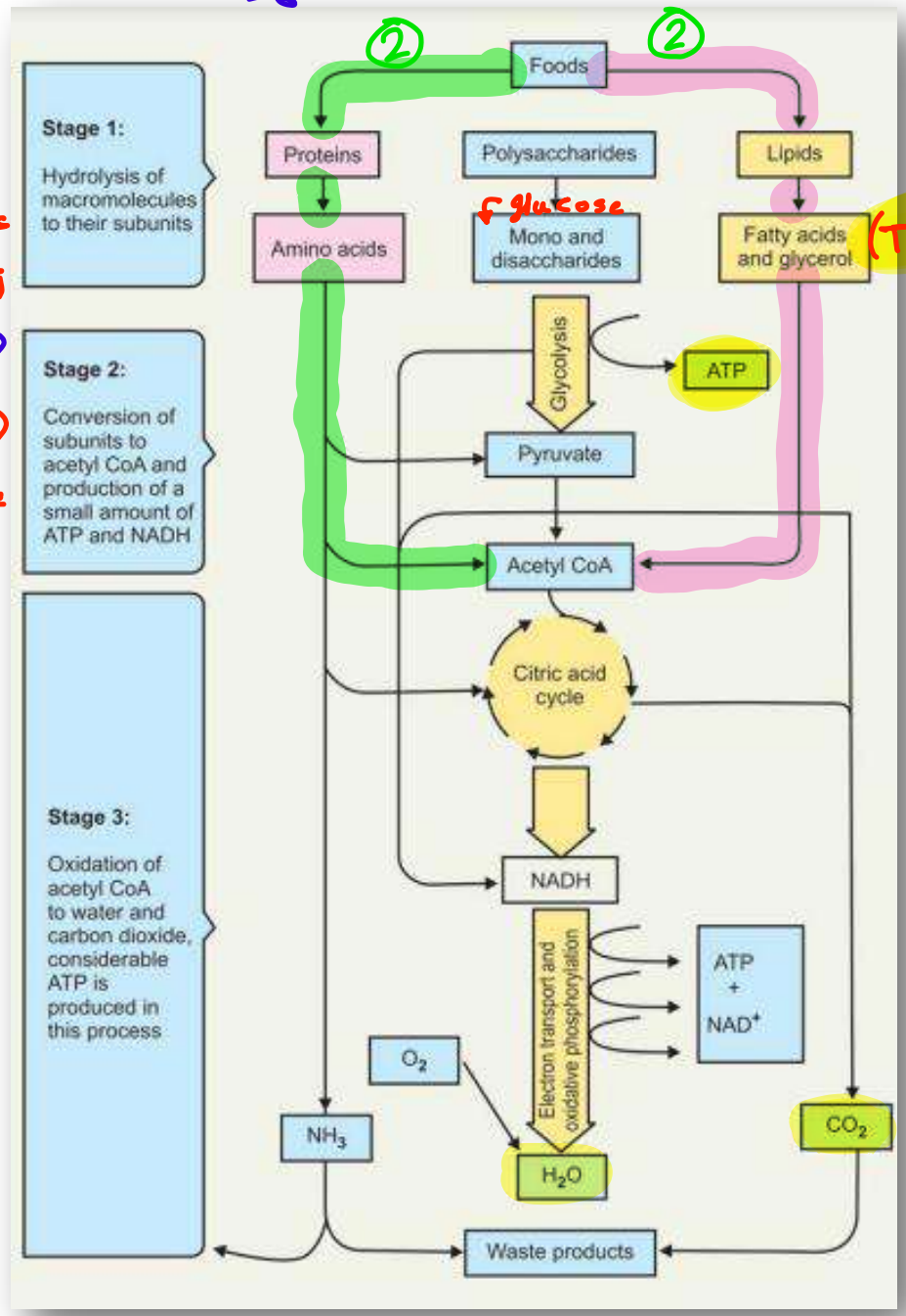
عن طريقة (Glycolysis) بنكسرها لـ (Pyruvate)

أو (Lactate) / عن طريق (Pyruvate)

. (acetylCoA) هم بتحول إلى (reaction)

صمة جوكرز (acetylCoA) و (Pyruvate) يعني بشتغلوا على كلّه .

Jokers



3

* (Krebs cycle) بدخل على (Acetyl CoA)

وبنحرق فبطلع عندك (Carbon monoxide and water)

بطاريات

وبعد هيك بطلع عندك (FADH2, NADH)

FATE OF GLUCOSE

Oxidation (احرقه لو محتاج)		Storage (أو اخزنه في الثلاجات)	Conversion (أو احوله لحاجات)
Major pathway	Minor pathway		
Glycolysis ↓ Pyruvate ↓ Acetyl Co-A ↓ Krebs cycle ↓ R. chain	- pentose phosphate pathway **Or** - Uronic acid pathway	As glycogen by glycogenesis in Liver and Muscles	e.g. - To lipid by lipogenesis or - To ptn

تكسير Glucose عشانه تطلع منها طاقة (ATP)

بتبني منهم احتياجاتك

بتبني أشياء من (Glucose)

إذا مخزنه (Glycogen) بنصيرنو ديهم على هيئة (lipids)

Glucose Metabolism		Galactose Metabolism	Fructose Metabolism
Feeding state واحنا واكلين هيكون في السولين	**Fasting state** واحنا صايمين		
1- Glycolysis Glucose → pyruvate 2- Pyruvate → A. Co-A 3- Krebs cycle NADH+H⁺ & $FADH_2$ 4- Respiratory chain ATP 5- Minor pathways PPP &UAP 6- Glycogenesis 7- Lipogenesis See lipid Metabolism	1- Glycogenolysis 2- Gluconeogenesis	1- Conversion of Glucose to Galactose 2- Conversion of Galactose to Glucose 3- Lactose synthesis 4- Ds	1- Catabolism 2- Conversion of Fructose to Glucose 3- Ds

إذا استنفذت هذا المخزنه بعد (18) ساعة أنت بتبلش تصنع (Glucose)

Glycolysis introduction

- Glycolysis means break down of glucose
- Imp pathway, operates in almost all tissues, both aerobic and anerobic
- All enzymes for this pathway are found in extra-mitochondrial **cytosol**
- Results in degradation of glucose (6C) to 3C pyruvate or lactate (anaerobic)
- **Aerobic conditions:** Glycolysis is preparatory pathway for complete oxidation of glucose to CO2 and H2O via TCA cycle (best seen in brain and cardiac muscle)
- **Anaerobic conditions** (lack of mitochondria [RBC] or non-functioning mitochondria due to decreased blood supply) → glycolysis is major pathway for ATP production
- Glycolysis is only source of energy in some mammalian cells (e.g. RBCs)
- It is the main pathway for metabolism of dietary fructose and galactose in the liver
- Some intermediates of glycolysis have synthetic function (serine and TAG synthesis)

Q in final

وين بصير كل ال (metabolic bathway) ؟ بال (cytoplasm)

Sequential reactions of glycolysis

- **<u>3 types of chemical transformations are important:</u>**

1. **Degradation** of carbon skeleton in glucose to pyruvate

انتاج

2. **Phosphorylation** of ADP to ATP by high energy compounds formed

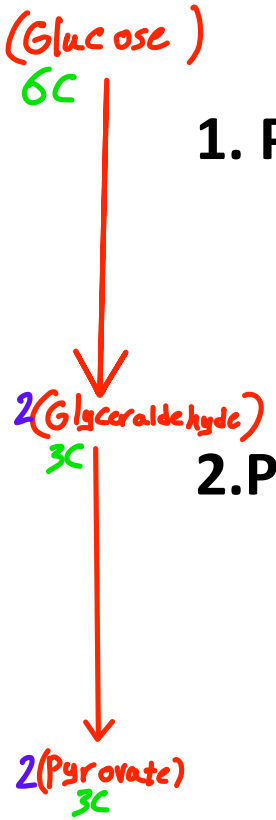
3. **Transfer** of hydride ion with its electron to NAD+ forming NADH

*ADP and ATP have high energy bonds, ← (طيب شوالفرق) ← (فيها (ATP) لكنه (ADP) مافيها أكبر أو يساوي (ج.ج) هي بس تساوي)

2 phases of glycolysis

- 2 phases and 10 steps

- End result is 2 x **3C pyruvate** or 2 x 3C Lactate



1. Preparatory phase:

- 5 enzymatic reactions
- Glucose → glyceraldehyde 3-P + glyceraldehyde 3-P
- 2 ATP **consumed** in this phase

a basic type of Aldehyde

(2) phosphate يضيف

Obticaly active

2.Payoff phase:

- 5 enzymatic reactions
- Oxidative conversion of glyceraldehyde 3-P to pyruvate
- Formation of ATP and NADH

Preparatory phase

Step 1: Phosphorylation of glucose

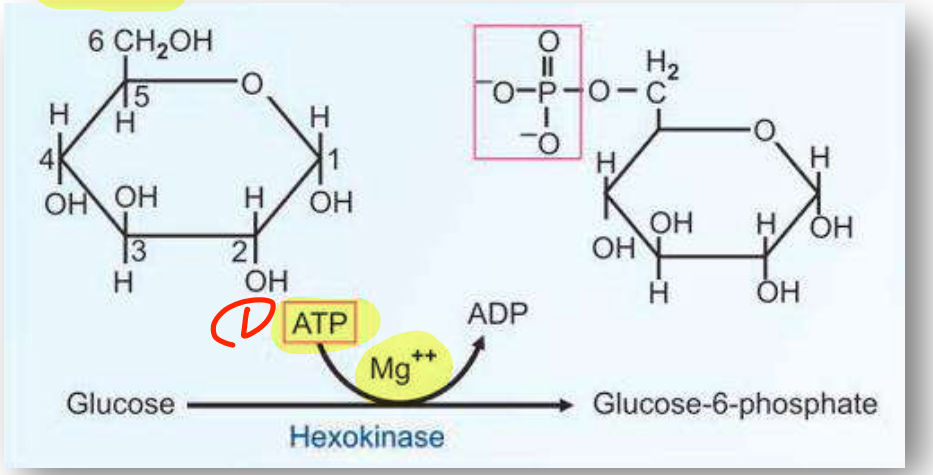
بخليه جوا الخلية بدون ميطلع بسبب الـ (gradient)

