



مقدم من فريق أفق الطبي



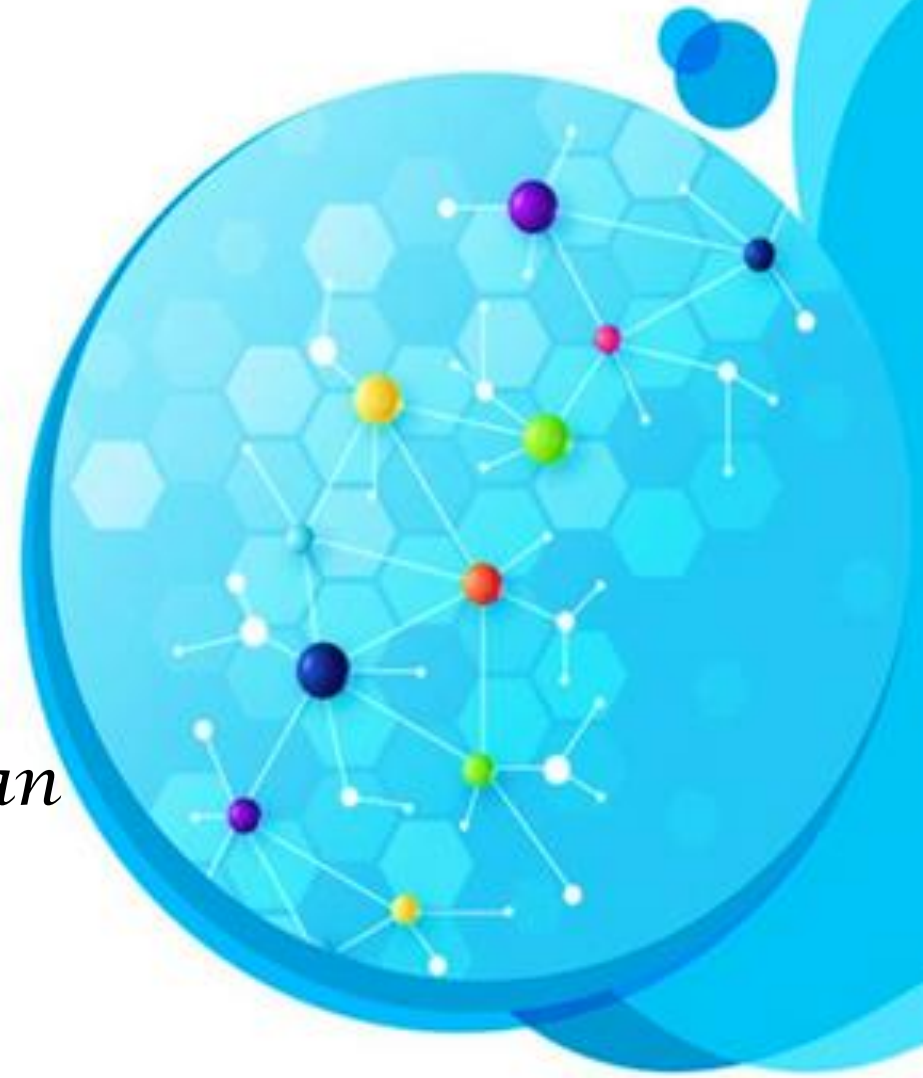
Medical Biochemistry

Enzymes

Asst. Prof. Mohammed Hasan Eleyan

Faculty of Medicine

Al-Azhar University-Gaza



Enzymes

Eduard Buchner in 1897

1

Cell-free yeast extracts could ferment sugar to alcohol

2

التخمير
Fermentation was promoted by molecules that functioned outside cells
تقدر تستغل خارج الخلية

3

The name "enzymes" was given to these molecules

The term "enzyme" comes from the Greek words en (meaning "in") and zyme (meaning "yeast"). It reflects their role in fermentation.

مواد داخل الخميرة



Enzymes

Enzymes are Biological

Catalysts

Enzymes accelerate chemical reactions in living organisms without being consumed in the process. They are essential for life because they enable metabolic reactions to occur at rates compatible with cellular needs.

مواد لها القدرة على زيادة معدل التفاعل الكيميائي من غير ما يتم استهلاكها

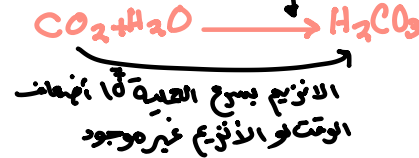
Highly Specialized RNA or Proteins

Most enzymes are proteins, but some are RNA molecules (e.g., ribozymes). Their three-dimensional structures are highly specialized to perform specific functions.

عشوائيه انزيم اذا الانزيم functional لانهم انزيم الشيف تشدشي في الـ 3D

Extraordinary Catalytic Power

Increase reaction rates
Example: Carbonic anhydrase hydrates CO_2 10^7 times faster than the uncatalyzed reaction.



↑ reaction rate

High Degree of Specificity

خصوصية لمادة معينة

Enzymes bind specific substrates via precise molecular interactions.
Example: Lactase hydrolyzes lactose but not other disaccharides



Function Under Mild Conditions

Operate efficiently in aqueous solutions at physiological pH and temperature.

Example: Trypsin functions optimally at pH 8.

37 °C

لا يحتاج الى ظروف قاسية حتى تشتغل

Unique Properties Compared to Non-Biological Catalysts

Non-biological catalysts often require extreme conditions (e.g., high temperature, ↑ pressure).

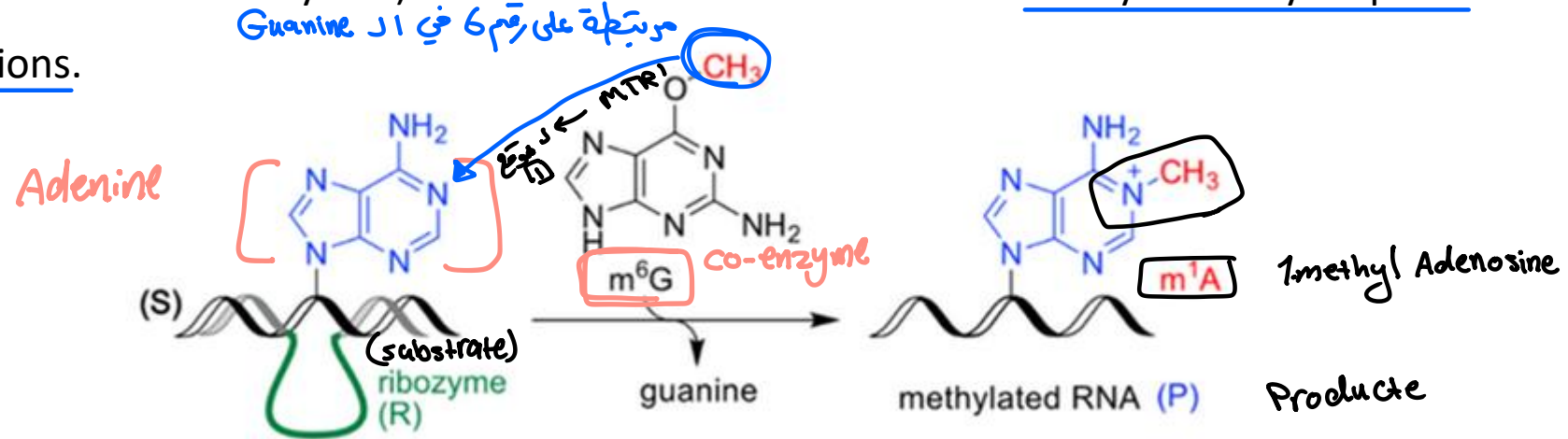


Ribozymes



Structure
(RNA) الإنزيمات

- Ribozymes (ribonucleic acid enzymes) are RNA molecules that have the ability to catalyze specific biochemical reactions.



Ex: Methyltransferase Ribozyme (MTR1): is a ribozyme **catalyzes** methyl transfer to generate **1-methyladenosine (m¹A)**.



Some Enzymes Need Other Chemical Groups

Not all enzymes are fully functional on their own. Many require additional molecules to catalyze reactions effectively.

RNA only
Protein

Inorganic cofactor

Active site

other molecule

Coenzyme
(organic cofactor)

Apoenzyme (protein)

Holoenzyme

1

Cofactors

2

Coenzymes

المكونة النشطة كانه
Functionally
inactive

لذلك هو بحاجة للمكون
الآخر عشانه يعمل فعال

Some Enzymes Need Other Chemical Groups

Cofactors: ~~ferus~~ **ferric**

Inorganic ions (e.g., Mg^{2+} , Zn^{2+} , $\text{Fe}^{2+}/\text{Fe}^{3+}$) that assist in catalysis.

Example: Carbonic anhydrase requires Zn^{2+} for activity.

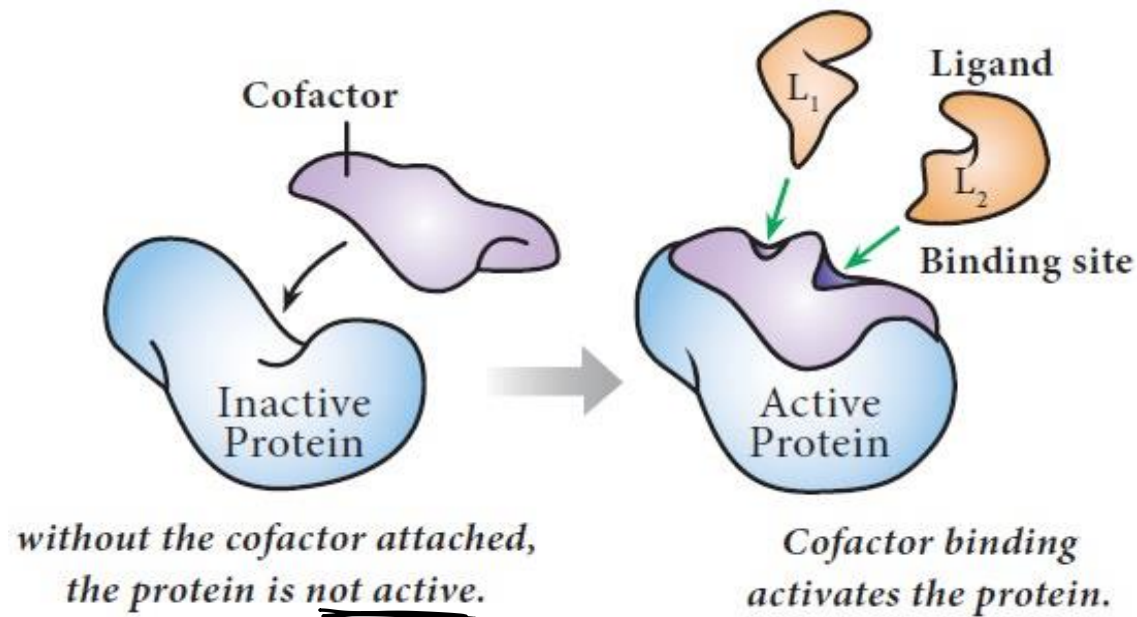
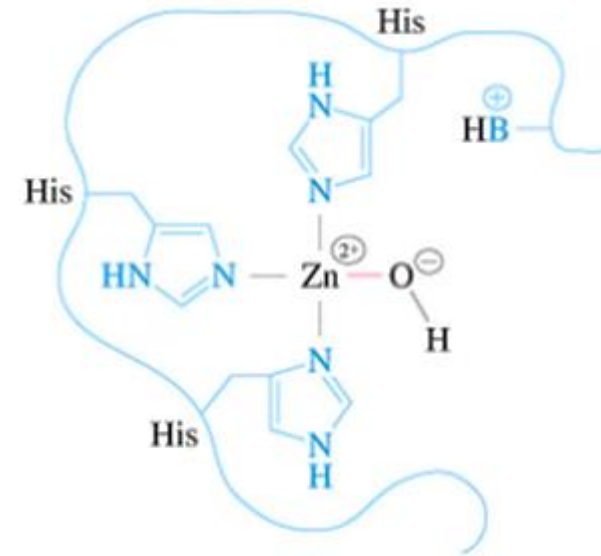


Figure 4.1 Cofactor binding





Some Enzymes Need Other Chemical Groups



Table 6-1 Some Inorganic Ions That Serve as Cofactors for Enzymes

Ions	Enzymes
Cu^{2+}	Cytochrome oxidase
Fe^{2+} or Fe^{3+}	Cytochrome oxidase, catalase, peroxidase
K^{+}	Pyruvate kinase
Mg^{2+}	Hexokinase, glucose 6-phosphatase, pyruvate kinase
Mn^{2+}	Arginase, ribonucleotide reductase
Mo	Dinitrogenase
Ni^{2+}	Urease
Zn^{2+}	Carbonic anhydrase, alcohol dehydrogenase, carboxypeptidases A and B



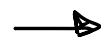
Some Enzymes Need Other Chemical Groups

organic part connect with inorganic part



Coenzymes:

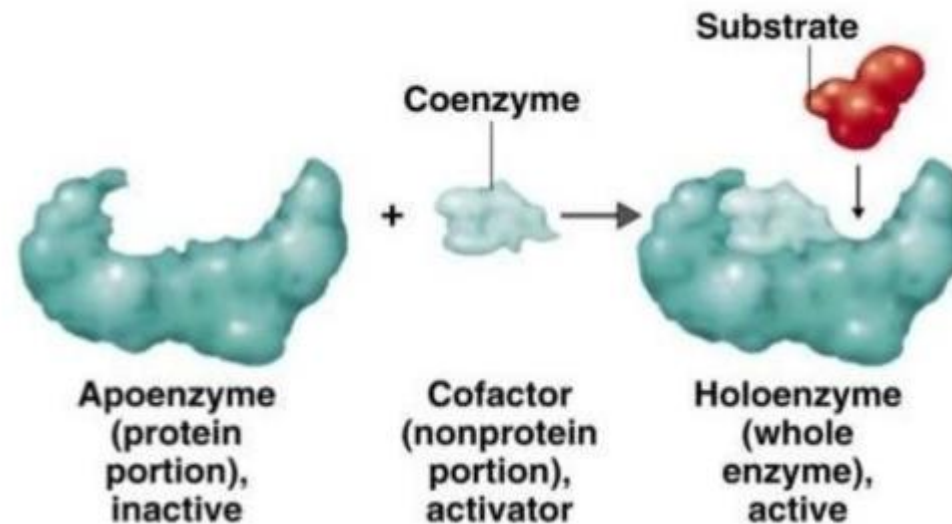
عاباً كحل



Organic or metalloorganic molecules that often act as carriers of specific functional groups (e.g., electrons, acyl groups).

Example: NAD^+ (nicotinamide adenine dinucleotide) is a coenzyme involved in redox reactions

تفاعلات الأكسدة والاختزال



Some Enzymes Need Other Chemical Groups

Table 6-2 Some Coenzymes That Serve as Transient Carriers of Specific Atoms or Functional Groups

Coenzyme	Examples of chemical groups transferred	Dietary precursor in mammals
Biocytin	CO ₂	Biotin (vitamin B ₇)
Coenzyme A	Acyl groups	Pantothenic acid (vitamin B ₅) and other compounds
5'-Deoxyadenosylcobalamin (coenzyme B ₁₂)	H atoms and alkyl groups	Vitamin B ₁₂
Flavin adenine dinucleotide	Electrons	Riboflavin (vitamin B ₂)
Lipoate	Electrons and acyl groups	Not required in diet
Nicotinamide adenine dinucleotide	Hydride ion (:H ⁻)	Nicotinic acid (niacin, vitamin B ₃)
Pyridoxal phosphate	Amino groups	Pyridoxine (vitamin B ₆)
Tetrahydrofolate	One-carbon groups	Folate (vitamin B ₉)
Thiamine pyrophosphate	Aldehydes	Thiamine (vitamin B ₁)

organic
or
metalloorganic

Coenzymes are further divided into two types

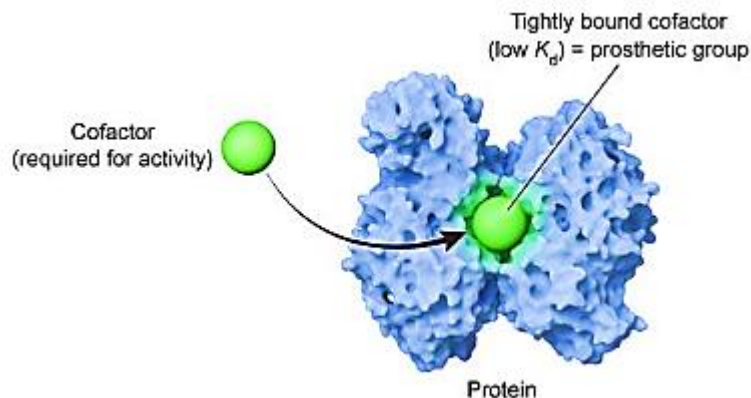
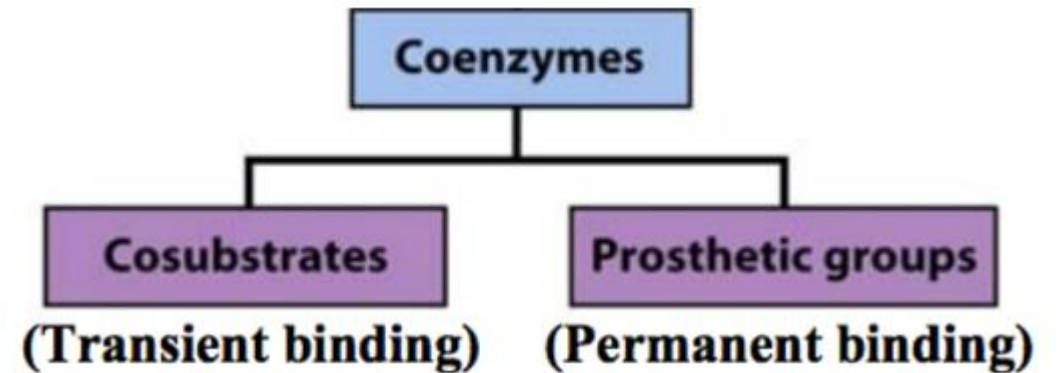
Prosthetic group: coenzyme that is **tightly** (or even **covalently** and, therefore, **permanently**) **bound** to the **enzyme**.

مؤقتة

Cosubstrates are **transiently** bound to the **protein**. Cosubstrates may be released from a protein at some point, and then **rebind** later.