- Initiates glycolysis & **intracellular trapping** of intermediates
- Reaction is **irreversible** → في حج بس من أصل (10)
- Catalyzed by hexokinase (present in all cells) or glucokinase (in liver)*

بحتغل على (Glucose) والأشياء الثانية

بس بحتغل على (Glucose)

- Requires Mg2+ as true substrate of enzyme is Mg2+-ATP complex



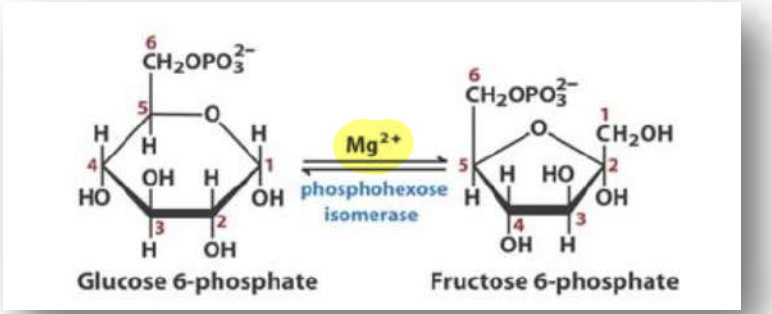
*Differ in catalytic and regulatory properties

يعني حتى لو نسبة الجلوكوز بالدم واطية كثير رح يشتغل يعني بنقدر نقول (بشتغل بكل الأوقات على عكس اللي بده تركيز الجلوكوز يكون عالي جدا بالدم)

	Hexokinase	Glucokinase
Occurrence	In all tissues	Only in liver
Km value	10^{-2} mmol/L	20 mmol/L
Affinity to substrate	High	Low
Specificity	Acts on glucose, fructose and mannose	Acts only on glucose
Induction	Not induced	Induced by insulin and glucose
Function	Even when blood sugar level is low, glucose is utilized by body cells	Acts only when blood glucose level is more than 100 mg/dl; then Glucose is taken up by liver cells for glycogen synthesis

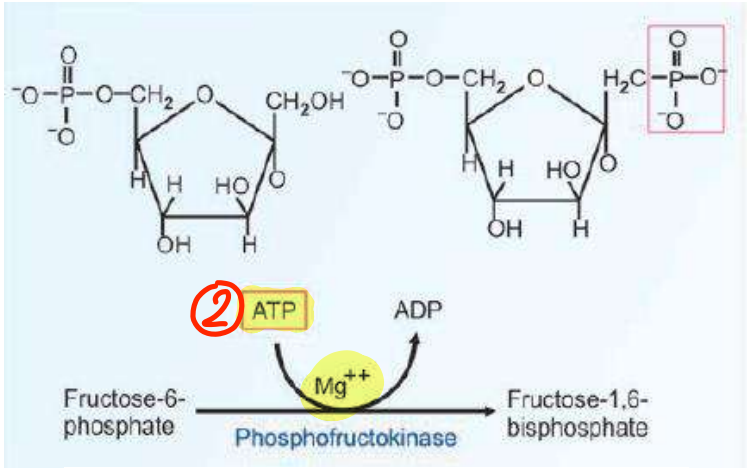
Step 2: conversion of glucose 6-P to fructose-6-P

- **Enzyme:** phosphohexose isomerase
- Reversible reaction

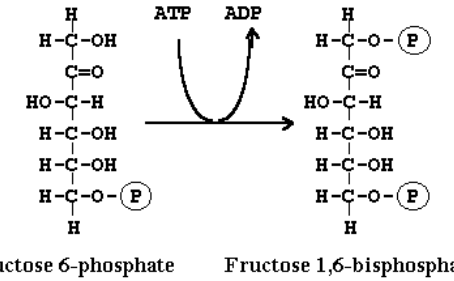


Step 3: phosphorylation of fructose 6-P to fructose 1,6 bis-P*?

- **Enzyme:** phosphofructokinase-1
- **Irreversible reaction**
- **Rate limiting enzyme (key enzyme) → considered major point of control of glycolysis**



When two phosphate groups are linked together and then attached to a parent compound, it is called diphosphate, e.g. adenosine-di-phosphate (Fig. 5.3).
But when phosphoric acid groups are present at two different sites of the compound, it is named as bisphosphate, e.g. fructose-1,6-bisphosphate

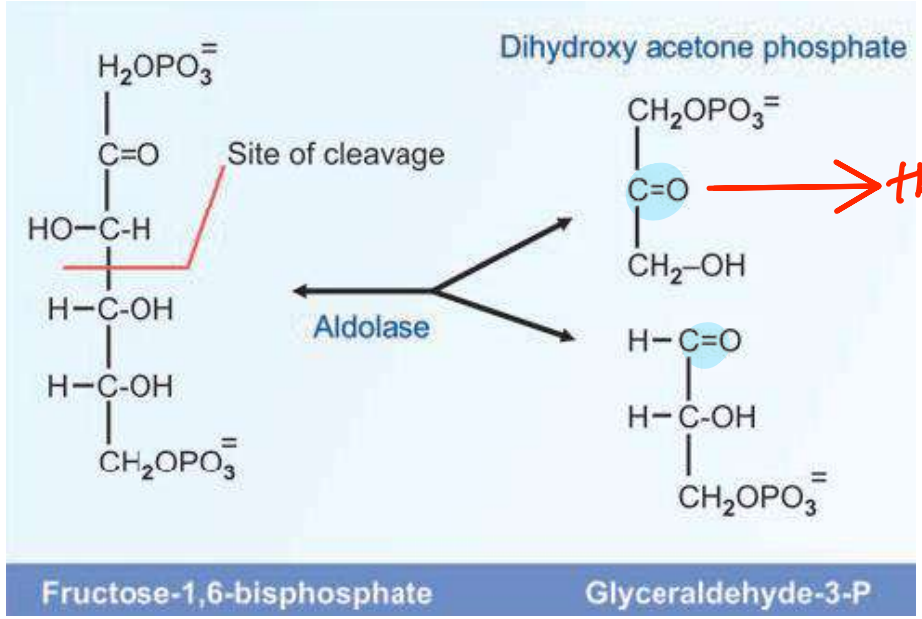


Step 4: cleavage of fructose 1,6 bis-P by aldolase

- Will yield 2 different triose phosphates:
  - Glyceraldehyde 3-P
  - Dihydroxyacetone P

- This reaction is reversible

(في هذه اللحظة عندي بس واحد (Glyceraldehyde-3-P))

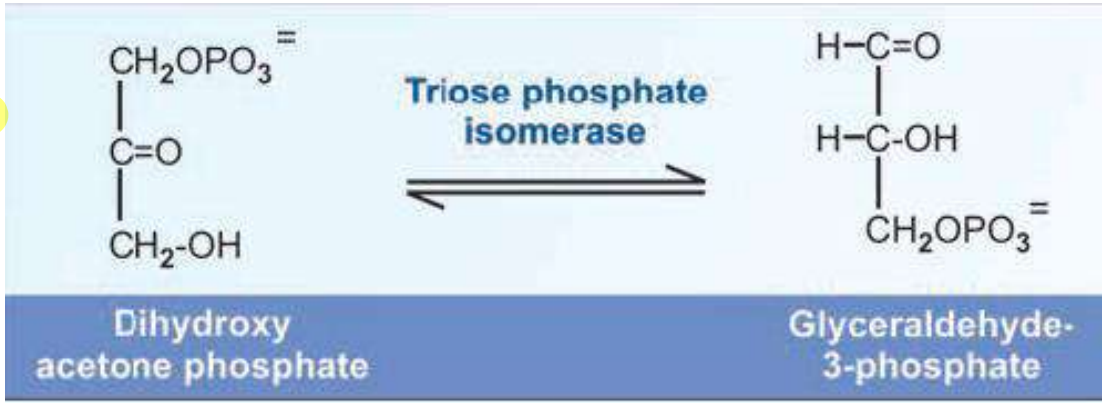


Step 5: Interconversion of triose phosphates

- **Enzyme:** triose phosphate isomerase

- **Reversible reaction**

هما صار عندي الـ (Glyceraldehyde-3-P)



Net result at end of preparatory phase of glycolysis

- Cleavage of glucose → 2 molecule of glyceraldehyde 3-phosphate

- 2 ATP molecules are consumed

Payoff phase

(احنا هنا 2(Glyceraldehyde-3-P) صار نكمل بوحدة فأي اشي بطلع اضربه ب (2))

* أكثر الأشياء اللي جاي بالإمتحان عن (integration, regulation) أو أشياء رح يقول صور ابصم زي أسماء اللي هم حطالين ال (pyruvate) وال (Acetyl CoA)

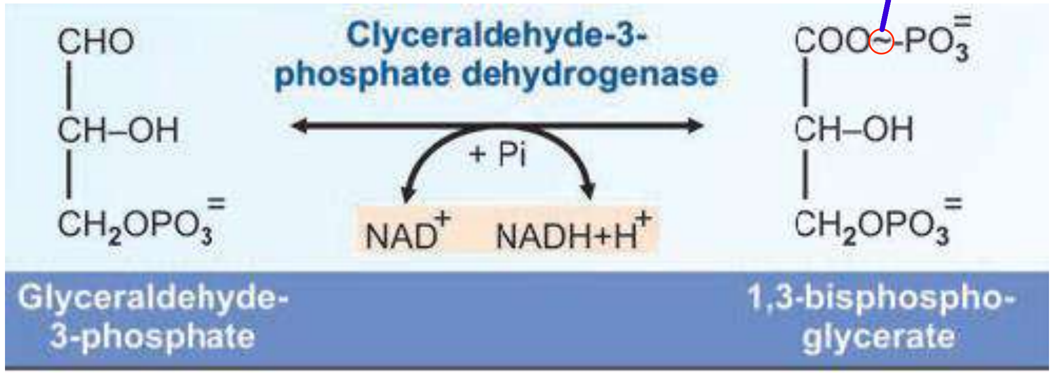
Step 6: oxidation of glyceraldehyde 3-P to 1,3 bisphosphoglycerate

- **Enzyme:** Glyceraldehyde 3-P dehydrogenase
- Reversible
- 2 main events take place:
  - 1) glyceraldehyde-3-phosphate is oxidized by the coenzyme nicotinamide adenine dinucleotide (NAD)
  - 2) the molecule is phosphorylated by the addition of a free phosphate group
- Produces high energy compound:
  - The oxidation of the aldehyde is an exergonic reaction that drives the synthesis of the high energy compound, 1,3 bisphosphoglycerate with high phosphoryl group transfer potential
- Enzyme is a thiol enzyme that has a cysteine residue at the active site
  - Inhibited by iodoacetate → امتحان
- As cells contain only limited amounts of NAD+, glycolysis would come to a stop if NADH formed in this step is not continuously reoxidised

لما تذكر أنه احنا محتاجين نرجع نكون (NAD^+) عشان الخطوة السادسة

NAD is **reduced** to NADH

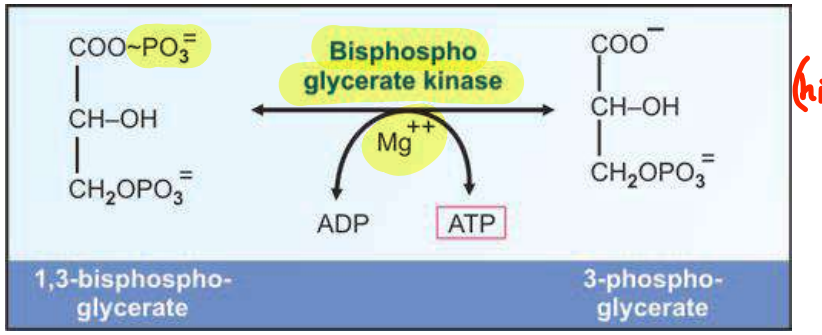
high energy bond



Step 7: Phosphoryl transfer from 1,3 biphosphoglycerate to ADP to form ATP

- This is an example of substrate level phosphorylation (without help of electron transport chain)
- **Enzyme:** phosphoglycerate kinase

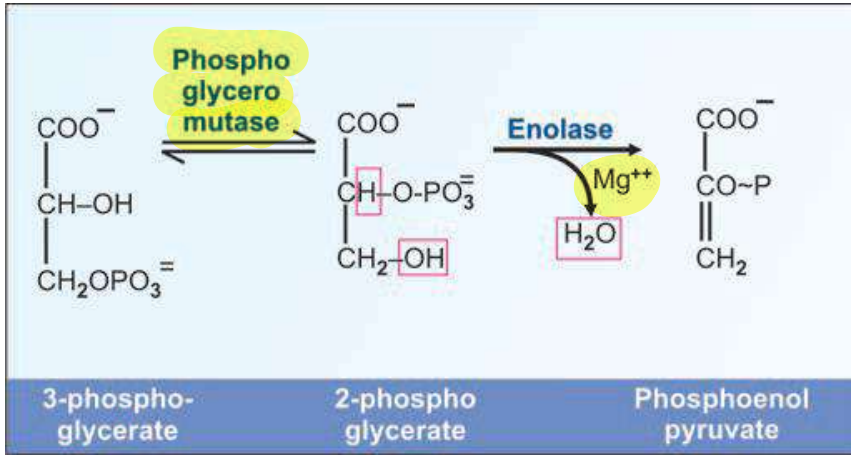
(phosphat group) يعني بشيل



(high energy) تخلصنا منه

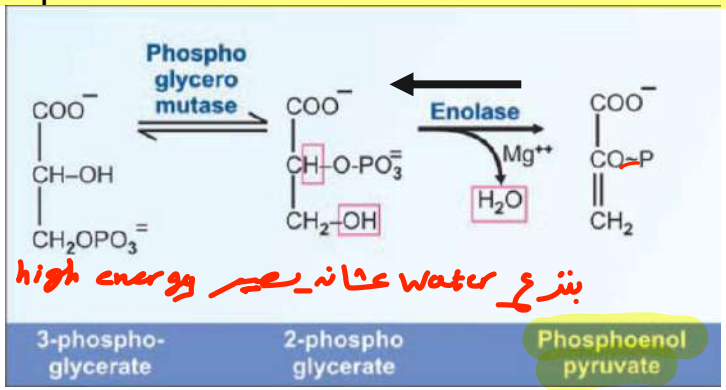
Step 8: conversion of 3-phophoglycerate to 2-phosphoglycerate

- Reversible reaction
- **Enzyme:** phosphoglycerate mutase



Step 9: Dehydration of 2-phosphoglycerate to phosphoenol pyruvate

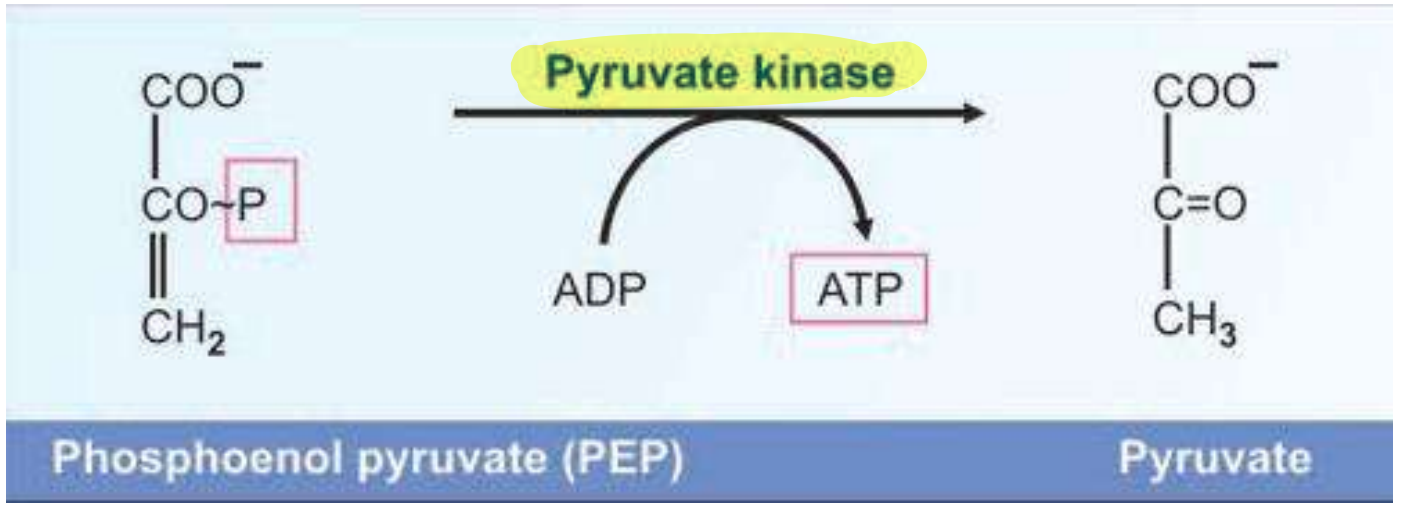
- **Enzyme:** enolase
- Reversible
- Loss of water results in energy redistribution and generation of **high energy phosphate compound (-14.8 kcal/mol)**
  - it has large negative charges on the phosphate groups that transfer into other organic compounds
- Enolase is *irreversibly* inhibited by fluoride which stops the whole process of glycolysis
  - This property of fluoride is used to inhibit glycolysis in blood specimens obtained for measurement of glucose



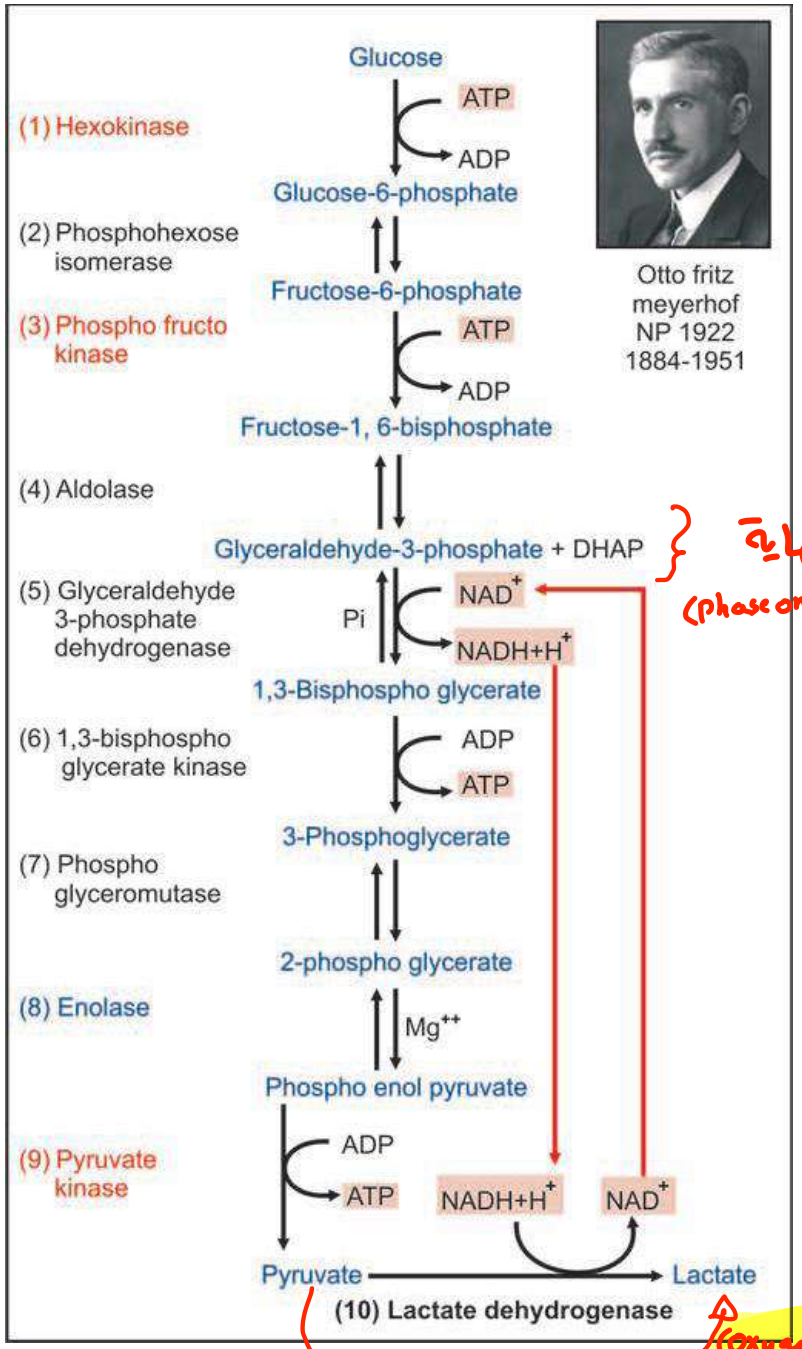
Step 10: Transfer of phosphoryl group from phosphoenopyruvate to ADP