مؤقتة، RNA، بروتين،
بشكل عام

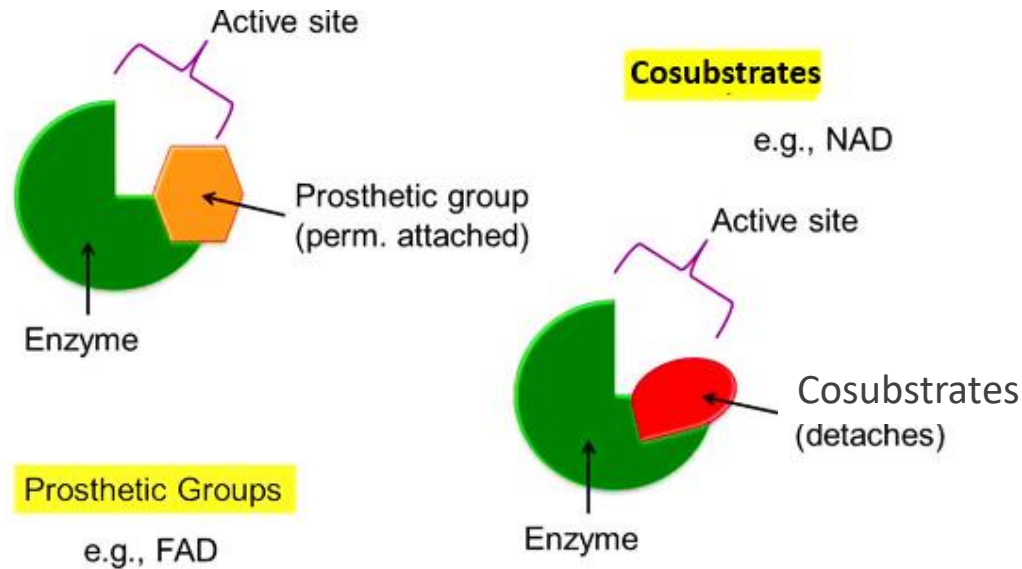
Both prosthetic groups and cosubstrates have the **same function**, which is to **facilitate** the **reaction** of enzymes and proteins.





Key Differences Between Prosthetic Groups and Cosubstrate

Feature	Prosthetic Group	Cosubstrate
Binding	Tightly bound (often covalent)	Loosely bound (non-covalent)
Release	Remains attached to the enzyme	Released and regenerated
Function	Permanent part of the enzyme	Acts as a carrier or shuttle
Examples	Heme, FAD, biotin	NAD ⁺ , CoA, ATP





Holoenzyme vs. Apoenzyme

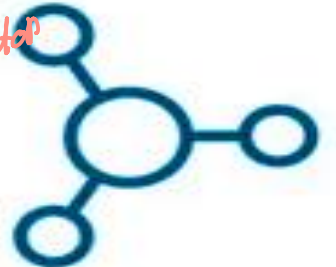
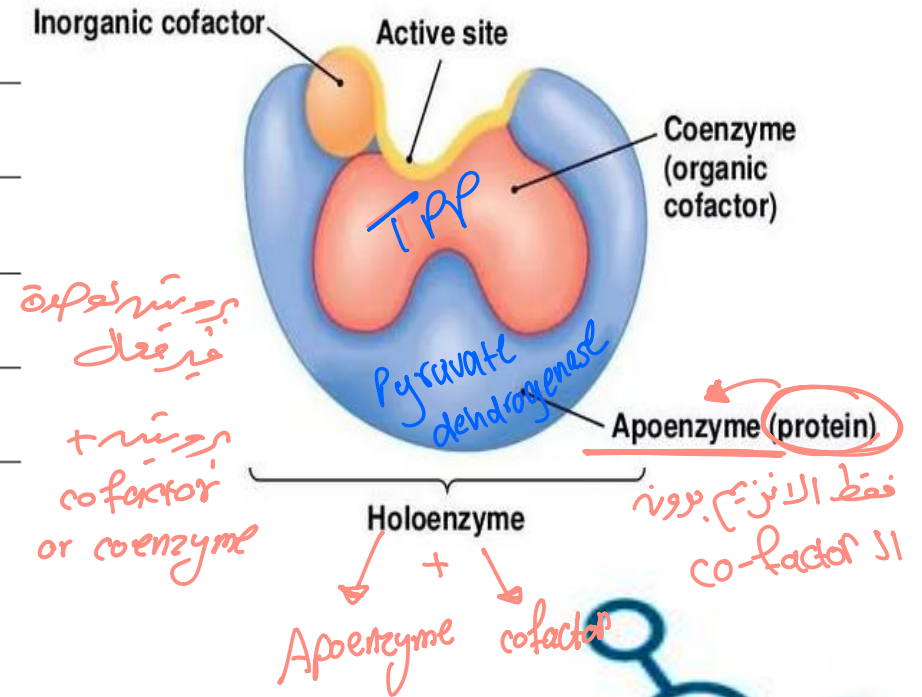


Apoenzyme: The protein part of the enzyme, inactive without its cofactor/coenzyme.

Holoenzyme: The active enzyme complex (apoenzyme + cofactor/coenzyme).

Example: Pyruvate dehydrogenase is a holoenzyme requiring thiamine pyrophosphate (TPP) as a coenzyme.

Enzyme Type	Requires Cofactor?	Term to Use
Enzyme without cofactor	No	Enzyme (e.g., lysozyme)
Enzyme with cofactor (inactive without it)	Yes	Apoenzyme (inactive form)
Enzyme with cofactor (active with it)	Yes	Holoenzyme (active form)





Active Site and Substrate

1. Active Site:

A specialized region of the enzyme where the substrate binds and the reaction occurs.

Provides a unique microenvironment (e.g., specific pH, charge distribution) to accelerate the reaction. لتسريع التفاعل

يوفر الظروف المناسبة
للمركب substrate
ليسير التفاعل

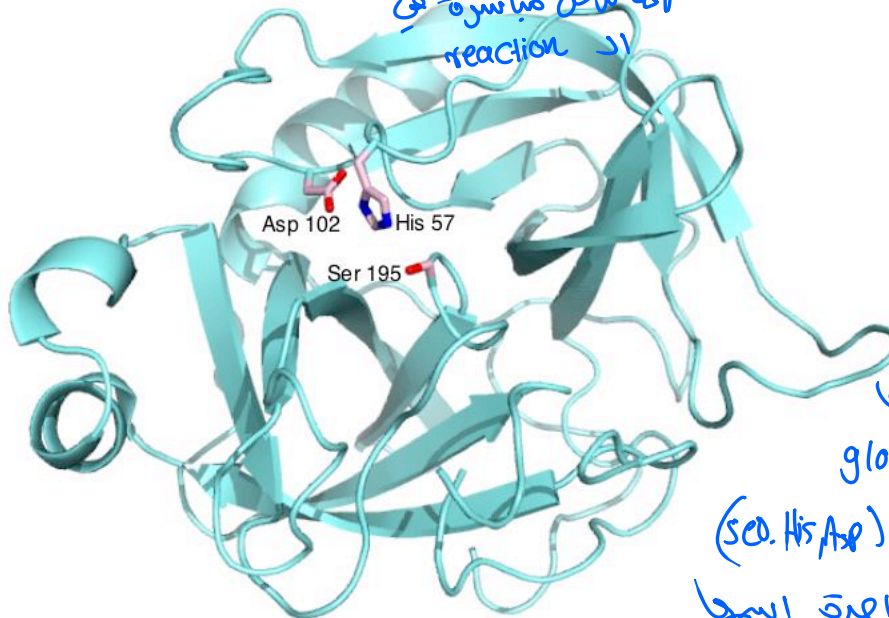
Contains catalytic residues that participate directly in the reaction.

Example: Chymotrypsin catalytic triad (Ser195, His57, Asp102).

amino acids residues

serine
↓
رقم
موقع
الارتباط

Histidine Aspartate



البروتين
Conformational
changes

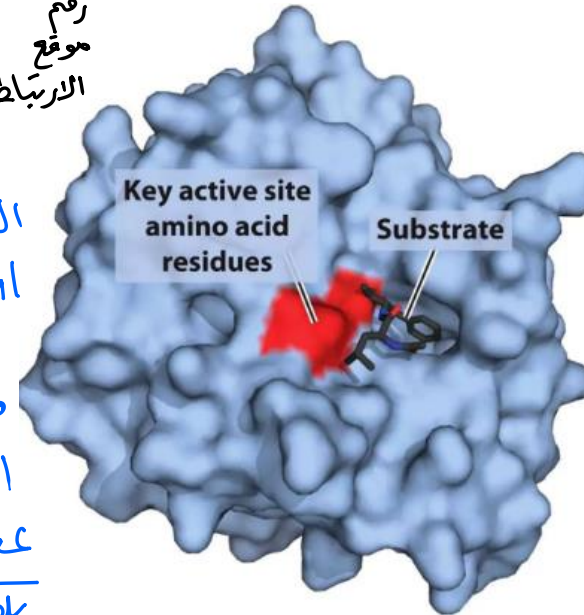
وتغير شكله
الأجسام و globular

عنه (Ser, His, Asp)

يكونا منطقة واحدة اسمها

Active site

substrate وليس التفاعل





Active Site and Substrate



2. Substrate

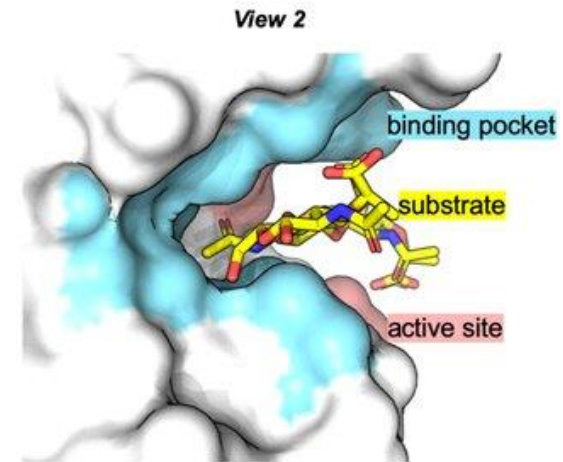
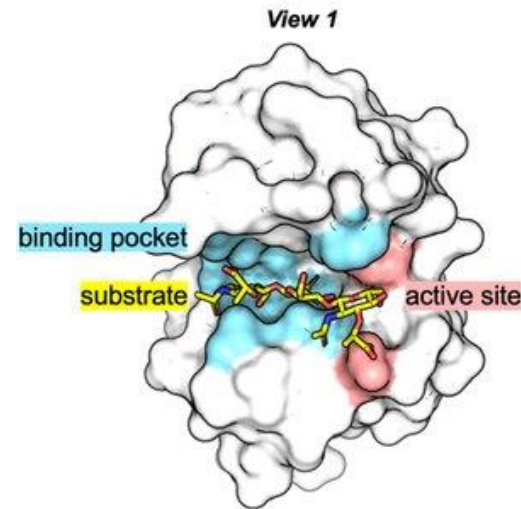
The specific molecule that binds to the active site and is transformed into the product(s).
 Binding is highly specific due to complementary shape and chemical properties. →

المسبب مع ارتباطه
مع الموقع

Example: Glucose is the substrate for hexokinase.

Lysozyme has negatively charged residues in its active site that bind to the positively charged regions of its polysaccharide substrate.

Binding groove and active site of lysozyme





Cellular distribution of enzymes



تُصنع وتُستعمل في داخل الخلايا

Intracellular enzymes: Produced and act inside the cells e.g. metabolic enzymes.

تُصنع داخل الخلايا

Extracellular enzymes: Produced inside the cells and act outside

the cells e.g. digestive enzymes.

و يُصلحها
visceres إلى خارج الخلايا
exporte بواسطة

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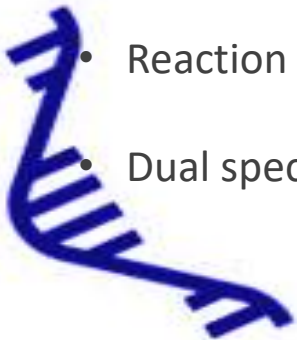




Enzyme specificity



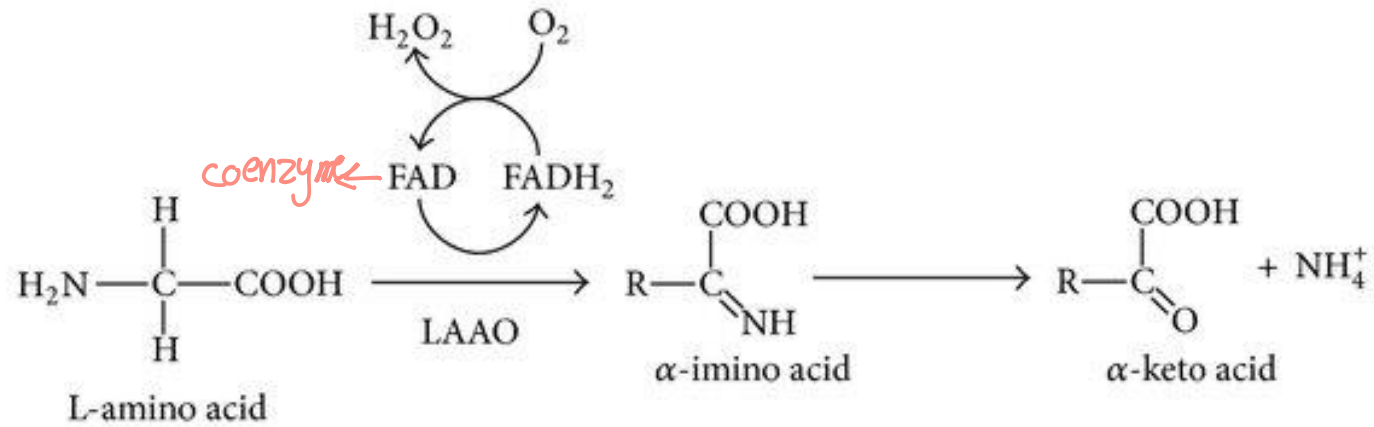
- Enzyme specificity refers to the ability of an enzyme to selectively recognize and catalyze a particular substrate or a group of substrates. There are several types of enzyme specificity, each describing a different level or type of selectivity
- Optical (stereo) specificity
- Group specificity
- Absolute specificity
- Relative specificity
- Reaction specificity
- Dual specificity



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Optical (stereo) specificity



- Enzymes act on one of 2 isomers
- L-amino acid oxidase acts only on L-amino acids, not D-amino acids.
- D-lactate dehydrogenase acts only on D-lactate, not L-lactate.



Group specificity



Hexokinase

على رقم 6 في
جزيء السكر
functional
group
(OH)

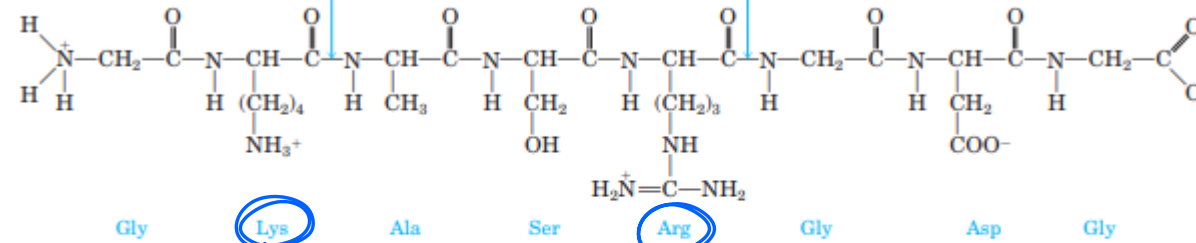
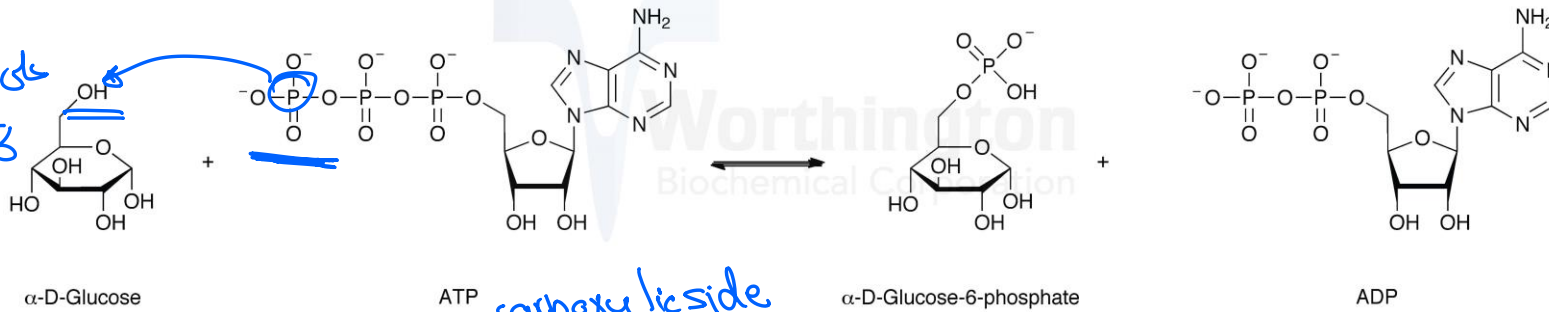


FIGURE 15.1 A typical amino acid sequence. The enzyme trypsin catalyzes the hydrolysis of this chain only at the points marked with an arrow (the carboxyl side of lysine and arginine).

نوع معين من الارتباط الكيميائي

The enzyme acts on a specific functional group or chemical bond within a group of structurally related substrates.

- Example: phosphorylation على رقم 6
- Hexokinase phosphorylates hexose sugars (e.g., glucose, fructose) at the 6th carbon.
- Trypsin cleaves peptide bonds on the carboxyl side of basic amino acids (lysine and arginine).



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ما یسختی ای علی ما زی
فقط تفسیر

Absolute specificity



Urea

amoniak

One enzyme acts only on one substrate e.g. urease enzyme acts only on urea.



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Relative specificity

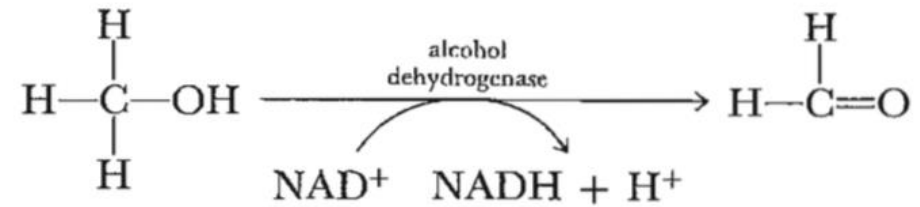
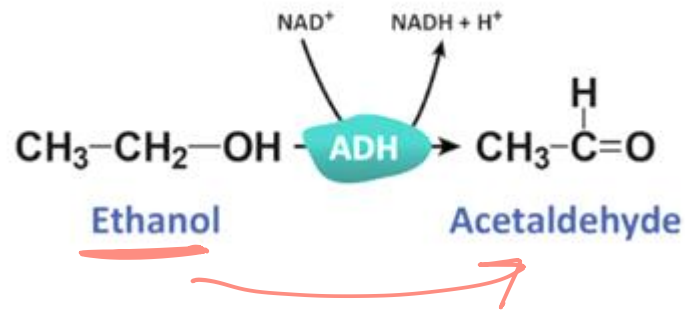
يعني اى range هذا

الإنزيم هو الكحوليات

Acts on a range of related substrates.

Example: Alcohol dehydrogenase oxidizes various alcohols.