- This is the last step

- This step is **irreversible**
- Pyruvate kinase is a key glycolytic enzyme

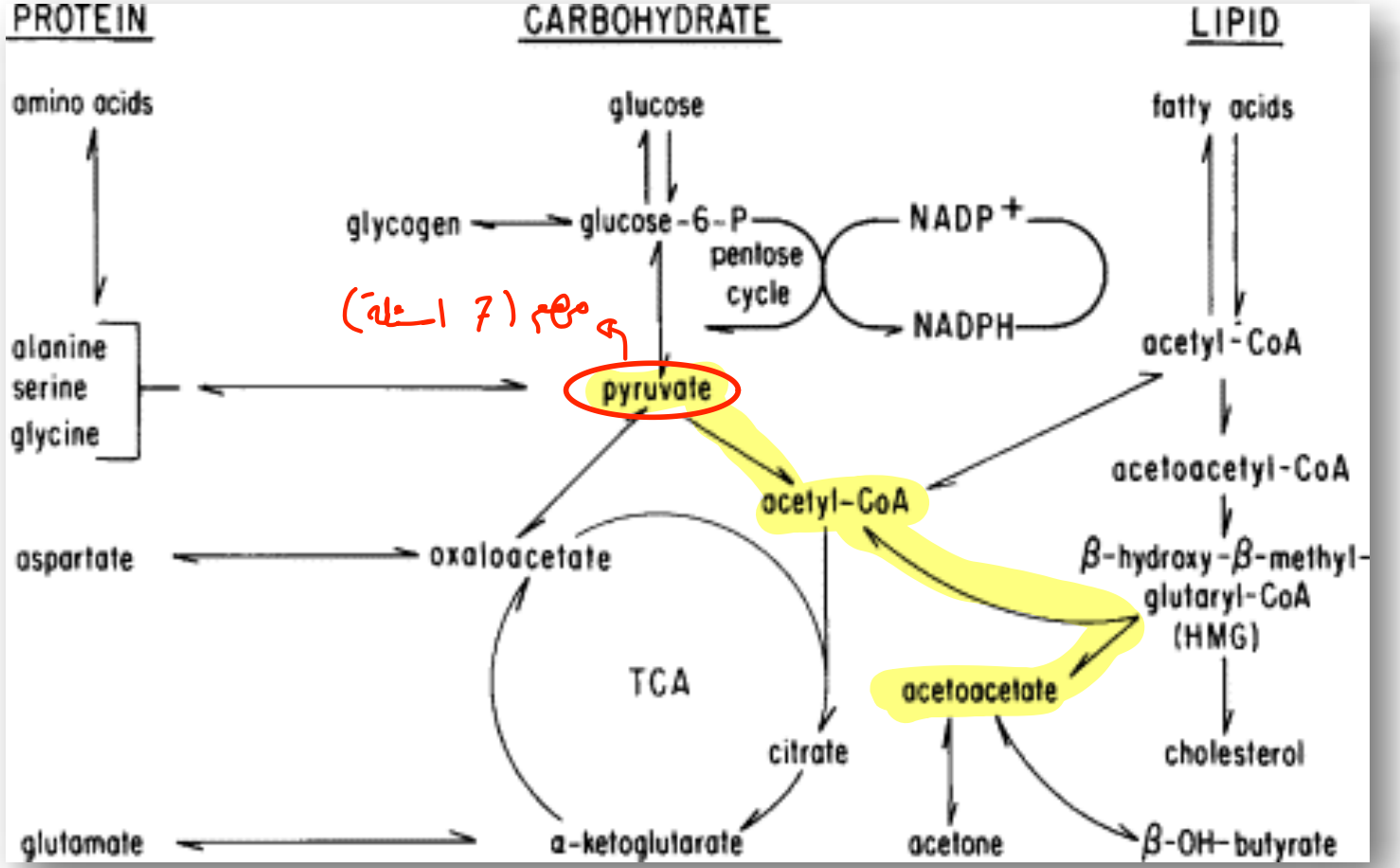


Embden-Meyerhof-Parnas (EMP) pathway



Otto fritz meyerhof NP 1922 1884-1951

نهاية (phase one) الـ



معهم (7 اسئلة)

سؤال بالإمتحان إذا ماعندك (oxygen)

Significance of glycolysis

1. It is the only pathway that is taking place in **all** the cells of the body

2. Glycolysis is the **only source of energy in RBCs**

3. In strenuous exercise, when muscle tissue lacks enough oxygen, anaerobic glycolysis forms **the major source of energy for muscles**

4. The glycolytic pathway may be considered as the **preliminary step before complete oxidation** الأولى

5. The glycolytic pathway provides carbon skeletons for **synthesis of non-essential amino acids as well as glycerol part of fat**

6. Most of the reactions of the glycolytic pathway are reversible, which are also used for **gluconeogenesis**

Energy yield and fate of glycolytic products

بنستهلك 2 وبننتج 4

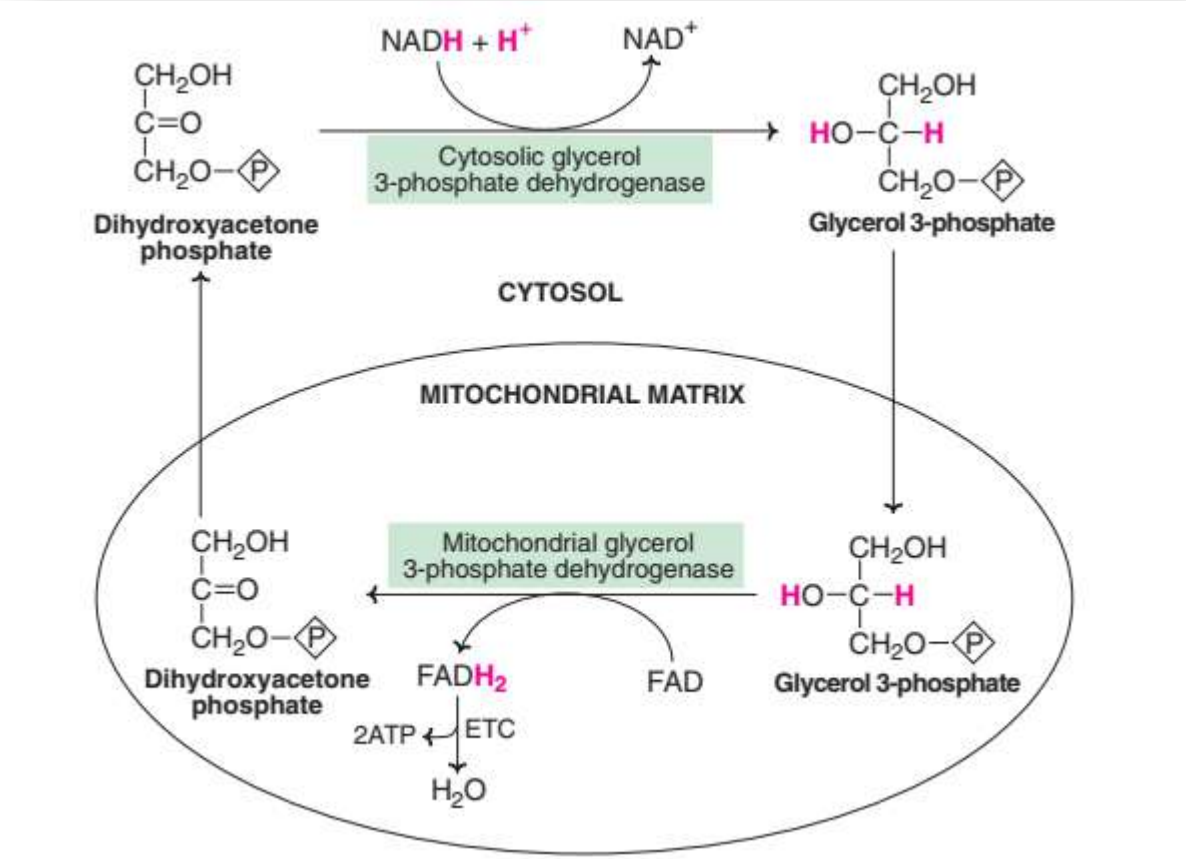
- **End products:** 2 ATP net gain (substrate level), 2 pyruvate, 2 NADH+2H (oxidative phosphorylation)

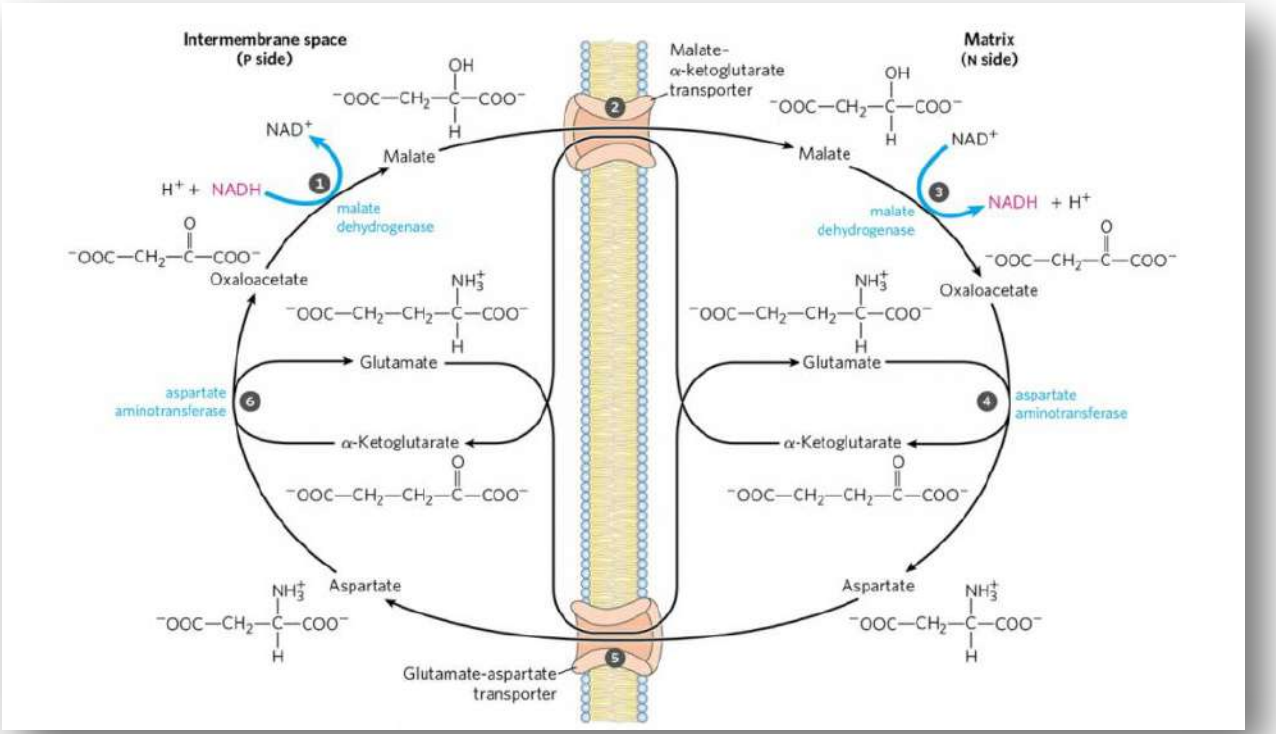
2 + 5 = 7 ATP

Glycolysis under aerobic conditions

- Means presence of **mitochondria and O2**
- Pyruvate will enter mitochondria and undergo oxidative decarboxylation to **acetyl coA**
- 2 molecules of NADH are source of energy but cannot cross inner mitochondrial
  - To overcome this problem, NADH is not transported but electrons are transferred on molecules using 2 shuttle systems:
    - **Glycerol phosphate shuttle:**
      - In skeletal muscle and brain
      - Yields 2 ATP/ NADH
    - **Malate aspartate shuttle:**
      - In liver, kidney and cardiac muscle
      - Yields 3 ATP/ NADH

Net energy yield of glycolysis under aerobic conditions = 6-8 ATPs (old system)





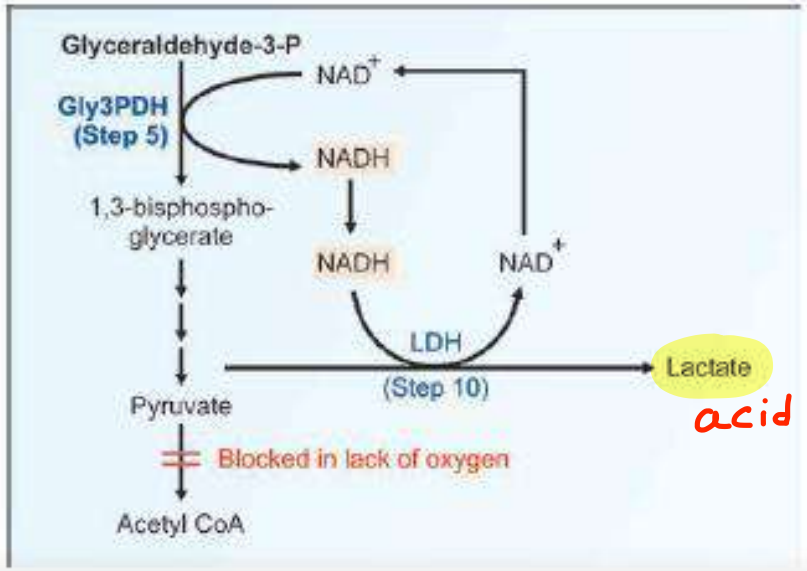
FAD can accommodate two hydrogens → electrons transferred to cytochrome II → less energy

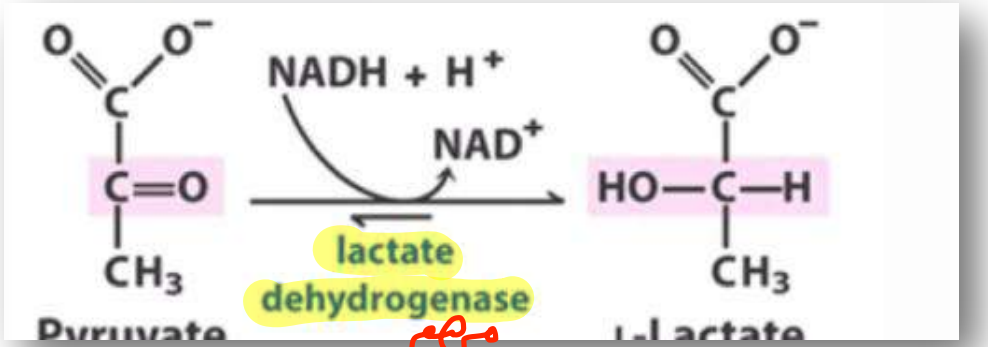
NAD accepts just one hydrogen
In NAD, a single hydrogen and an electron pair is transferred, and the second hydrogen is freed into the medium
→ Electrons transferred to cytochrome I → more energy

Glycolysis under anaerobic conditions

- Means absence of mitochondria or under low O2 tension as:
  - Skeletal muscles during strenuous exercise (lack of oxygen)
  - RBCs

- Note 2 imp facts:
  - Reduced NADH must be converted back to NAD+ for continuity of glycolysis
  - Pyruvate must be removed from cytosol as otherwise it will result in inhibition of glycolysis
  - → these 2 objectives are achieved by reduction of pyruvate to lactate which is easily washed out of the cell with regeneration of NAD+





Net energy yield of glycolysis under anaerobic conditions = 2 ATPs + 2 lactate + 2 NAD+

Energy gain of glycolysis:

- **Energy consumed:**

Step (1) by glucokinase/ hexokinase: One ATP is lost (spared if we start with glycogen).

Step (3) by phosphofructokinase: One ATP is lost. **So, the total lost 2 ATPs**

- **Energy gained:**

Step (6) by glyceraldehyde -3 P dehydrogenase: 2 $NADH+H^+$ (6 ATPs) gained **only** in the presence of O_2., reduced to 4 in using Glycerol phosphate shuttle

5 in the new system

4 أو

$FADH_2$ بـ!

Step (7) by phosphoglycerokinase: 2 ATPs gained.

Step (10) by pyruvate kinase: 2 ATPs gained. **So, the total gains 8-10 ATPs**.

So, Energy gained under anaerobic condition: (i.e.) Glucose to 2 molecules of lactic acid is **2 ATPs** and 3 ATPs if we start with glycogen.

Energy gained under aerobic condition: (i.e.) Glucose to 2 molecules of pyruvic acid and 2 $NADH+H^+$ equal to 2 ATPs + 4-6 ATPs (from 2 $NADH+H^+$) = **6-8 ATPs (old system)** and 9 ATPs if we start with glycogen.

Pathway	Step	Enzyme	Source	Method of ATP formation	No of ATPs gained per glucose (new calculation)		No of ATPs as per old calculation
Glycolysis	1	Hexokinase	-		Minus	1	Minus 1
Do	3	Phospho-fructokinase	-		Minus	1	Minus 1
Do	5	Glyceralde-hyde-3-P DH	NADH	Respiratory chain	2.5 x 2 =	5	3 x 2 = 6
Do	6	1,3-BPG kinase	ATP	Substrate level	1 x 2 =	2	1 x 2 = 2
Do	9	Pyruvate kinase	ATP	Substrate level	1 x 2 =	2	1 x 2 = 2
Pyruvate to Acetyl CoA	-	Pyruvate dehydrogenase	NADH	Respiratory chain	2.5 x 2 =	5	3 x 2 = 6
TCA cycle	3	Isocitrate DH	NADH	Respiratory chain	2.5 x 2 =	5	3 x 2 = 6
Do	4	alpha keto glutarate DH	NADH	Respiratory chain	2.5 x 2 =	5	3 x 2 = 6
Do	5	Succinate thiokinase	GTP	Substrate level	I x 2 =	2	I x 2 = 2
Do	6	Succinate DH	$FADH_2$	Respiratory chain	1.5 x 2 =	3	2 x 2 = 4
Do	8	Malate DH	NADH	Respiratory chain	2.5 x 2 =	5	3 x 2 = 6
Net generation in glycolytic pathway					9 minus 2=	7	10 minus 2= 8
Generation in pyruvate dehydrogenase reaction					=	5	= 6
Generation in citric acid cycle					=	20	= 24
Net generation of ATP from one glucose mol					=	32	= 38

امتحانه

1.5 x 2 for FADH2 if glycerol phosphate shuttle

Lactate is the end product of glycolysis in:

- Cells that lack mitochondria as RBCs
- Cells that work vigorously (بسرعة) under "oxygen lack" conditions like contracting muscle
- Tumors as they often contain areas of hypoxia (نقص oxygen) (cancer)