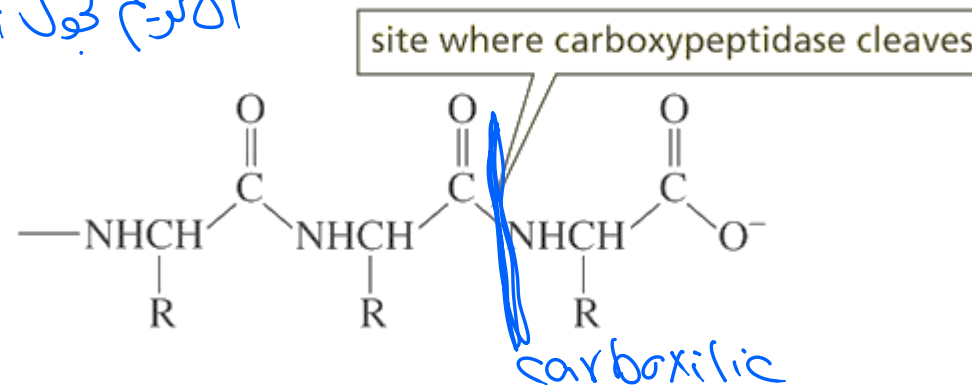
Carboxypeptidase cleaves amino acids from the C-terminus of various peptides.



methanol → *Formaldehyde*

corresponding aldehyde

الإنزيم يحوّل الكحول إلى

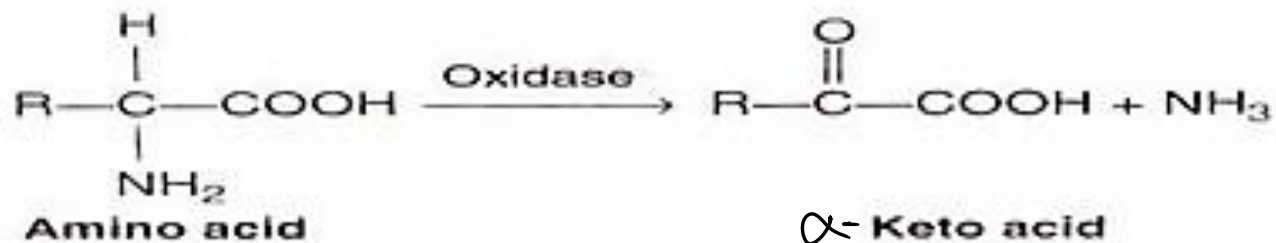


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Reaction specificity



بغني مائة مئة تقدر تخدم بأكثر من تفاعل يعني الهاكتريسه انزيم ممكنه كل تفاعل لواله ما نوع خاص فيه

- The same substrate can undergo different types of reactions, each catalyzed by a separate enzyme and this is referred to as reaction specificity.

نزع NH_2

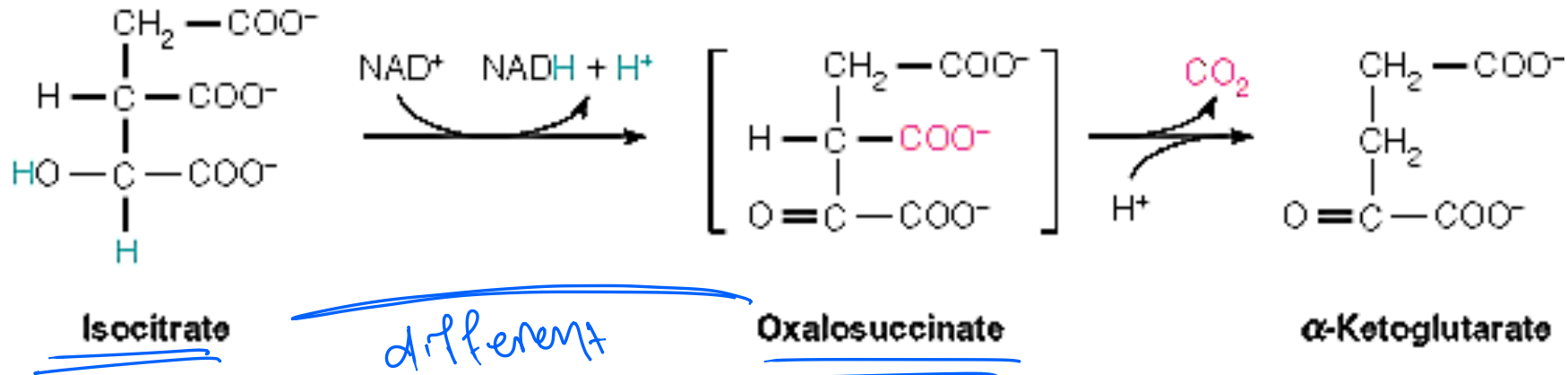
نزع NH_2 من الحمض

نزع COOH

- An amino acid can undergo transamination, oxidative deamination, decarboxylation etc. The enzymes are different for each of these reactions.



Dual specificity



One enzyme acts on 2 different substrates e.g. isocitrate dehydrogenase enzyme acts on isocitrate and oxalosuccinate.

عَنِ عِيَالِي خَطْوَيْهِ مُتَلَفَتَيْنِ يَقُومُ لِحَا نَفْسِ الْاِتْرَاعِ وَلِلَّهِ
الْاِتْرَاعُ يَقُومُ بِقَوْلِ مَادَتَيْنِ مُتَلَفَتَيْنِ

Zymogens

يعني الانزيم يتم تصنيع على صورة غير نشطة لانه غالباً ان active site يكون مغطى

Zymogens (or proenzymes) are inactive precursors of enzymes.

They are synthesized in an inactive form to prevent unwanted enzymatic activity within the

cell or during secretion. تمنع نشاط الانزيم الا غير مرغوب فيه و زي الانزيم الي بلس البروتينات في خلاصون الخلية و ولله طما الخلية حية بصير الانزيم inactivation عشان ما بلس البروتينات الخلية

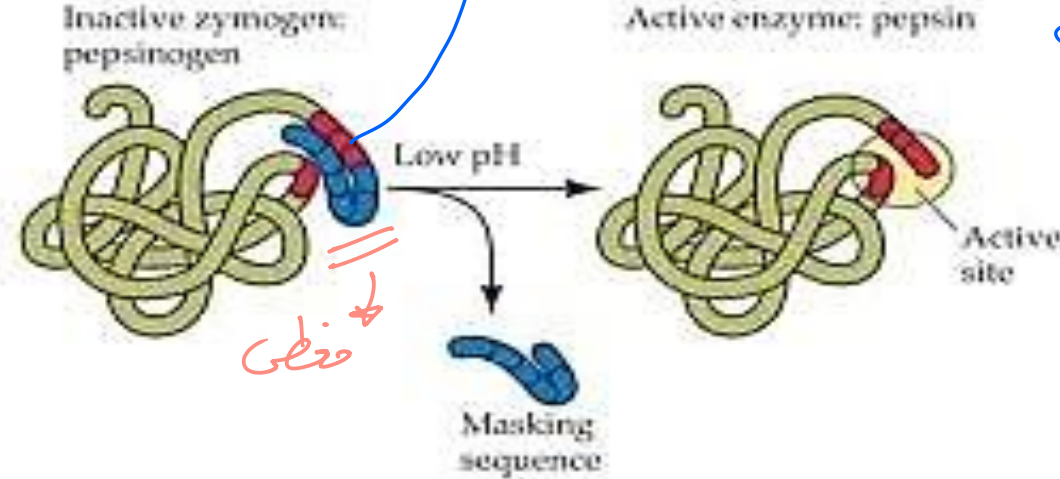
Activation of zymogens occurs through proteolytic cleavage or changing the configuration,

where a portion of the polypeptide chain is removed to expose the active site.

يعني الانزيم منه
تتغير حركته
الروابط الكيميائية حيث
يصير expose

Proteolytic cleavage
عشان يفر الانزيم اخر منه سبب

تتغير منه polypeptides بصير انه
pH او



Zymogens

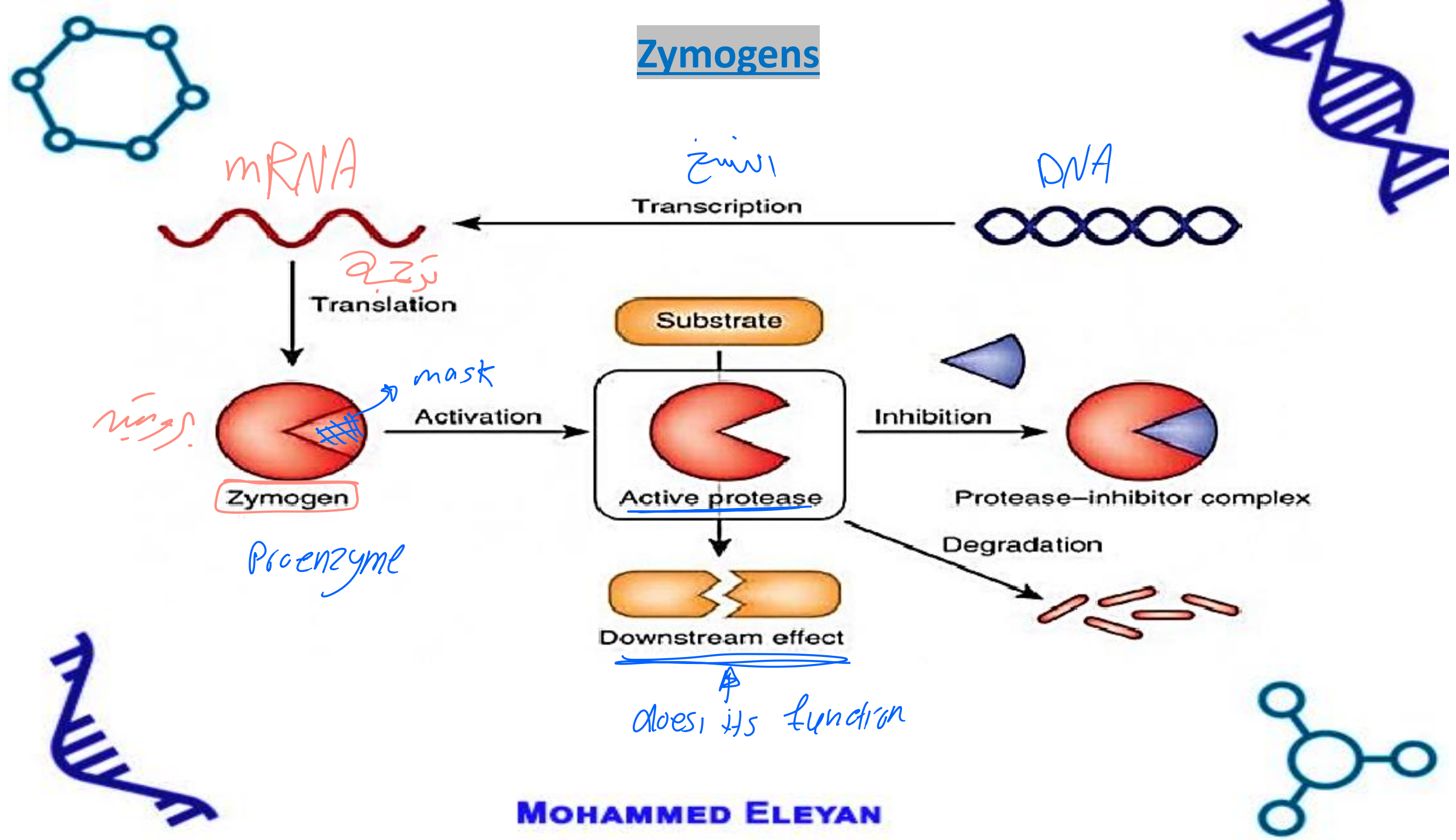




Table 14.1 Gastric and pancreatic zymogens

Site of synthesis	<u>Zymogen</u>	Active enzyme
<u>Stomach</u>	<u>Pepsinogen</u>	Pepsin
Pancreas	<u>Chymotrypsinogen</u>	Chymotrypsin
Pancreas	<u>Trypsinogen</u>	Trypsin
Pancreas	Procarboxypeptidase	Carboxypeptidase
Pancreas	Proelastase	Elastase





Thanks Part 1



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Chapter I

Introduction

I- Enzymology:

Enzyme terminology:

- Kinase = Phosphate transfer $ATP \rightarrow ADP + P_i$ أو $GTP \rightarrow CDP + P_i$

- Phosphatase = Remove phosphate from a substrate

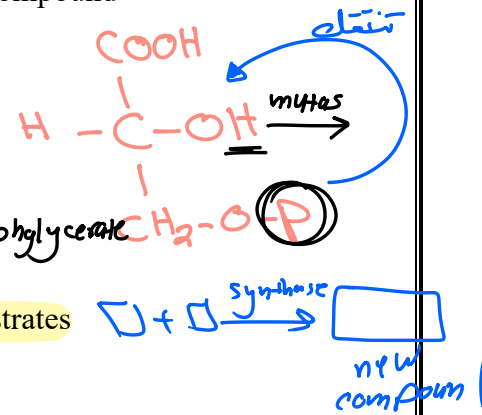
- Dehydrogenase = Add or remove hydrogen molecules from a compound

- Hydroxylase = Add hydroxyl group to a substrate

- Carboxylase = Transfer COOH group CO_2

- Mutase = Relocate a side group in the same substrate

- Synthase/synthetase = Synthesize a product from different substrates

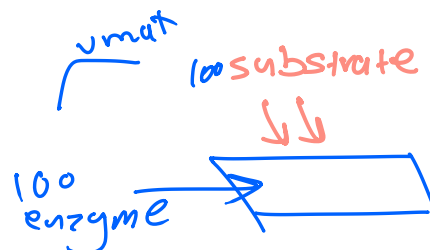


Maximum velocity (V_{max})

Def: the point where any further increase in the amount of substrate causes no increase in the velocity of the reaction (Fig.1: A).

Michaelis constant K_m

- Def:** It is substrate concentration that produces half maximum velocity ($\frac{1}{2} V_{max}$) (Fig.1: B).
- K_m reflects the affinity of the enzyme for the substrate.
- K_m is used to compare the affinity of different enzymes to the same substance.



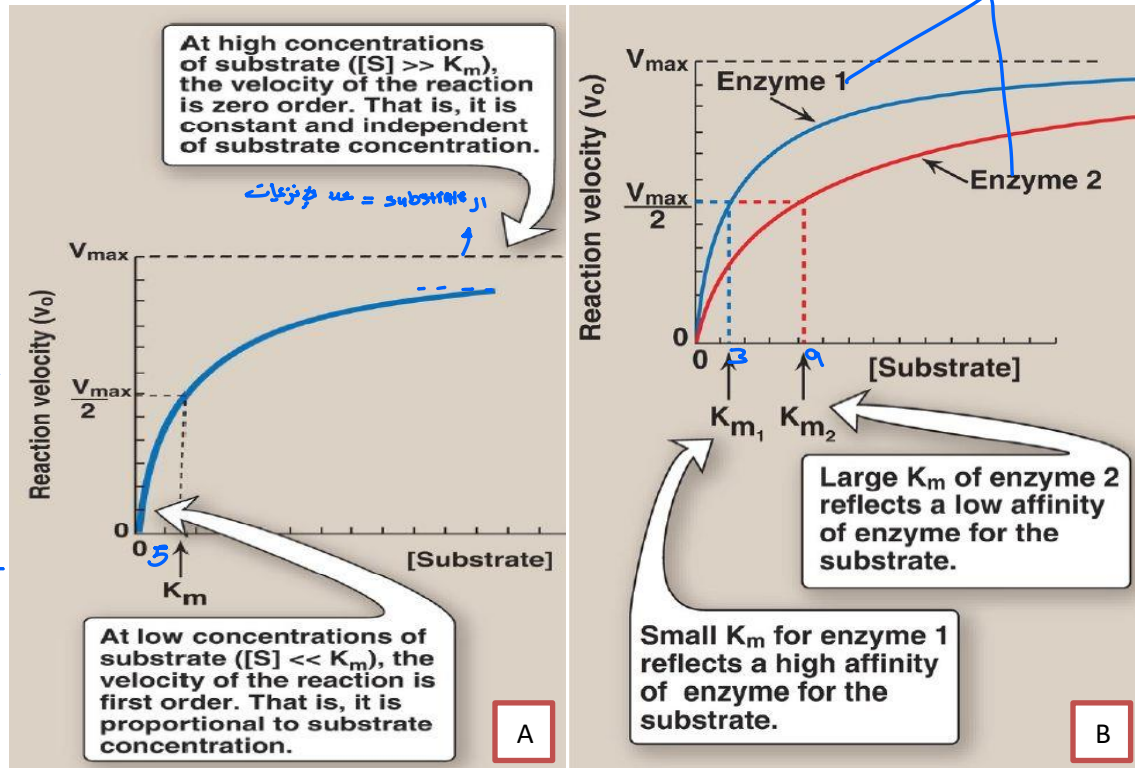


Fig.1: A. Maximum velocity & Michaelis constant; B. V_{max} & K_m vs affinity

Example Hexokinase and glucokinase

Affinity $\propto 1/k_m$

- Low k_m & V_{max} reflects a high affinity of the enzyme for substrate i.e. low of concentration of substrate is needed to half saturate the enzyme.
- High k_m & V_{max} reflects a low affinity to the enzyme for substrate i.e. high concentration of substrate is needed to half saturate the enzyme.

II- Transport Across a Cell Membrane

1. Passive transport:

- The movement of substances across a cell membrane without the input of energy,
 ↳ from an area of higher concentration to an area of lower concentration.

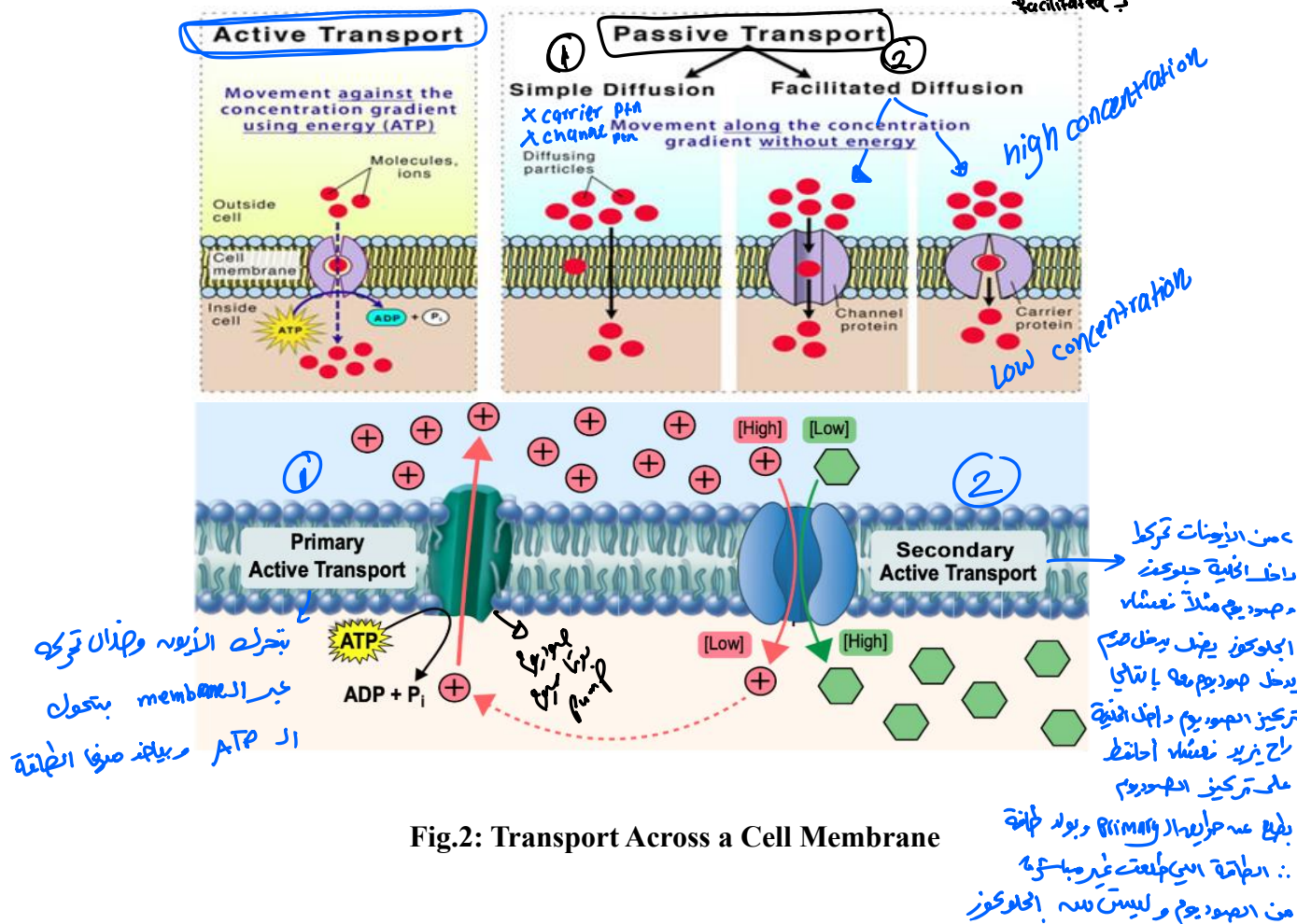
ion $\rightarrow$ from an area of higher concentration to an area of lower concentration
along concentration gradient

2. Active transport:

- The movement of substances across a cell membrane against their concentration gradient, from an area of lower concentration to an area of higher concentration.

This process requires the input of energy, usually in the form of ATP.

➤ **Secondary active transport:** The transport of an ion (glucose) in the direction of its increasing electrochemical gradient coupled to the facilitated diffusion of a second ion (Na^+) in the direction of its decreasing electrochemical gradient (Fig.2).



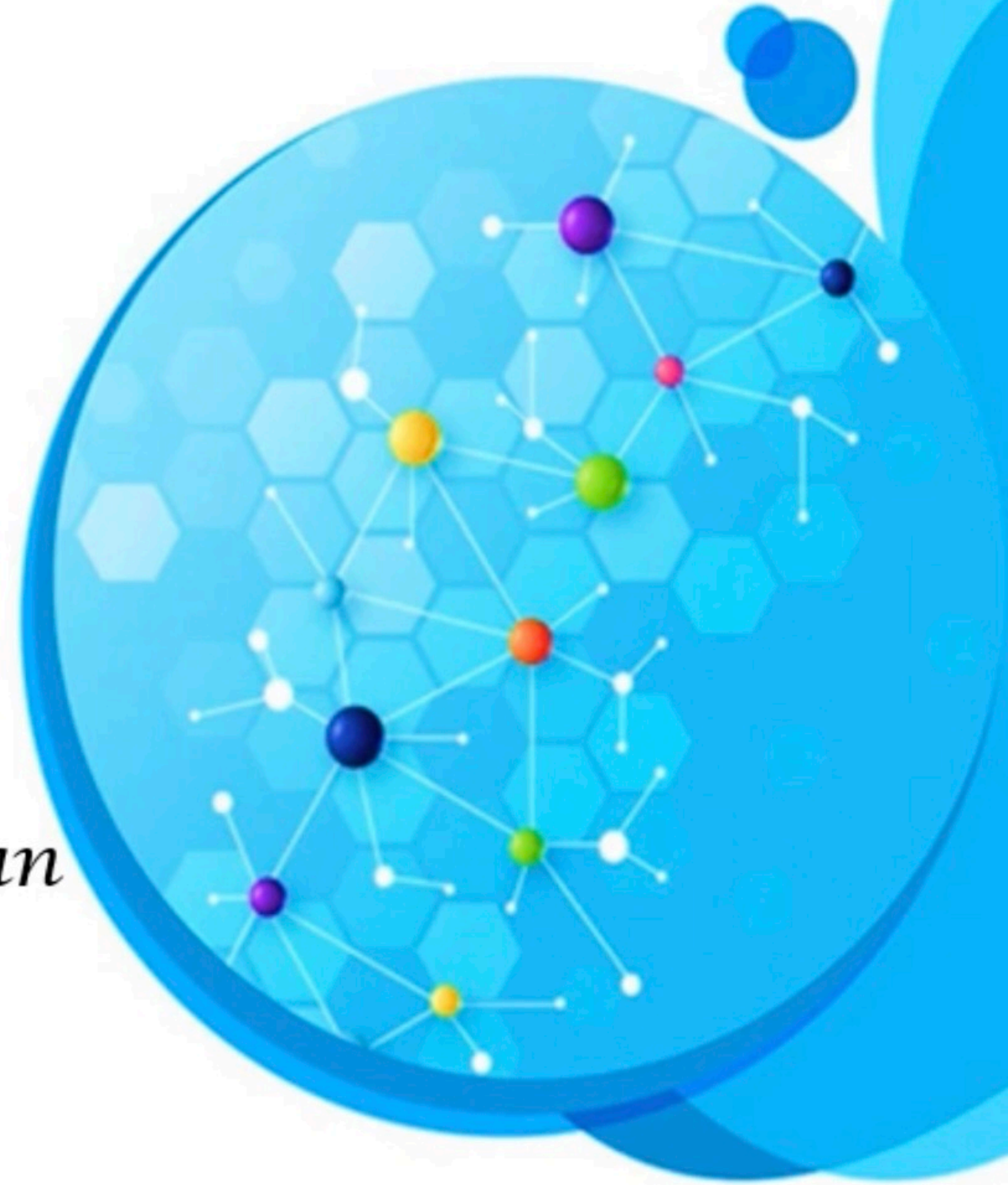
Medical Biochemistry

Carbohydrate Metabolism

Asst. Prof. Mohammed Hasan Eleyan

Faculty of Medicine

Al-Azhar University-Gaza



السكراتيد
glycose

Food → Starch → digestion by GIT → 2 glucose
 Food → Lactose → " " " → galactose + glucose
 Food → Sucrose → " " " → Fructose + glucose

① galactose ② Fructose → conversion by liver → glucose → ^{تجزئ} ^{التي يوصلها إلى الأجزاء}

Fate of glucose

^{عنية الهضم} Catabolism → ^{بسرعة} glucose → ^{ATP}

^{عليه بناء} Anabolism → ^{يستخدم الـ glucose} ^{عشان} ^{أنتج مواد ثانية}

	① Oxidation pathways	② Storage	③ Conversion
Major	Glycolysis (Production of Acetyl Co-A).... <u>ATP</u>	Glycogenesis (liver & Muscles)	lipogenesis
Minor	1. <u>Pentose phosphate pathway</u> 2. <u>Uronic acid pathway</u>	glycogen	lipid أو Protein

أدخل الـ glucose في

عشان أنتج الـ
 1- Pentose phosphate
 2- Uronic acid

Fate ^{التي بتحكم بدار} → Body need

- كمية قليلة → ATP ^{بدني}
- كمية كبيرة → storage ^{بدني أعمل}
- كمية كبيرة جداً → Lipid + protein ^{بدني أحول الـ glucose لـ}

oxidation ^{تعمل} ^{في كبد} ^{على}
 مجموعة الألدومل الموجودة في السكر (CHO) حتى تتحول
 لمجموعة كربوكسيلية (COOH) ^{بشقة من السكر}

Introduction:

بعض السكريات (الأحادية) هي آخر شيء يخرج من عملية الهضم (أبسط نوع)

- The end products of carbohydrate digestion are monosaccharides: glucose, galactose and fructose.
- They are absorbed from the jejunum to portal veins to the liver, where fructose and galactose are transformed into glucose.
- Two mechanisms are responsible for absorption of monosaccharides: active transport and passive transport

process of conversion of 1 glucose to 2 molecule of pyruvate.

↑ Glycolysis (Embden Meyerhof Pathway) (major pathway)

• Definition: Breakdown of glucose:

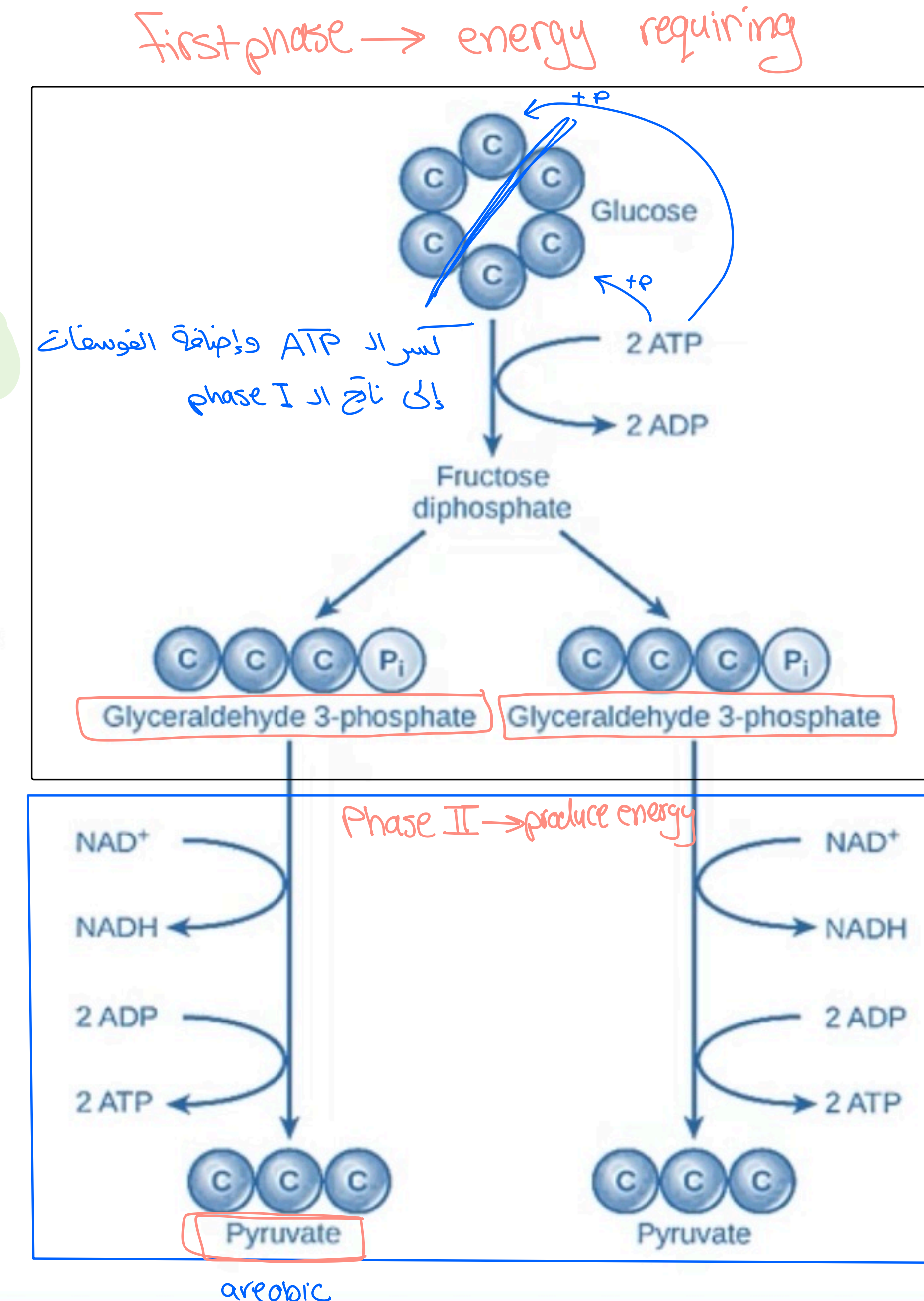
1. Into 2 molecules of pyruvate aerobically[↑] (in the presence O₂ and mitochondria) OR
2. Into 2 molecules of lactate anaerobically (in the lack of O₂ or absence of mitochondria).^{Ex. RBCs + severe exercise}

→ تحدث في

- Site: Essentially all cells carry out glycolysis in the cytosol.

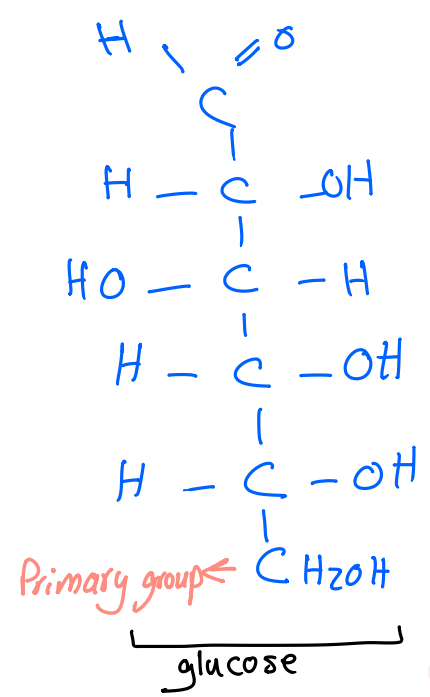
The Overall Pathway of Glycolysis

- Glycolysis is divided into two phases.
 - The first phase converts glucose to two glyceraldehyde-3-phosphates and is the energy requiring phase.
 - The second phase conversion of two molecules of glyceraldehyde-3-phosphate into pyruvate (aerobic glycolysis) or lactate (anaerobic glycolysis) and is the energy producing phase.

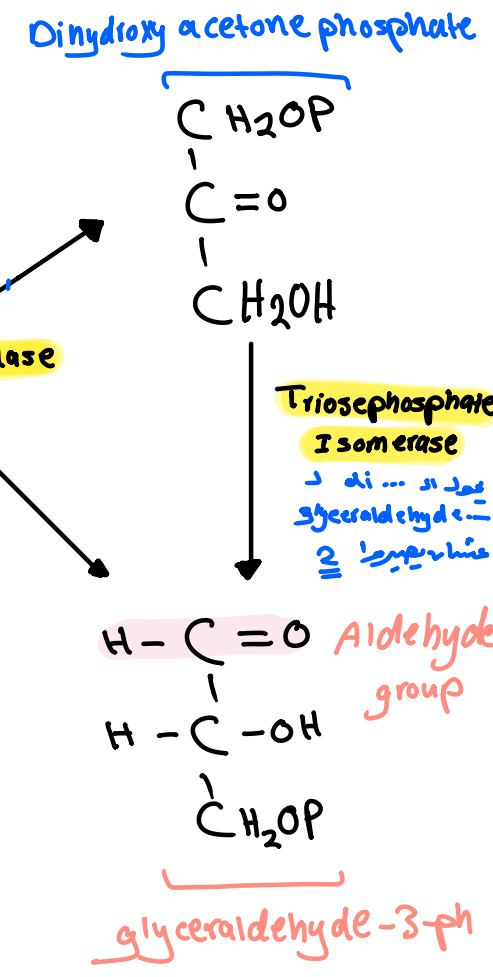
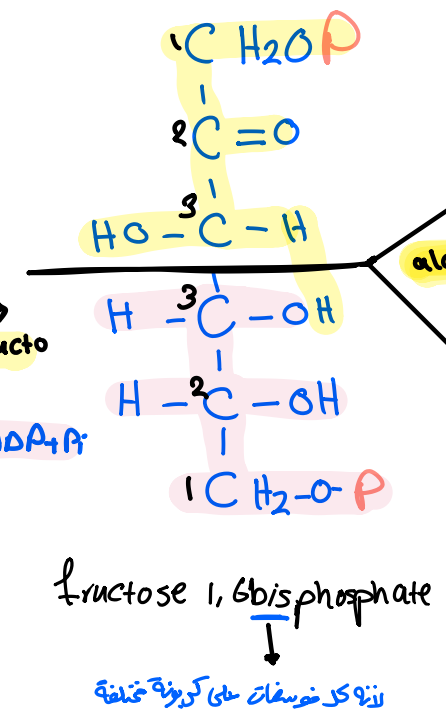
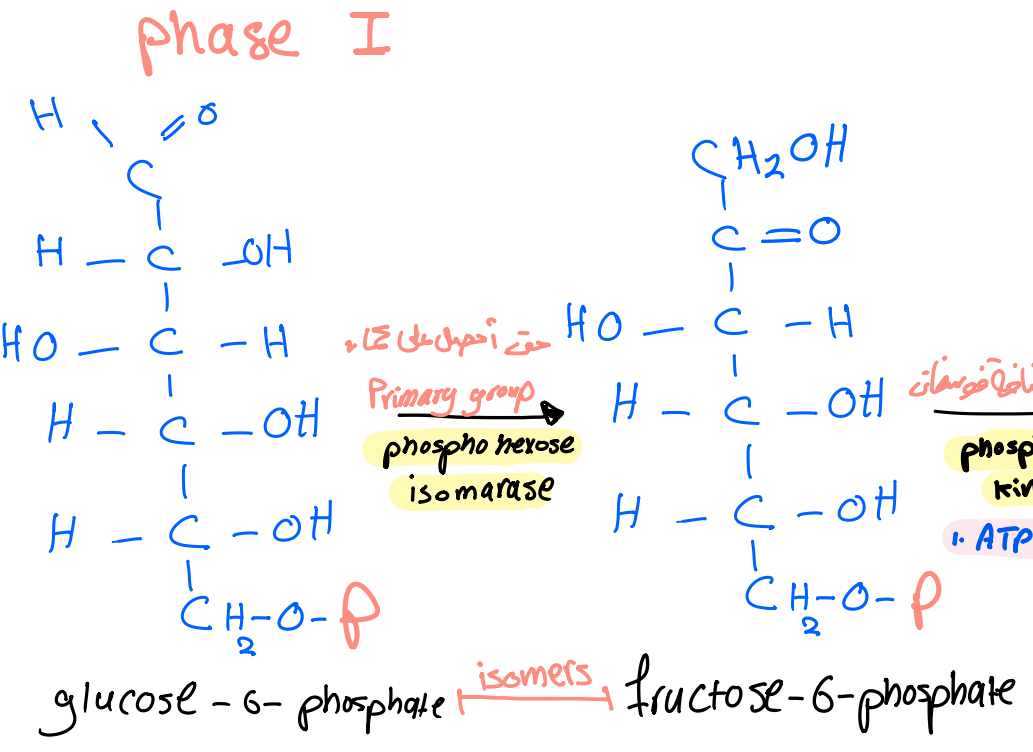


Trapping the glucose in the cell by Adding charge on it "phosphate"