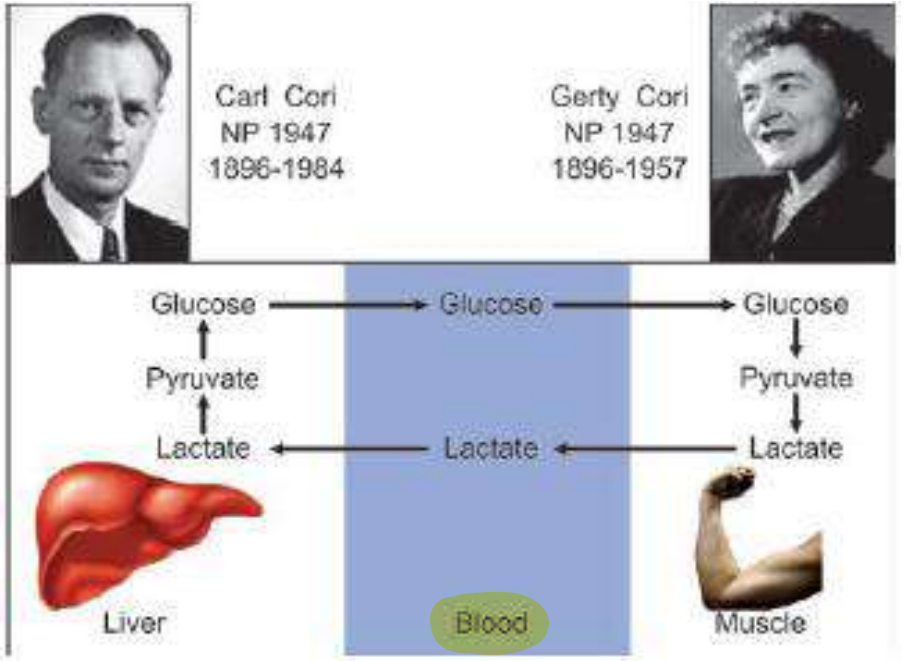
Question: Why is the rate and total amount of glucose consumption is higher under anaerobic conditions? لأنه بيعطيك كمية قليلة من ATP فأنت بتحتاج تحرق كمية كبيرة من الـ glucose وكمان لأنه الـ glucose مصدر الطاقة الوحيد له

Cori cycle

- **Definition:** It is a process in which glucose is converted to lactate in the muscle; and in the liver this lactate is re-converted into glucose
    - In an actively contracting muscle, pyruvate is reduced to lactic acid which may tend to accumulate in the muscle
    - The muscle cramps, often associated with strenuous muscular exercise, are thought to be due to lactate accumulation

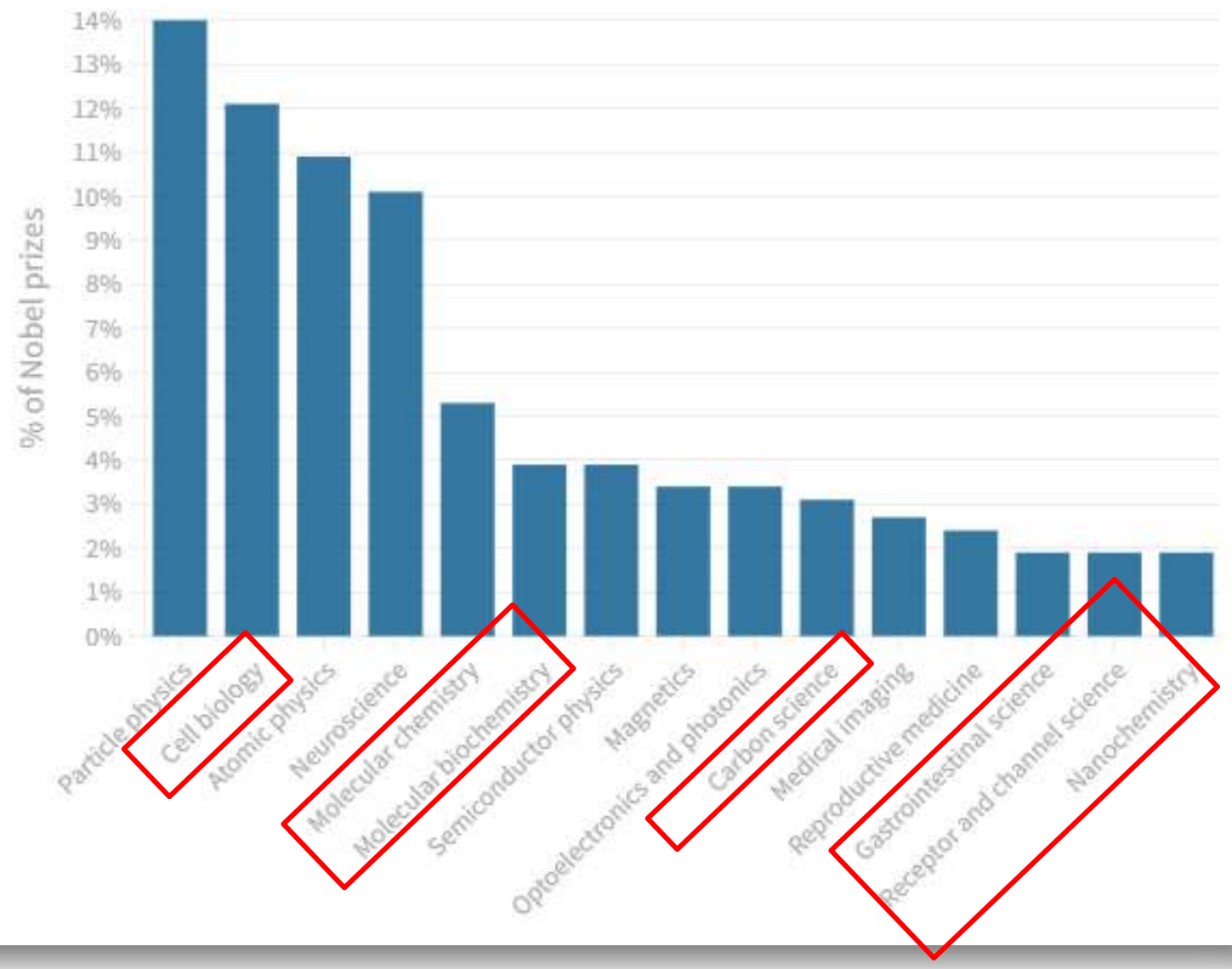
- To prevent the lactate accumulation, body utilises Cori's cycle

- **Significance of the Cori's cycle:** The lactate produced in the muscle is efficiently reutilized



The prize collectors

Just 5 disciplines account for over half of all Nobel Prizes in science awarded between 1995 and 2017.



Alternative substrates for glycolysis

- Glycolytic pathway is also utilized by fructose and galactose

- Glycogenolysis yields glucose 1-P, which is converted to glucose 6-P:
  - This bypasses initial phyosphorylation of glucose
  - → conversion of 1 glucosyl unit of glycogen to 2 lactate molecules yields 3 ATP

- Glycerol from TAG hydrolysis enters into glycolysis through its conversion to dihydroxyacetone phosphate

Clinical aspects of glycolysis

- **Lactic acidosis**
  - Lactate is metabolized by liver under normal conditions
  - A common cause of lactic acidosis is shock, lung failure, alcohol abuse and DM
  - Oxygen deprivation leads to ↓ ATP and ↑ NADH which promotes conversion of pyruvate to lactate

Diabetes mellitus

(لانه بتقل كفاءة الـ Krebs cycle, oxphos)

(حليب أو لبن) وتوقفت العمليات المعتادة فكيف تحول؟ عن طريق تحويل (P) إلى (L) (NAD+)

- **Glycolytic enzyme deficiencies in RBCs**
  - Glycolysis only pathway to provide ATP in RBCs as they lack mitochondria
  - ATP is required to maintain RBC structural integrity and NA K ATPase pump
  - Deficiency of glycolysis enzymes → reduce normal life span of RBCs
  - Most common enzyme deficiencies are pyruvate kinase and hexokinase
    - --> hemolytic anemia and jaundice

ينتج عنه اصفرار بالجسم

Regulation of Glycolysis:

Regulation of the 3 irreversible reactions

a) Glucokinase (GK) or (Hexokinase, HK)

b) Phosphofructokinase (PFK) which is the rate limiting Enzyme & most important regulatory site of glcolysis.

c) Pyruvate kinase (PK)

Regulation of glycolysis according to the feeding status

Regulation of the 3 irreversible reactions

- **Induction and Repression of the key enzymes:** Insulin induces (increases) the synthesis of these enzymes, while glucagon and adrenaline inhibit their synthesis

- **Allosteric regulation:**

- ***GK (Glucokinase)***: No regulation
- Hexokinase is allosterically inhibited by G-6-P.

N.B. hexokinase is present in all cells except liver and pancreatic islets/ glucokinase is present only in liver and pancreatic islets.

- ***PFK (Phosphofructokinase):***

- Allosterically activated by fructose-2,6-bis-phosphate, AMP& ADP
- Allosterically inhibited by ATP & Citrate and low pH

Fructose-2, 6-Bisphosphate: [F-2, 6–BP] is formed by phosphorylation of F-6-P by the enzyme phosphofructokinase–2 (PFK-2)

- ***PK (Pyruvate kinase):***

-Allosterically activated by Fructose-1,6- bis-phosphate, AMP

-Allosterically inhibited by ATP

A possible explanation for the acid- induced protein catabolism and increased amino acid oxidation is that impairment of glycolysis by low pH restricts the pyruvate supply to mitochondria, leading to catabolism of amino acids from protein as an alternative metabolic fuel.