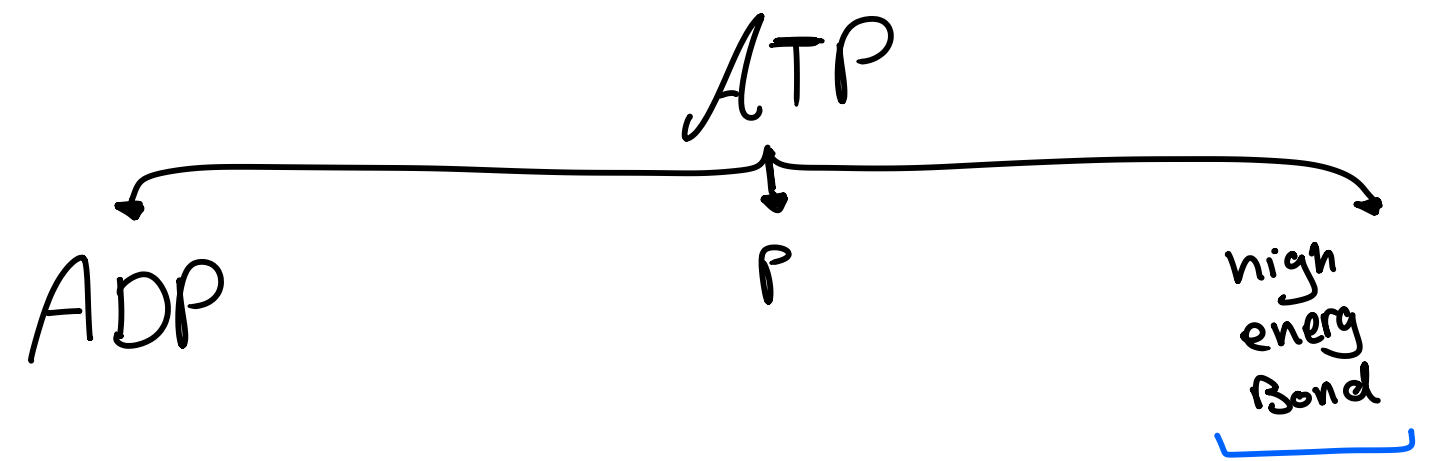
نفسر وصمّر
↑
بشبكة
في الكلية
بصفا
موسلات



علاقة قايمة
Hexokinase
أو
glucokinase
liver & oad
1. (Mg) → coenzyme
2. ATP → ADP + P_i

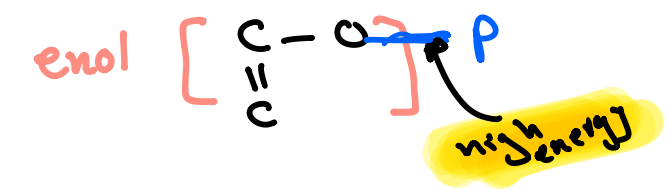


NOTES

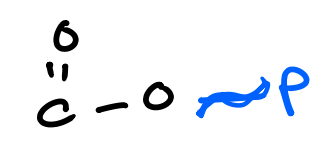


الرابطة الي لما نحلها
hydrolysis
بتعطيني 3 energy x أكثر من 7.3 kcal/mol

Ex: Enol phosphate Bond

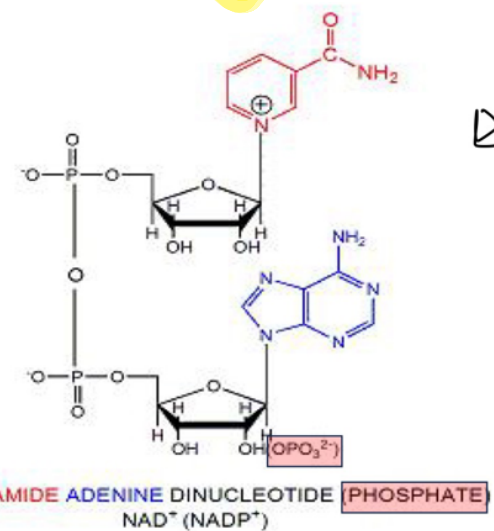
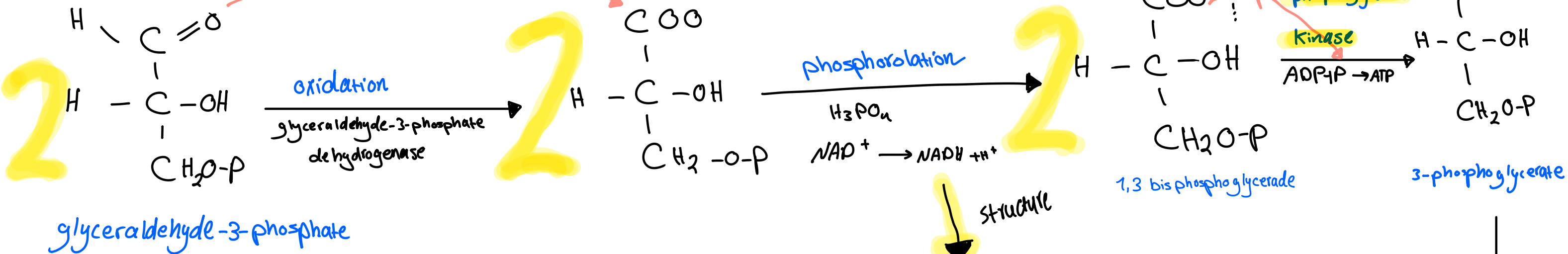


carboxyl phosphate Bond



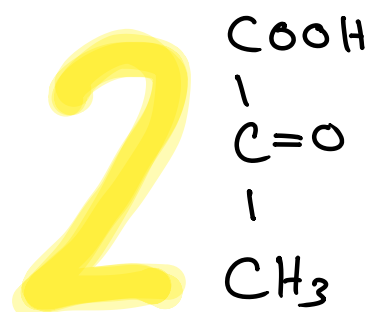
Phase II

يقل الأستيل إلى مجموعة كربوكسيل مشبعة أضيف مجموعة الفوسفات

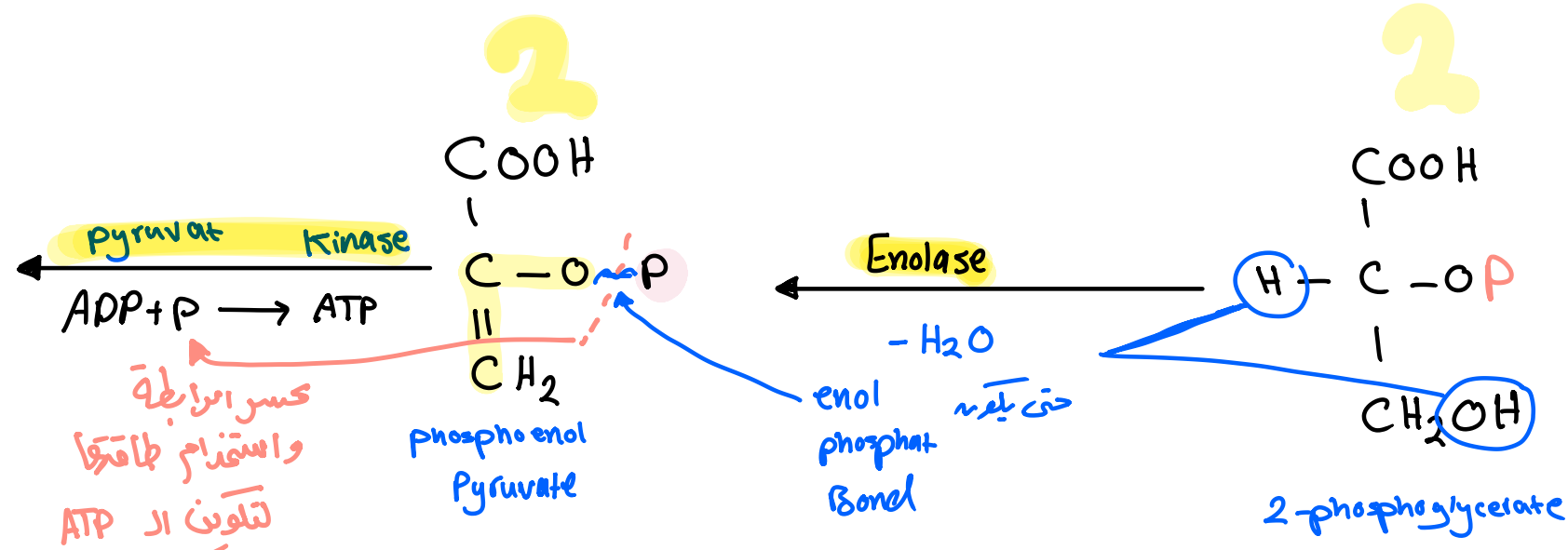
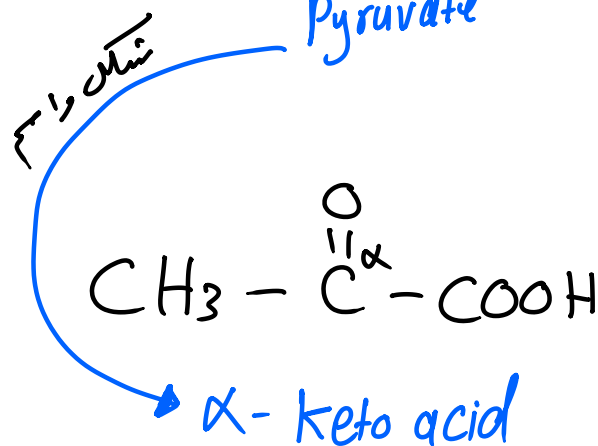


حتى
أكون
High
energy
Bond
تالية

+ 2ATP

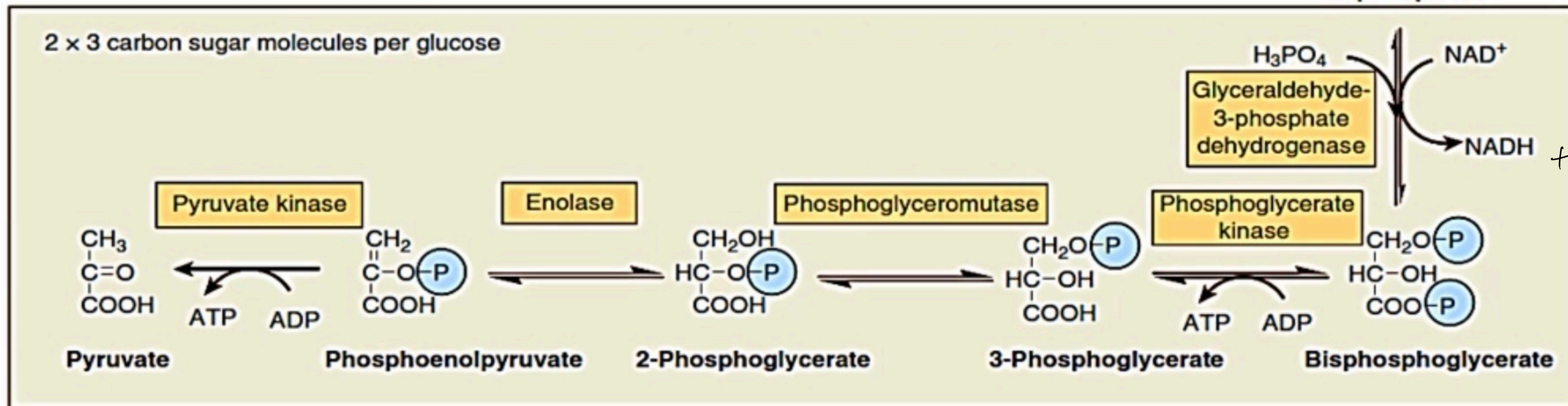
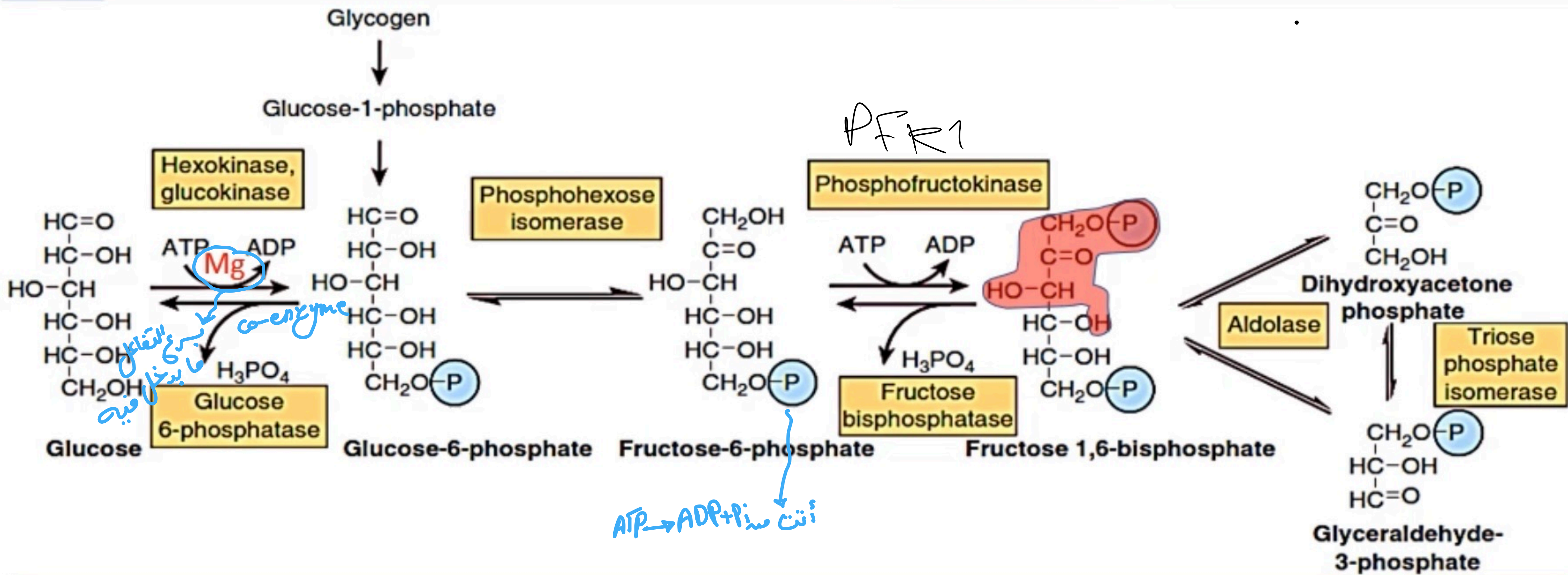


Pyruvate



نقل الـ P من C3 إلى C2

المركبات الأساسية في structures في التسلسل

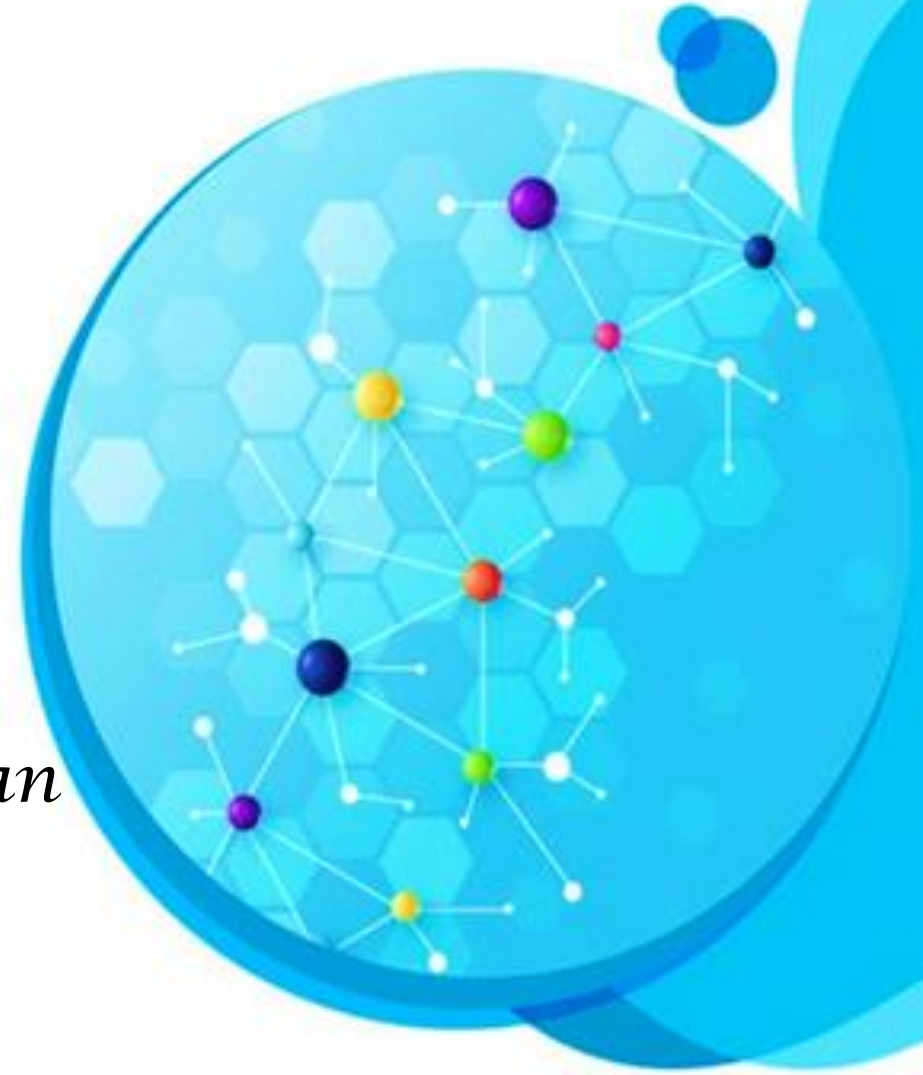


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Faculty of Medicine

Al-Azhar University-Gaza



Important Notes

Glycolysis Enzymes and substrates

BPG mutase (Enzyme)

- It is found in RBCs

من 1,3 BPG | يتقل ارتباط الأوكسجين مع الهيموغلوبين بالتالي والنسيج يحتاجه بقدرة عالية

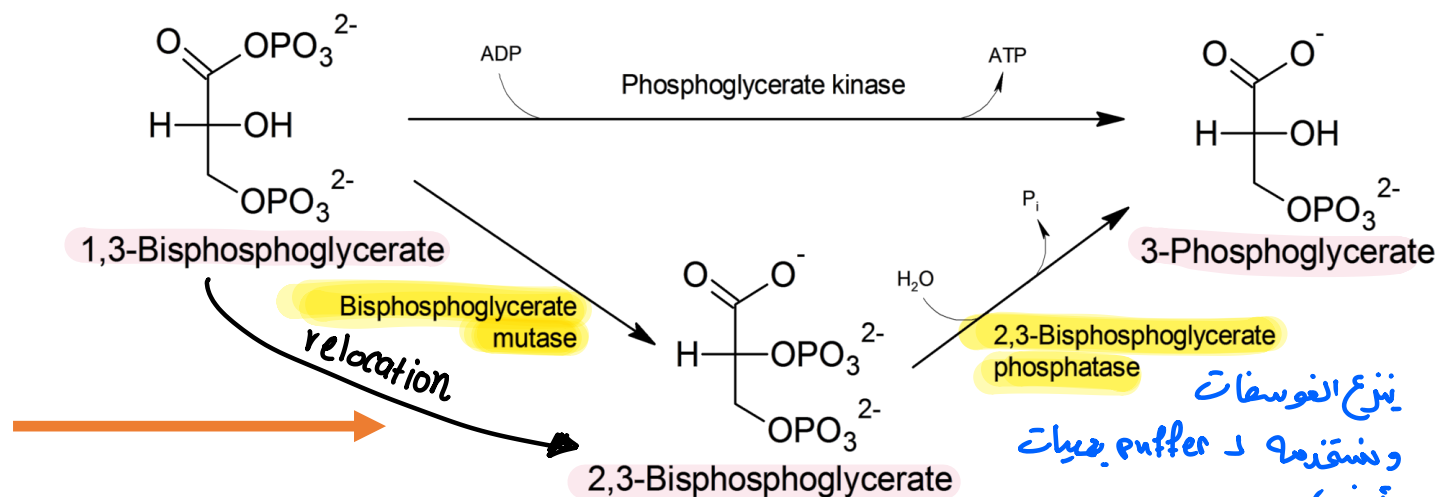
- It forms 2, 3 BPG which Facilitates oxygen unloading from hemoglobin (Hb) by

decreasing its affinity to oxygen at tissues

اسمها

Luebering–Rapoport pathway

Luebering–Rapoport shunt



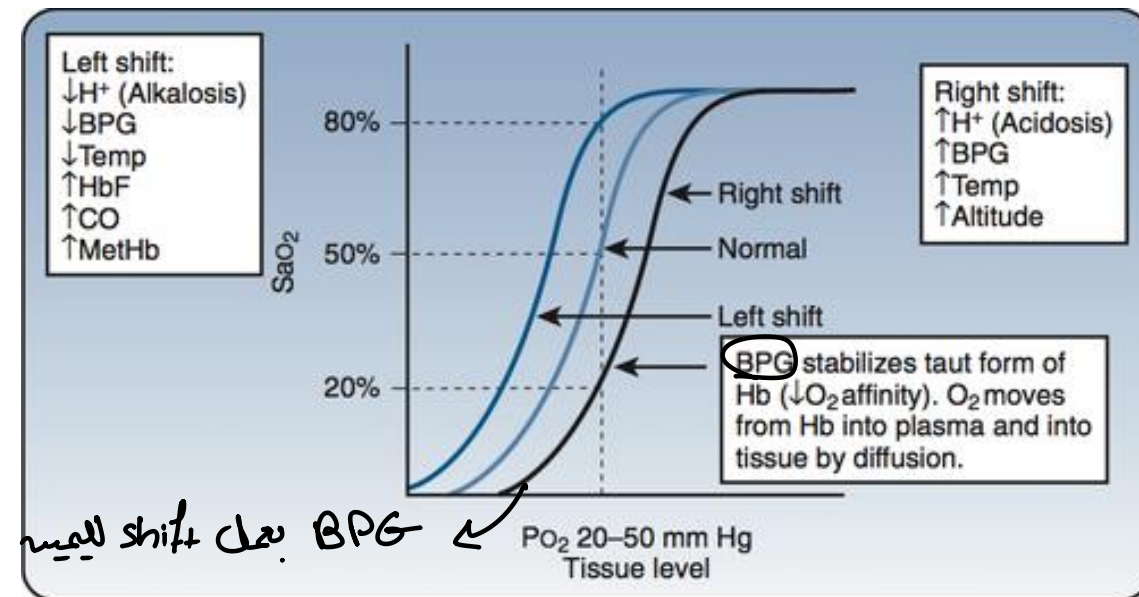
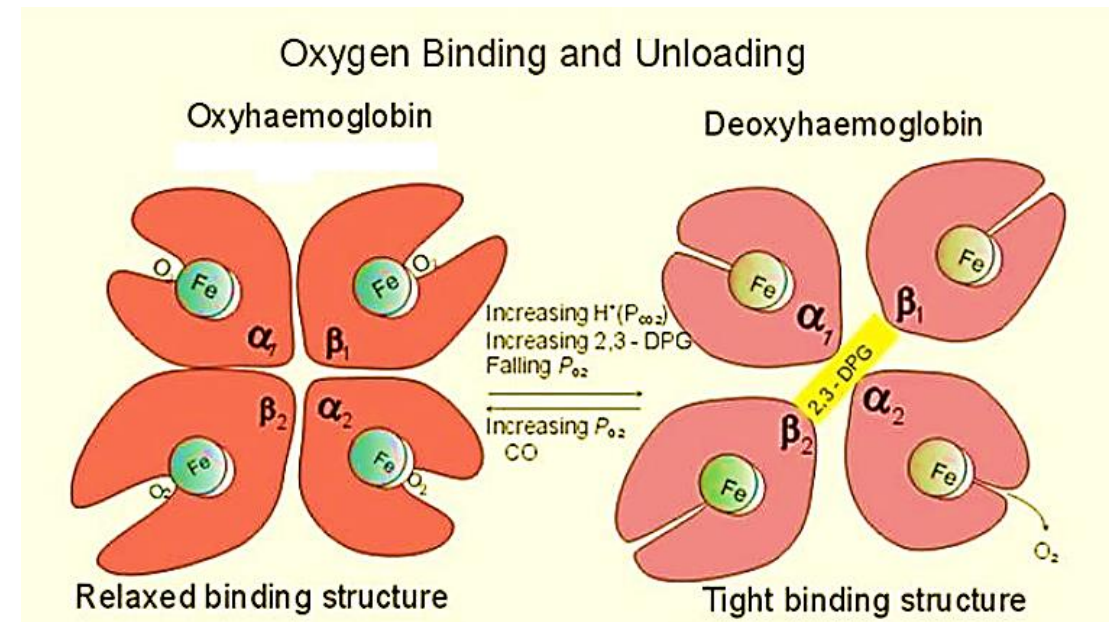
تفرغ الفوسفات
ونستعمله كـ buffer جزيئات
أخرى

BPG mutase (Enzyme)

- When 2,3-BPG binds to hemoglobin, it reduces hemoglobin's affinity for oxygen. This makes it easier for oxygen to unload from hemoglobin and reach the tissues that need it. **See physiology!!.**

بتقل قوة ارتباط الأوكسجين بالهيموغلوبين

بالتالي يصير سهل إنه يرجع للـ tissue التي بحاجة لأكسجين



BPG بعد shift لليمين

Glyceraldehyde-3-PO4 dehydrogenase (Enzyme)

1. It removes H + ion from Glyceraldehyde-3-PO4 and adds Pi.

2. Importance:

A. Formation of 1, 3 BPG with high energy bond.

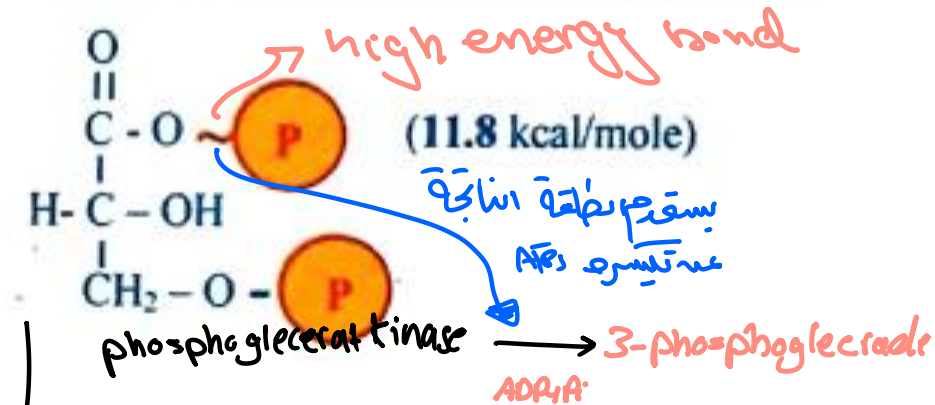
B. Release of NADH which is H⁺ carrier. $NAD^+ + H^+$

- NADH can enter mitochondria in presence of oxygen to form ATP by ETC. (Next side and chapter).

ATP $\rightarrow$ [Electron transport chain] $\rightarrow$ Oxidative phosphorylation Level

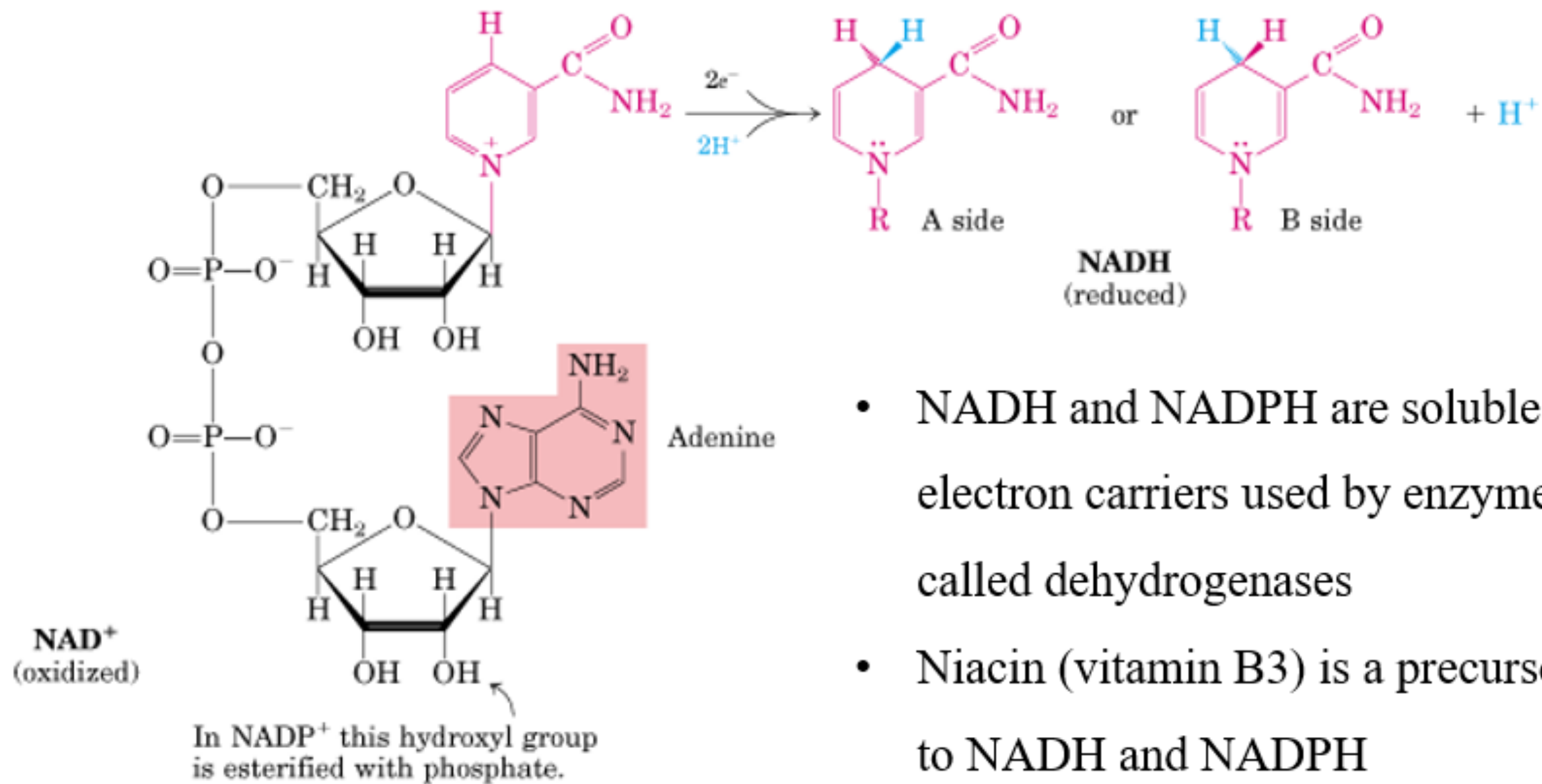
Carboxyl phosphate bond

1,3- Bisphosphoglycerate (1,3 BPG)



② substrate level

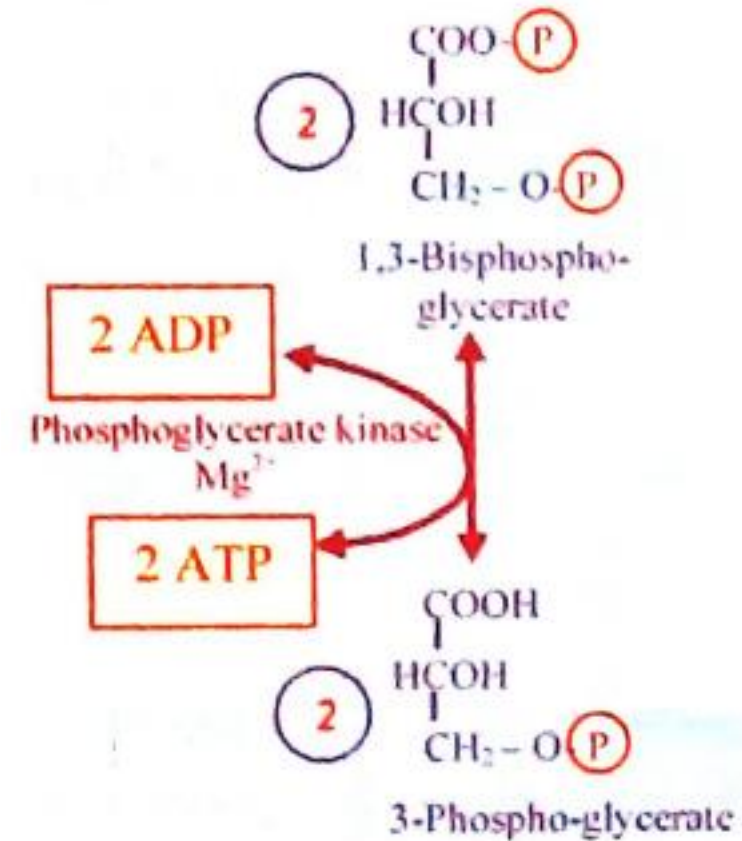
High energy



- NADH and NADPH are soluble electron carriers used by enzymes called dehydrogenases
- Niacin (vitamin B3) is a precursor to NADH and NADPH

BPG kinase or phosphoglycerate kinase (PGK) (Enzyme)

- It breaks high energy bond in 1,3 BPG storing it as ATP.
ATP (12V) → P_i + ADP
- ATP here, is an example of substrate level phosphorylation; ATP formation from substrate not ETC.

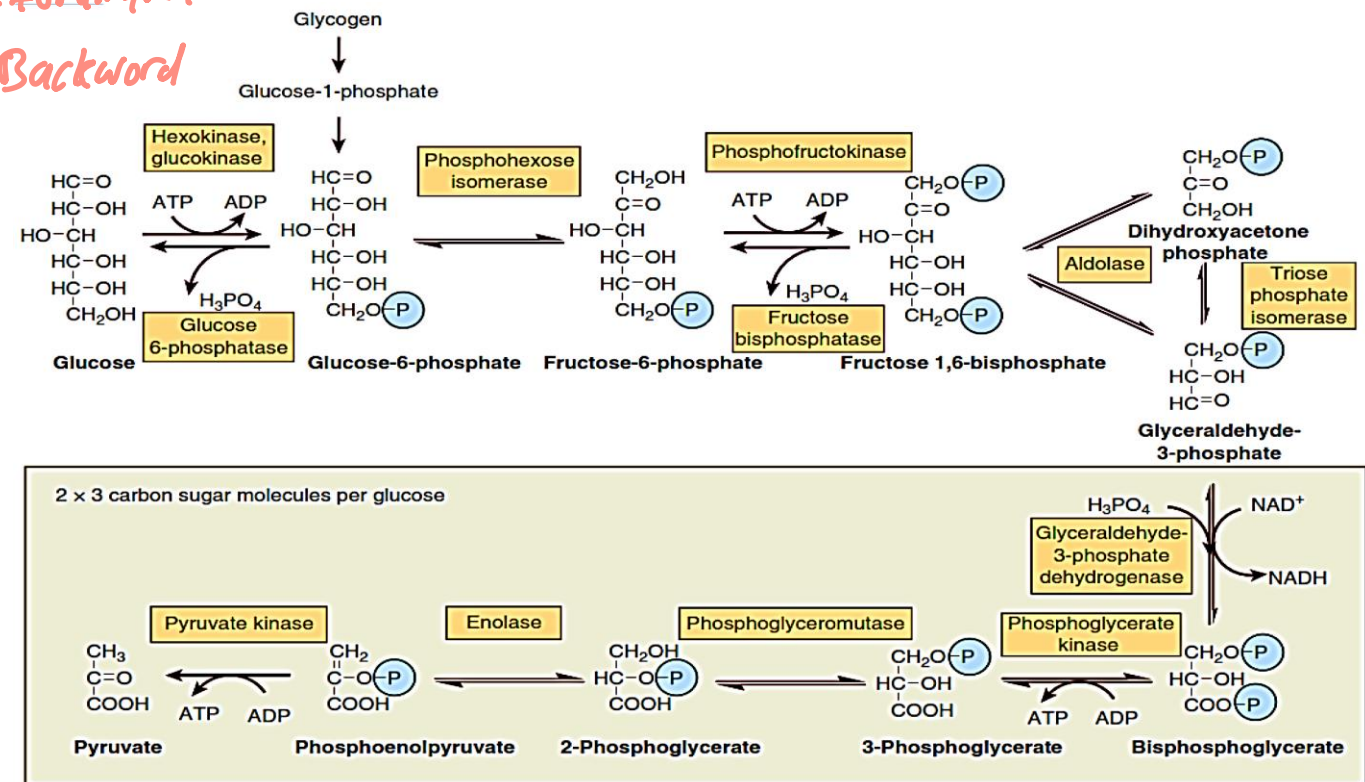


Regulation of Glycolysis

Allosteric and Hormonal Regulation

Regulation of Glycolysis

- Reversible reaction means that the same enzyme can catalyze the reaction in both directions. *Forward* *Backward*
- All reactions of glycolysis - except 3 - are reversible.



Regulation of Glycolysis

- The 3 irreversible reactions (those are catalyzed by kinase enzymes),
- Key enzymes: glucokinase (or hexokinase), phosphofructokinase-I (PFK-I) and pyruvate kinase (PK).