Covalent modification:

The pyruvate kinase (PK) is regulated by covalent modification (phosphorylation / dephosphorylation)

- Phosphorylated pyruvate kinase is inactive and **inhibits glycolysis**
- **Insulin** ↑ its' activity by dephosphorylation
  - Dephosphorylated pyruvate kinase is active leading to stimulation of glycolysis
- **Glucagon** ↓ its' activity by phosphorylation through action of cAMP

Regulation of glycolysis according to the feeding status

- **Carbohydrates feeding:**

  Intake of carbohydrates stimulates insulin secretion which leads to:

  - Increase glucose uptake by tissues
    - Glucose transporter-4 (GluT4) transports glucose from the extracellular fluid to muscle cells and adipocytes
  - Increase synthesis of GK, PFK & PK.
  - Increase PK by dephosphorylation. So, **carbohydrates feeding stimulate Glycolysis.**

- **Fasting (starvation): It leads to:**

1-Decrease insulin and decrease glucose uptake by tissues

2-Increase glucagon and adrenaline leads to:

- Decrease synthesis of GK, PFK &PK.
- Decrease PK by phosphorylation. So, **fasting inhibits glycolysis.**

لو توقف (Glycolysis) ستموت 😵 بس أنت بتخفف عشان تحافظ على نسبة السكر بالدم

Table 9.3. Regulatory enzymes of glycolysis

Enzyme	Activation	Inhibition
HK		G-6-P
GK	Insulin	Glucagon
PFK	Insulin, AMP F-6-P, PFK-2 F2,6-BP	Glucagon, ATP Citrate, Low pH Cyclic AMP
PK	Insulin, F1,6-BP	Glucagon, ATP Cyclic AMP
PDH	CoA , NAD	Acetyl CoA, NADH

(حكى مطلوب تعرفهم بالإسم)

Inhibitors of glycolysis

Fluoride:

- They inhibit enolase enzyme (binds to Mg^{++}) so we add fluoride to blood sample to estimate its blood glucose

Iodoacetate:

- It blocks the SH group at the active site of glyceraldehyde-3-phosphate dehydrogenase enzyme

Arsenite:

(Pathway) وليس الـ

- It inhibits ATP formation by competing with inorganic phosphate (Pi) as a substrate for glyceraldehyde-3-P dehydrogenase
  - → forming 1-arseno-3-phosphoglycerate instead of 1,3 BPG so no high energy no ATP. **(So prevents net ATP production by glycolysis without inhibiting the pathway itself)**

Pyruvate (أهم موضوع بهذه المحاضرة)

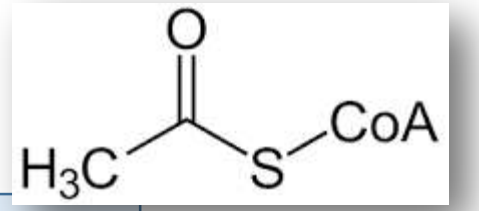
- Occupies an imp junction btwn various metabolic pathways:
  - Reduced to lactate in anaerobic conditions
  - Oxidatively decarboxylated forming acetyl coA → (بتتنزع منه كربونة فبصير (2C) بدل (3))
  - Transaminated to alanine (والعكس) — reversible
  - Converted to oxaloacetate (by pyruvate carboxylase)

- **Oxalacetate** can:
  - Combine with acetyl coA to form citrate in Krebs cycle
  - Form aspartate
  - Used in gluconeogenesis

* لو بدنا نكمل تكسير الجلوكوز الكامل لازم ندخل بـ (Krebs) وعشان ندخل لازم نحول الـ (Pyrovate) الى (AcetylCoA) عن طريق (Decarboxilation) (فرع كربوني)

AEROBIC PHASE OF GLUCOSE OXIDATION

- **Definition:** Pyruvic acid is completely oxidized to CO_2, H_2O and 15 ATP are produced (per 1 pruvate)
- **Site:** Mitochondria of all cells.



Pyruvic acid

(Cyto plasm) لـ ننتجه في الـ
بس لازم يروح على الـ (Mito chondria)
عشان يعمل باقي الخطوات

Oxidative decarboxylation

Acetyl-COA + 3ATPs

Krebs' cycle

2CO2 + H2O + 12 ATPs

Pathway	Step	Enzyme	Source	Method of ATP formation	No of ATPs gained per glucose (new calculation)		No of ATPs as per old calculation
Glycolysis	1	Hexokinase	-		Minus	1	Minus 1
Do	3	Phospho-fructokinase	-		Minus	1	Minus 1
Do	5	Glyceralde-hyde-3-P DH	NADH	Respiratory chain	2.5 x 2 =	5	3 x 2 = 6
Do	6	1,3-BPG kinase	ATP	Substrate level	1 x 2 =	2	1 x 2 = 2
Do	9	Pyruvate kinase	ATP	Substrate level	1 x 2 =	2	1 x 2 = 2
Pyruvate to Acetyl CoA	-	Pyruvate dehydrogenase	NADH	Respiratory chain	2.5 x 2 =	5	3 x 2 = 6
TCA cycle	3	Isocitrate DH	NADH	Respiratory chain	2.5 x 2 =	5	3 x 2 = 6
Do	4	alpha keto glutarate DH	NADH	Respiratory chain	2.5 x 2 =	5	3 x 2 = 6
Do	5	Succinate thiokinase	GTP	Substrate level	I x 2 =	2	I x 2 = 2
Do	6	Succinate DH	$FADH_2$	Respiratory chain	1.5 x 2 =	3	2 x 2 = 4
Do	8	Malate DH	NADH	Respiratory chain	2.5 x 2 =	5	3 x 2 = 6
Net generation in glycolytic pathway					9 minus 2=	7	10 minus 2= 8
Generation in pyruvate dehydrogenase reaction					=	5	= 6
Generation in citric acid cycle					=	20	= 24
Net generation of ATP from one glucose mol					=	32	= 38

1.5 x 2 for FADH2 if glycerol phosphate shuttle

Oxidative decarboxylation of pyruvic acid

- It occurs in the **mitochondria**
- It is **irreversible** → (لأنه (Acetyl CoA) اللي جاي منه الدهون لا يمكن تصنيع السكر منه)

- It needs:

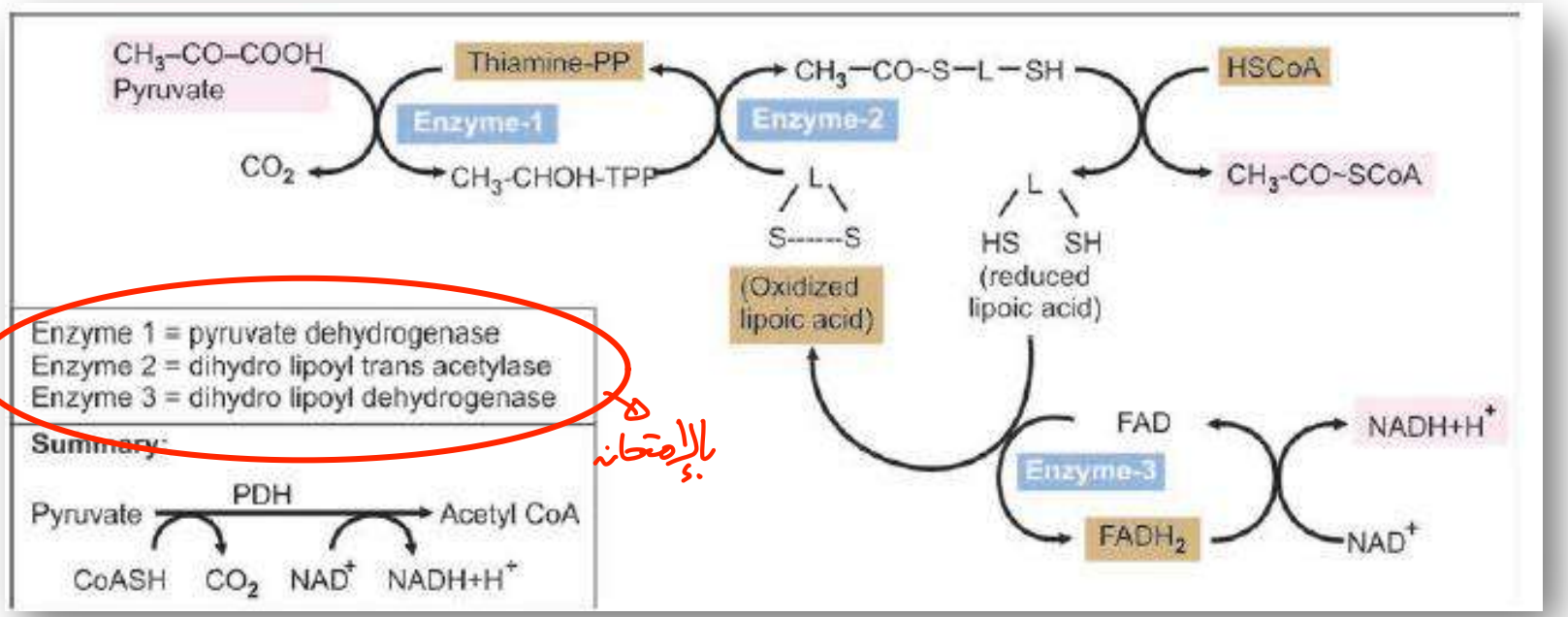
1-Pyruvate dehydrogenase complex + 2 other enzymes

2-5 coenzymes: TPP (thiamine pyrophosphate*), lipoic acid, FAD, NAD^+, CoASH (TLFNC), and + Mg2+ as cofactor