- a) Glucose → Glucose-6-phosphate
- b) Fructose-6-phosphate → F 1,6 Bisphosphate
- c) Phosphoenol pyruvate. → Pyruvate

Hormonal regulation

”وإنتاجها وإكثاف هيموغلوبين في أنسولين“

1. Insulin: Stimulates synthesis of all key enzymes of glycolysis. It is secreted after meal (in response to high blood glucose level). *Feeding state*
عندما ال Insulin يدفع إلى التمثيل في ال glycolysis
2. Glucagon: Inhibits the activity of all key enzymes of glycolysis. It is secreted in response to low blood glucose level. *Fasting state*

ار glycolysis من وذا نغنا ال energy production لو غني كمية كافية من الطاقة بجل
slow down للعزل وبقا من ال glycolysis

Energy regulation:

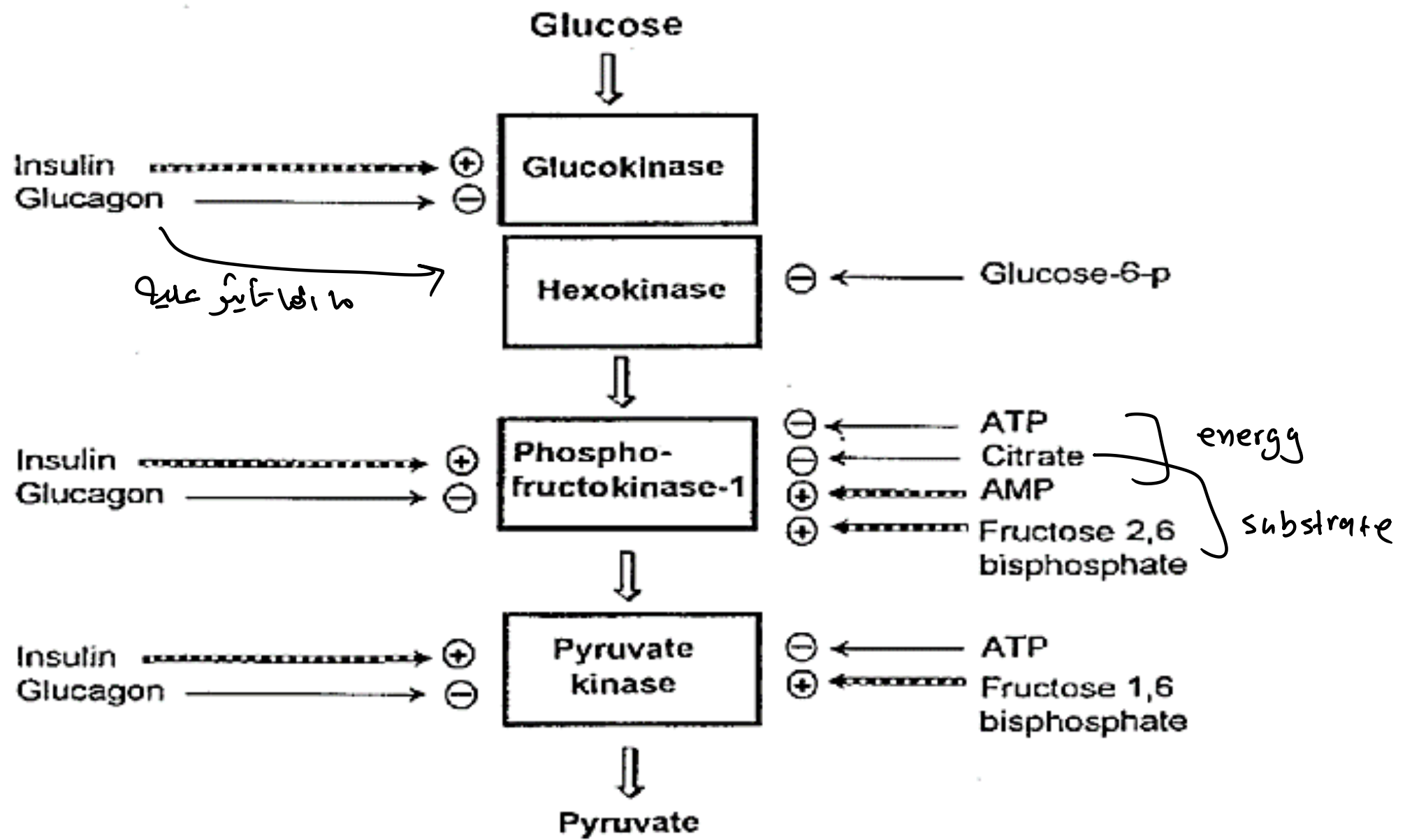
لو كان غني كمية قليلة من الطاقة والخلية تحتاج الى طاقة ← glycolysis ↑

1. High level of ATP inhibits PFK-1 and pyruvate kinase.
2. High level of ADP and AMP stimulate PFK-1.

Substrate regulation:

1. Glucose-6-phosphate inhibits Hexokinase (and not Glucokinase).
2. Fructose 2, 6 bisphosphate stimulates PFK-1.
3. Citrate inhibits PFK-1.
4. Fructose 1,6 bisphosphate stimulates pyruvate kinase.

2



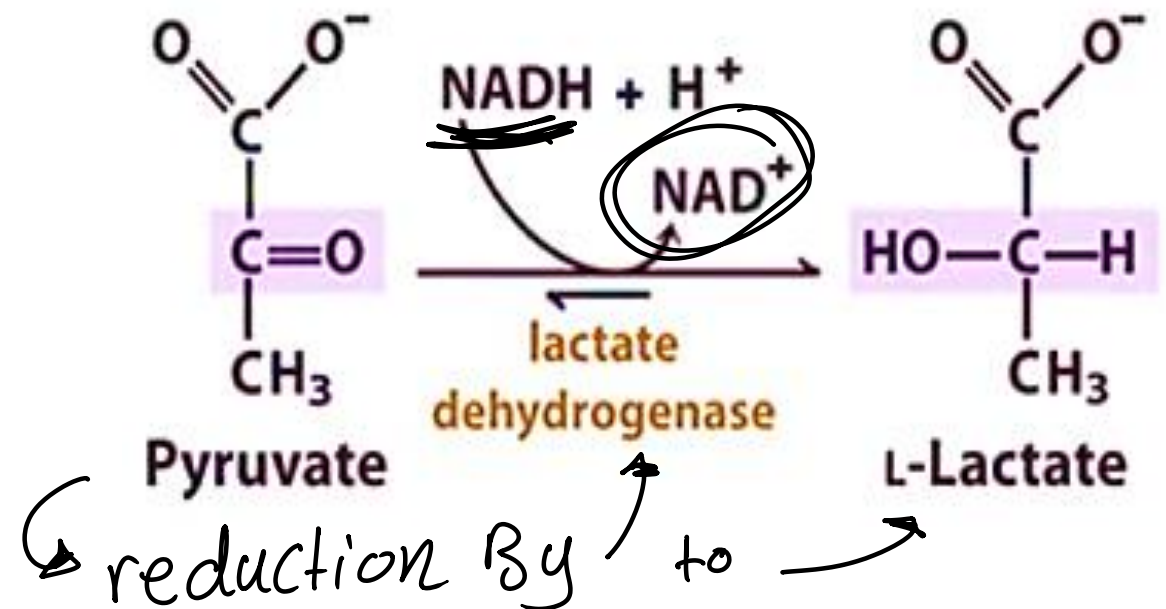
hormonal

Anaerobic respiration (Glycolysis)

Lactate dehydrogenase (LDH)

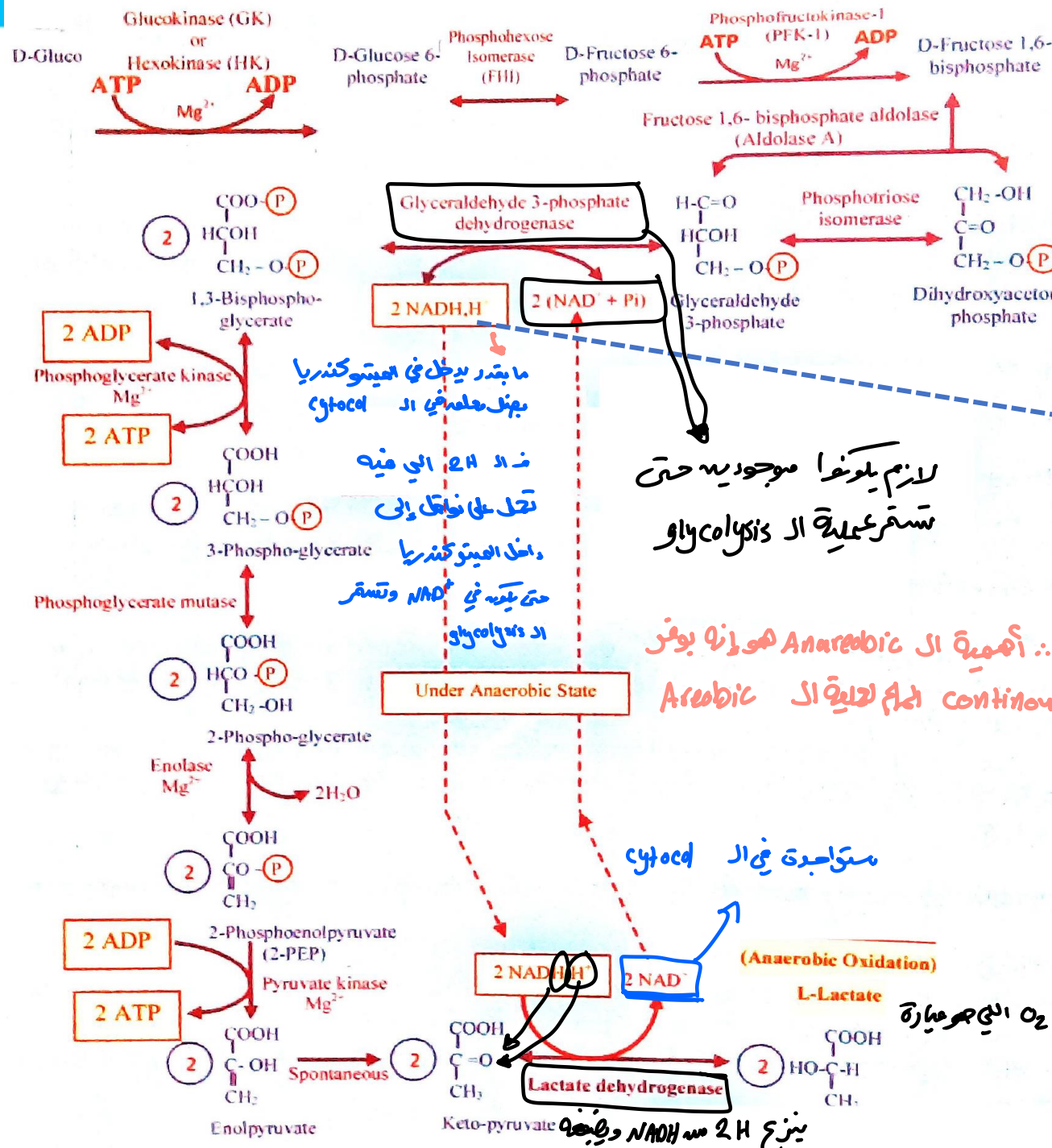
Anaerobic respiration

- In anaerobic tissues:
- Lactate dehydrogenase (LDH) is an enzyme that catalyzes the conversion of pyruvate to lactate.



Anaerobic respiration

- Muscle Cells During Intense Exercise: When muscle cells are working vigorously and the oxygen supply is limited they can switch to anaerobic glycolysis.
↓ O_2
- Red Blood Cells: Red blood cells lack mitochondria, which are the cellular organelles responsible for aerobic respiration.



① $\text{NADH} + \text{H}^+$ الموجود في السيتوبلازم والـ 2 FATES
 يتبرع بـ 2H و 2e^- في $\text{ADP} \rightarrow \text{ATP}$ في Skeletal و Heart بالتالي يصير FADH_2 التي يتجه حركته بـ ETC وينتج 2 ATP
 من حركته الـ cytochrome P-450

② يتبرع بـ 2H و 2e^- في NAD^+ في Heart و Kidney بالتالي يصير $\text{NADH} + \text{H}^+$ التي يتجه حركته بـ ETC وينتج 2 ATP

Shuttles

Problem: Cytosolic NADH cannot penetrate the mitochondria

Solution: Pass the electrons to something that can penetrate the mitochondria membrane

Two Shuttles

Skeletal muscle and brain
 $\text{Glycerol-PO}_4 \rightarrow \text{FADH}_2 \rightarrow 2 \text{ ATP per NADH}_c$

Liver, kidney, and heart
 $\text{Malate-aspartate} \rightarrow \text{NADH} \rightarrow 3 \text{ ATP per NADH}_c$

∴ في حالة الـ anaerobic الـ 2H يتوجه على الميتوكوندريا عن طريقه فاعقل
 في حالة الـ anaerobic الـ 2H ما في ميتوكوندريا باد RBCs واد skeletal في نقص O_2 التي هو عبارة
 عنه final acceptor في الـ ETC عندها يصير حركه الـ FAD و الـ NAD
 بالتالي يتم تسهيل $\text{lactate dehydrogenase}$ حركته المتخلف على الـ NAD^+

ما يقدر يدخل في الميتوكوندريا
 بشكل طبيعي الـ cytochrome
 فلا 2H التي فيه
 تدخل على نقل إلى
 داخل الميتوكوندريا
 حتى يقدر في NAD^+ وتنتقل
 الـ cytochrome

لازم يكونوا موجودين حتى
 تستقر عملية الـ cytochrome

∴ أهمية الـ Anaerobic هو انه يوفر
 continuous NAD^+ لتمام العملية الـ Anaerobic

متواجدة في الـ cytochrome

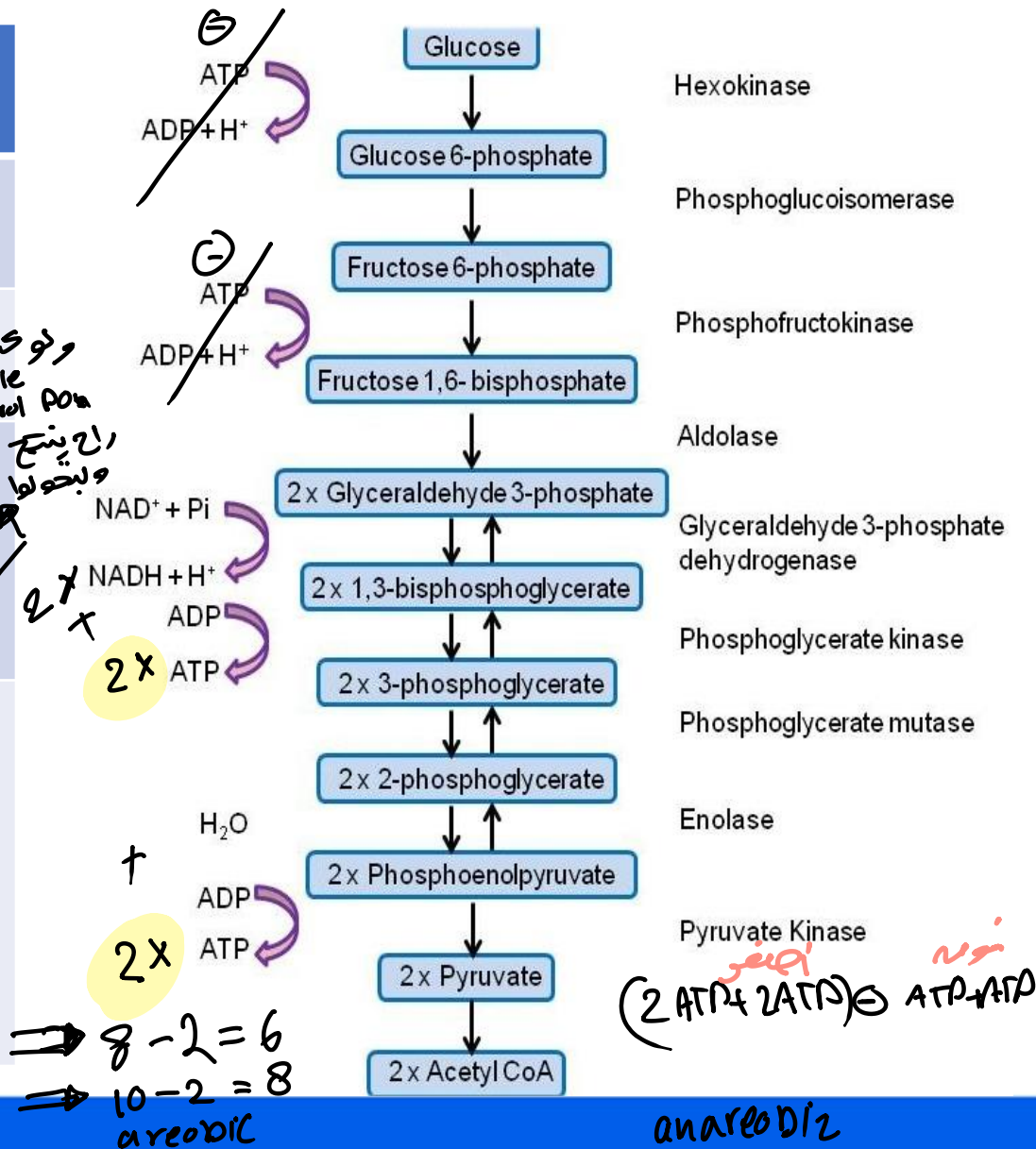
ينتج 2H من NADH و ينتج

Importance of lactate production in anaerobic glycolysis:

- Lactate production in anaerobic glycolysis is a vital survival strategy for cells and tissues when oxygen is not readily available.
 - It enables the continued production of ATP and the maintenance of essential metabolic processes by ensuring a steady supply of NAD^+ for glycolysis.