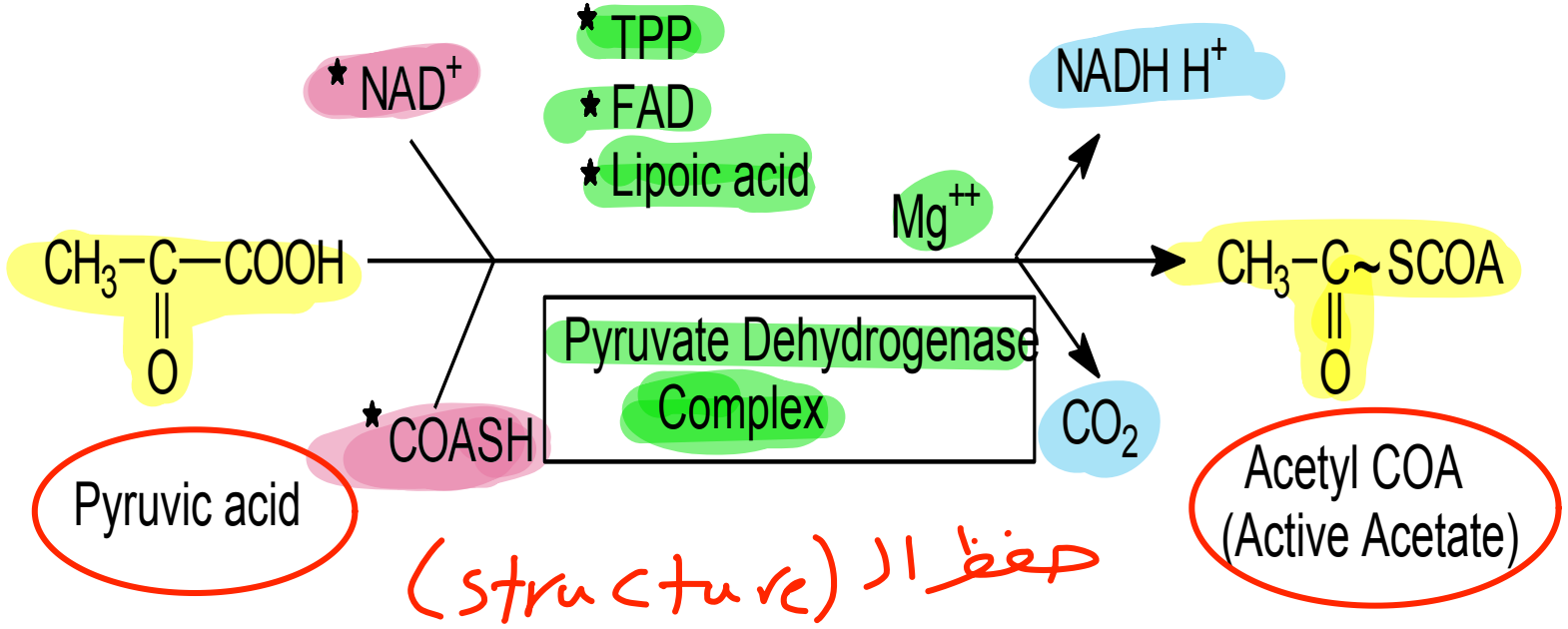
كله حفظ وجاي بالامتحان

* عشان هيك اللي عنده (Alcohol Abuse) بكون عنده (thiamine deficiency) كتير فبصير عنده مشكله في الـ (Pyrovate dehydrogenase) فبزيد الـ (Pyrovate) فيتحول إلى (lactate) يتراكم ويصير lactic acidosis

هذا الحكي مهم ومكن يكونه على سؤال كيس بالإمتحانه

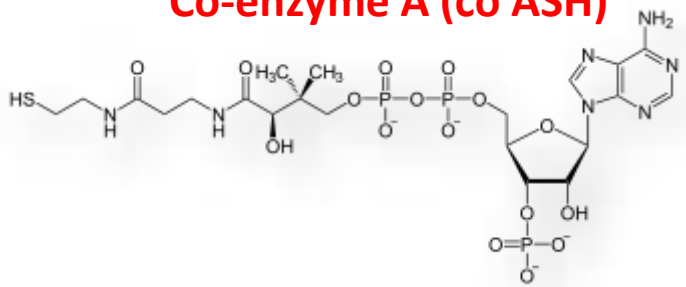


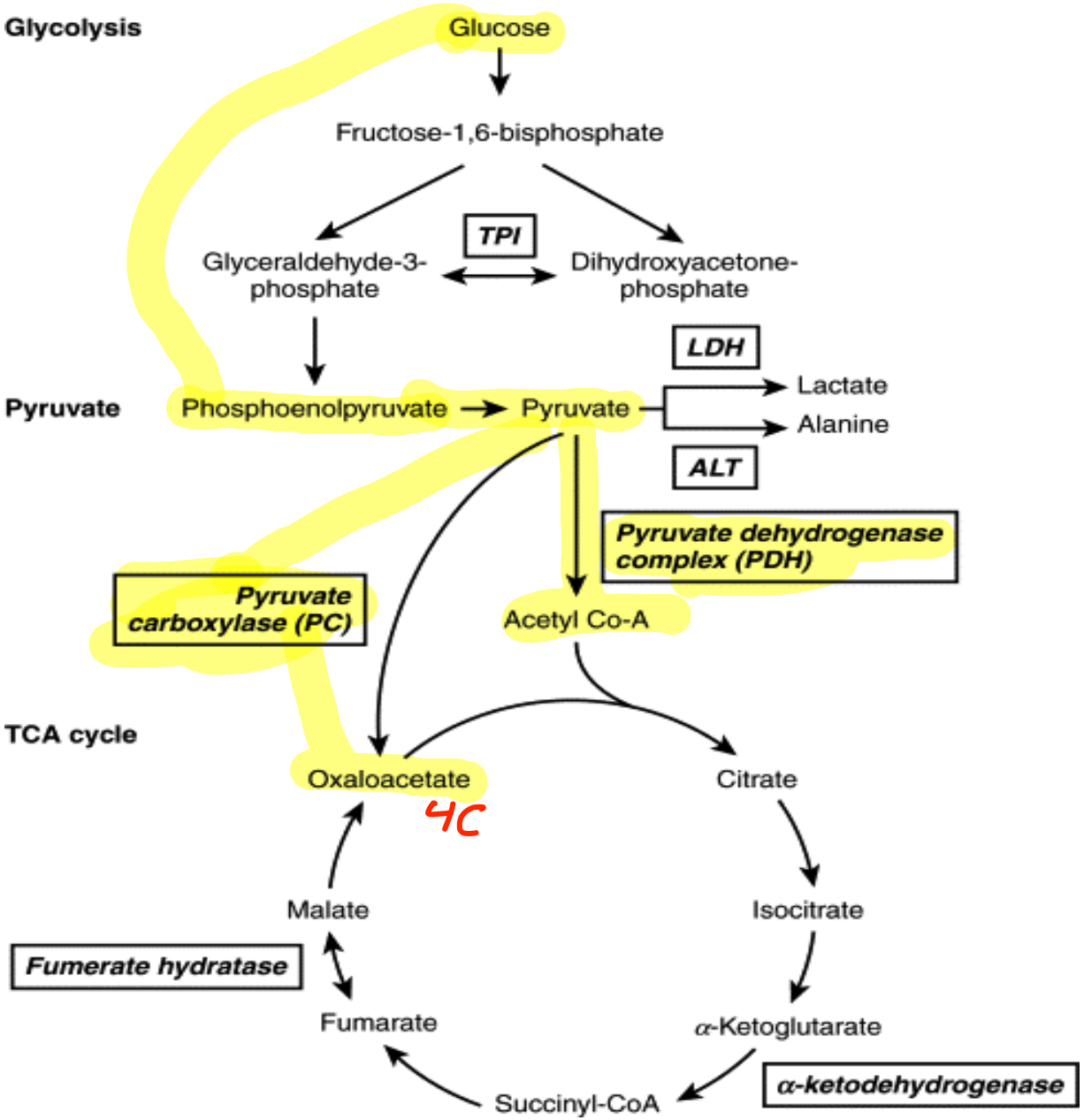
بالإمتحان



حفظ الـ (structure)

Co-enzyme A (co ASH)




Glycolysis
Glucose
Fructose-1,6-bisphosphate
TPI
Glyceraldehyde-3-phosphate
Dihydroxyacetone-phosphate
LDH
Pyruvate
Phosphoenolpyruvate
Pyruvate
Lactate
Alanine
ALT
Pyruvate dehydrogenase complex (PDH)
Pyruvate carboxylase (PC)
Acetyl Co-A
TCA cycle
Oxaloacetate
4C
Citrate
Malate
Isocitrate
Fumerate hydratase
Fumarate
α-Ketoglutarate
α-ketodehydrogenase
Succinyl-CoA

Abnormalities of pyruvate dehydrogenase

- **Causes:**
  - Dietary deficiency of thiamine (Beri Beri)
  - Nutritionally deprived alcoholics (thiamine deficiency)
  - Arsenite and mercury poisoning

- **Effects**:
  - All pyruvate will be converted to lactate → accumulation of lactate → lactic acidosis

Glycolysis In Erythrocytes (Rapaport Lubering cycle)

(داخلة بالإمتحان)

The reaction catalyzed by phospho-glycerate kinase is sometimes replaced by an alternative two-step reaction that avoids ATP formation and produces 2,3-bisphospho-glycerate (diphospho-glycerate or DPG) as shown below. **2, 3-BPG binds haemoglobin and reduces its affinity for oxygen** and thus makes oxygen more readily available for tissues.

في طريقتين للتحويل: خطوتين أو خطوات

Glyceradehyde-3-phosphate

Glyceraldehyde-3-phosphate Dehydrogenase

1,3-Bisphosphoglycerate

ADP

Phosphoglycerate Kinase

ATP فقد

3-Phosphoglycerate

Bis-phospho-glycerate mutase

2,3-Bisphosphoglycerate (BPG)

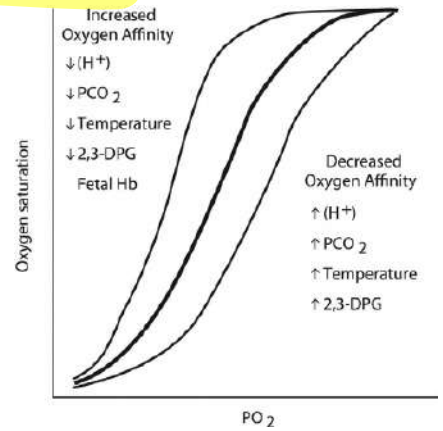
H_2O

2,3-Bis-phospho-glycerate Phosphatase

Pi

خاصية مهمة

In blood transfusion: give inosine to synthesize 2,3 BPG in stored blood to help release of oxygen



Every DPG mole produced decreases ATP production in erythrocytes by 1 mole as the phosphor-glycerate kinase step is omitted.

* بقلل الـ (Affinity) تاعت الهيموغلوبين للـ (Oxygen) .

- للناس اللي ساكنين في مناطق عالية مثل (جبل في mexico city) على ارتفاع (3000m) الـ (Affinity) تاعتهم (Affinity) واطية عشان يقدر يتكيف بشكل أسهل فبزيد عندهم (2,3 BisphosphoglycerateBPG) اللي بنقل الـ (Oxygen) باتجاه معين فعندما أنت بتصير تعطي الـ (Oxygen) بشكل أسهل للـ (tissues) (hemoglubon saturated cerve)

بس بالمقابل أنت قاعد بتخسر (ATP)

Final Exam

الشرح الذي في الأعلى مهم وسيأتي عليه سؤال في الإمتحان النهائي