Differences between aerobic and anaerobic glycolysis

	Aerobic	Anaerobic
End product	Pyruvate	Lactate
Energy	6 or 8 ATP	2 ATP
Regeneration of NAD ⁺	Through <u>ETC</u> in mitochondria	Through lactate formation
Availability of TCA in mitochondria	Available and 2 pyruvate can oxidize to give 30 ATP	ATP Not available as lactate is cytosolic substrate



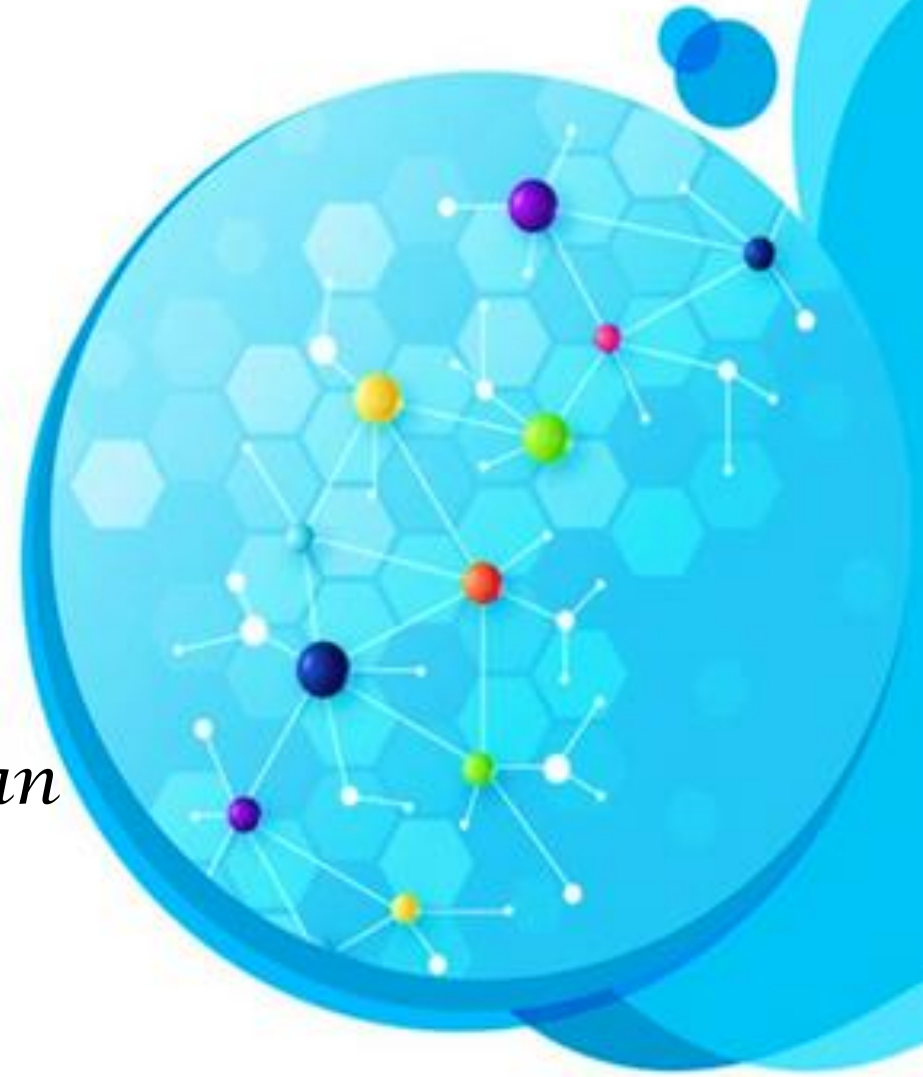
Thanks

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Faculty of Medicine

Al-Azhar University-Gaza

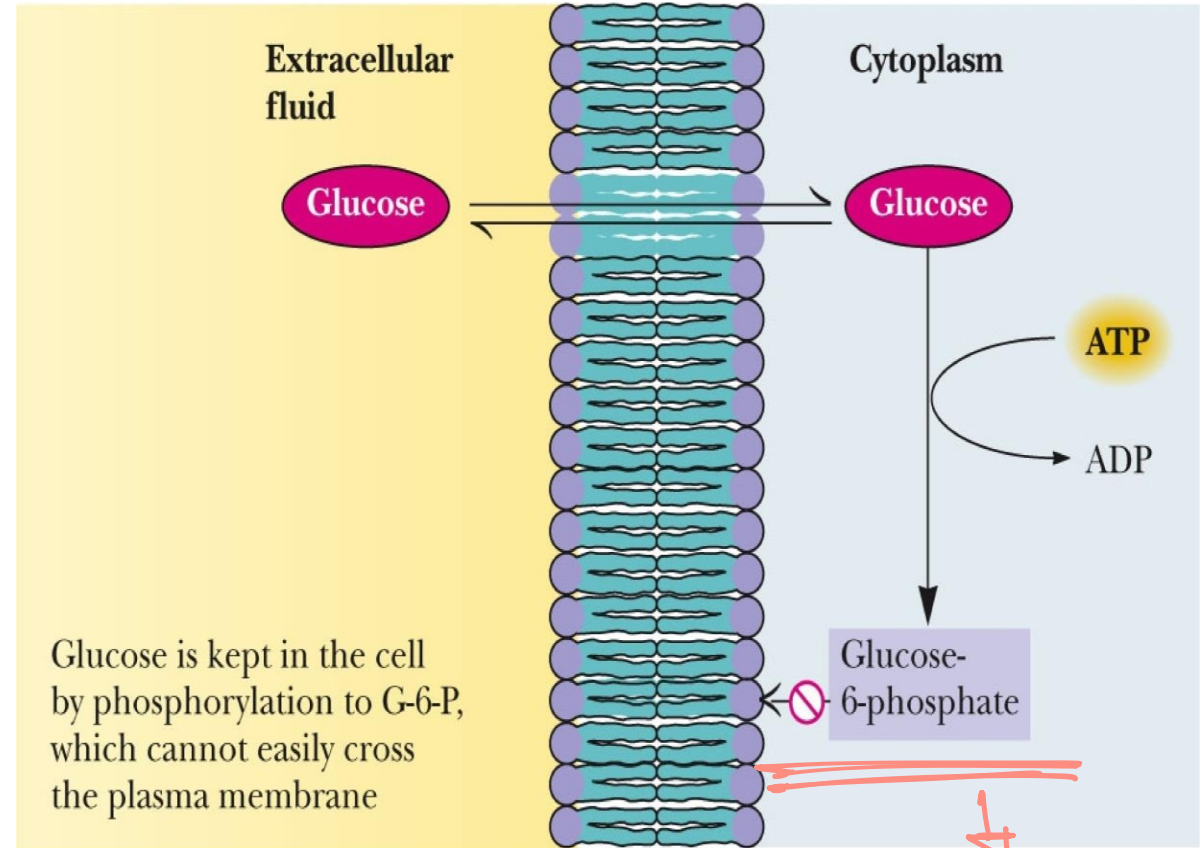


Important Note (Glycolysis)

Enzymes and substrates

Phosphorylation keeps G6P in the Cell

- Glucose phosphorylation for its intracellular trapping.



Glucokinase (GK)/ Hexokinase (HK) (Enzymes)



يعني يرتبط حتى لو في كمية قليلة (low concentration)

- HK is found in most tissues and has a high glucose affinity (inhibited by G-6-P).

- GK is found in liver and has low glucose affinity.

Gul

خاص فيه

يعني لازم يكون في high concentration
يبدأ يرتبط

بعد ما الخلايا تاخذ حاجتها من glucose-G-ph

بصير في negative feedback ويرتبط ال G-6-P

حتى يحد inhibition للأنزيم

- Insulin induces the synthesis of GK and has no direct effect on HK.

لما يقل ال G-6-ph ما الكما specific site

على glucokinase بالآتي ما يعيد ال

inhibition بالآتي ال GK لا يكون في ال liver

يقول ال G-6-ph بالآتي بهما ينتج مواد

∴ ال عدد ال درود للجلوكوز هو ال insulin اعيد

Induction ولحفظ المنتج ال GK حتى يتم التخلص

من الجلوكوز ويحول ال G-6-P حتى يصير storage

High level ال glucose في الجسم (الدع)

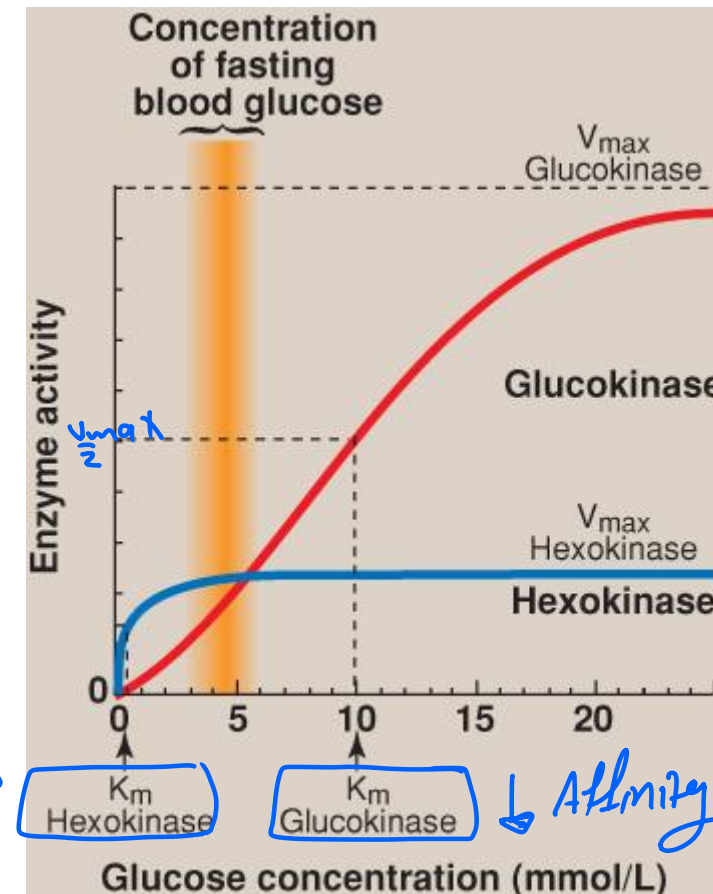
Glucokinase (GK)/ Hexokinase (HK) (Enzymes)

- Effect of glucose concentration on the rate of phosphorylation catalyzed by hexokinase and glucokinase.
①
②
same substrate ← 2 enzymes

- K_m = Michaelis constant; V_{max} = maximal velocity.

$$K_m \propto \frac{1}{\text{affinity}}$$

high affinity
G-concentration



↑ G-concentration

	Glucokinase	Hexokinase
Site	Liver	All tissue cell
Affinity to glucose	Low affinity i.e. it acts only in the presence of high Glucose blood concentration.	High affinity i.e. it acts even in the presence of low blood Glucose concentration.
$V_{\max}$	High	Low
K_m	High	Low
Substrate	Glucose only	Glucose, galactose and fructose
Role	Captures glucose from the bloodstream in the liver, facilitating glucose uptake and glycogen synthesis.	Also facilitates glucose uptake but is not primarily involved in regulating blood glucose levels.
Feedback Inhibition	Not subject to feedback inhibition by its product	Subject to feedback inhibition by its product (G6P)

Phosphofructokinase-1 (PFK-1) (Enzymes)



- Also known as 1-phosphofructokinase

- PFK-1 is a key enzyme (catalyzes committed reaction: means that under physiological conditions, the reaction proceeds in the forward direction).



Phosphofructokinase-1 (PFK-1)

طاقة منخفضة $\therefore$ glycolysis $\uparrow$

• Regulation of PFK-1:

يعني يستدعي عليه إذا كان موجود في كمية عالية من
① ②

1. Activation: High levels of ADP and AMP (indicators of low cellular energy) activate PFK-1, promoting glycolysis for ATP production.

موجود بحجم كبير

2. Inhibition: Conversely, high levels of ATP (indicating sufficient energy) and citrate (a metabolite signaling abundant energy stores)

في كوكبي إذا كان مرتفع يعني الخلية منتجة طاقة كبيرة بالتالي نخل

inhibit PFK-1, slowing down glycolysis to prevent energy waste.

طاقة عالية $\therefore$ glycolysis $\downarrow$

need
الخلية

Feedback inhibition

Phosphofructokinase-2/ fructose-bisphosphatase-2

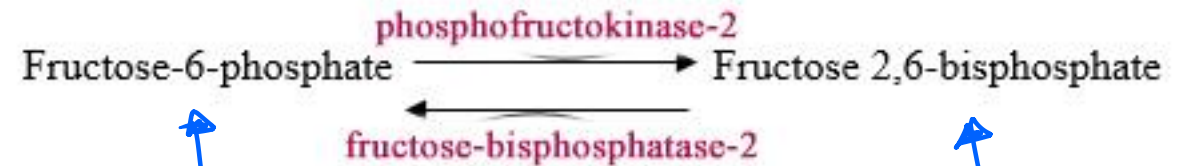
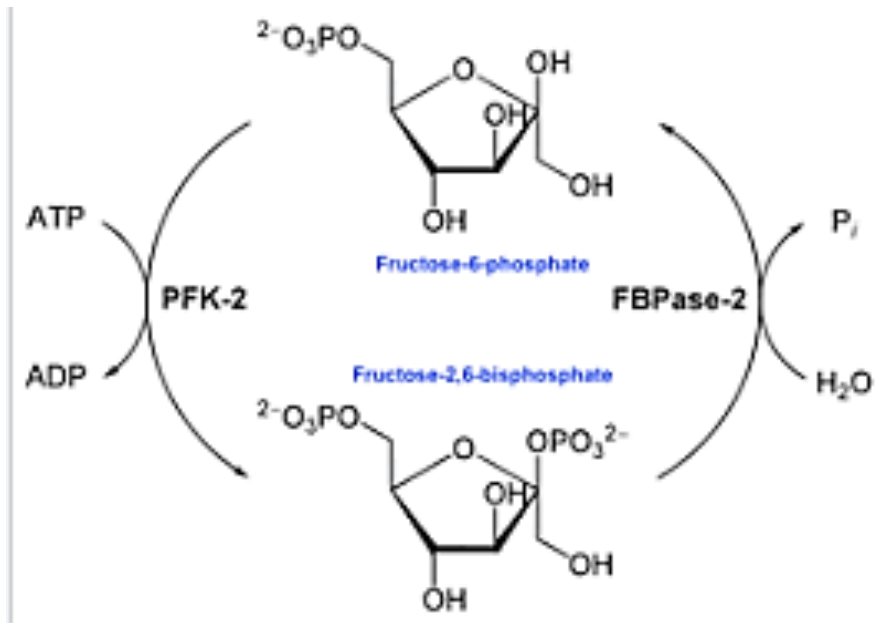
① kinase $\downarrow$ بجز

② $\ominus$ P $\downarrow$ from substrate

- This PFK-2/FBPase-2 has two enzymatic activities kinase [(phosphofructokinase-2)] and phosphatase [FBPase-2 (fructose-bisphosphatase-2)] residing on the same protein molecule.



Phosphofructokinase-2/ fructose-bisphosphatase-2

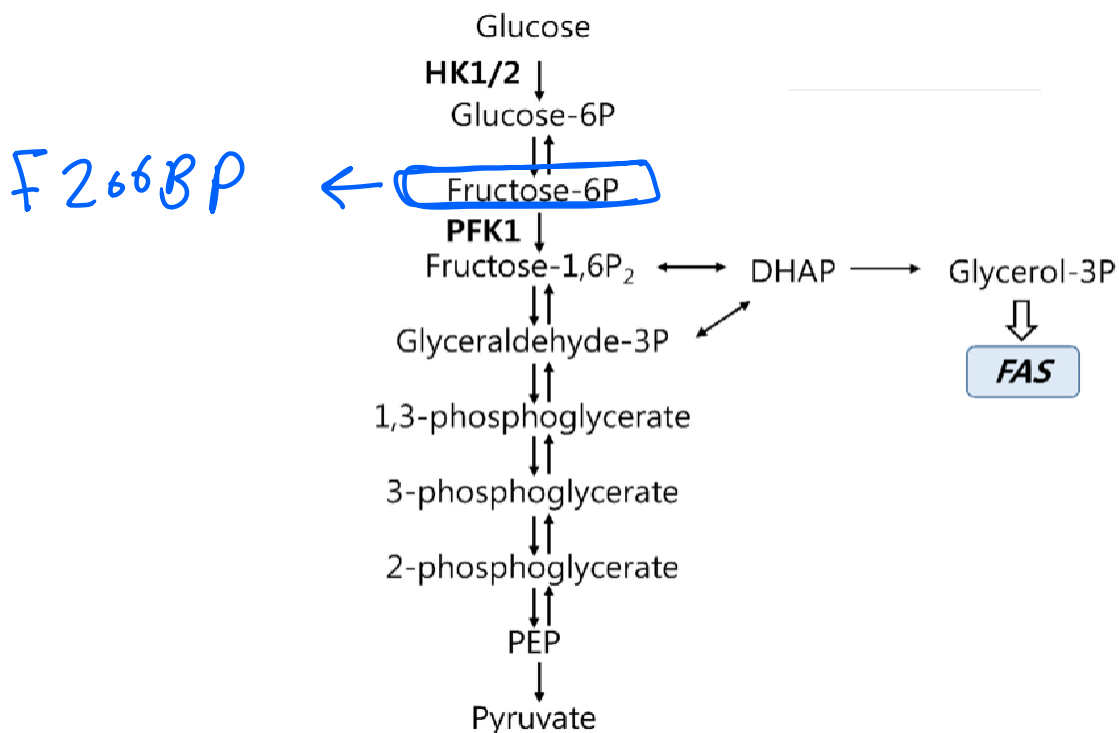


إذا برى هار في
الخطه بسقم
FBP-2

إذا برى هار باليه
بسقم PFK-2

Phosphofructokinase-2/ fructose-bisphosphatase-2

- F2,6BP is a potent activator of PFK-1.

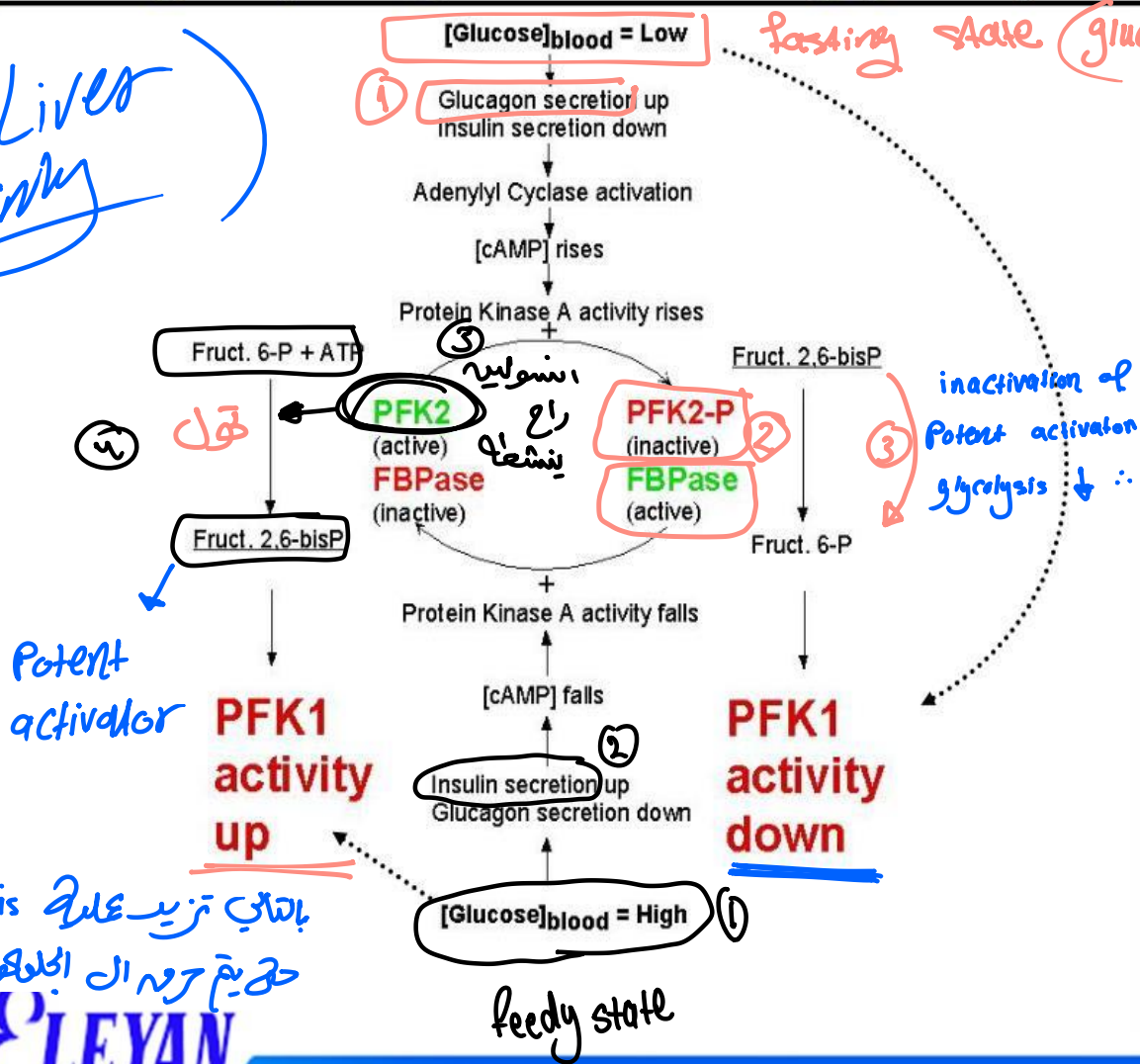


کو بدی از گلیکولیز و فصل ششامه از هم به شغل
از PFK-2 علی F-6P و این به ماده
F2,6BP

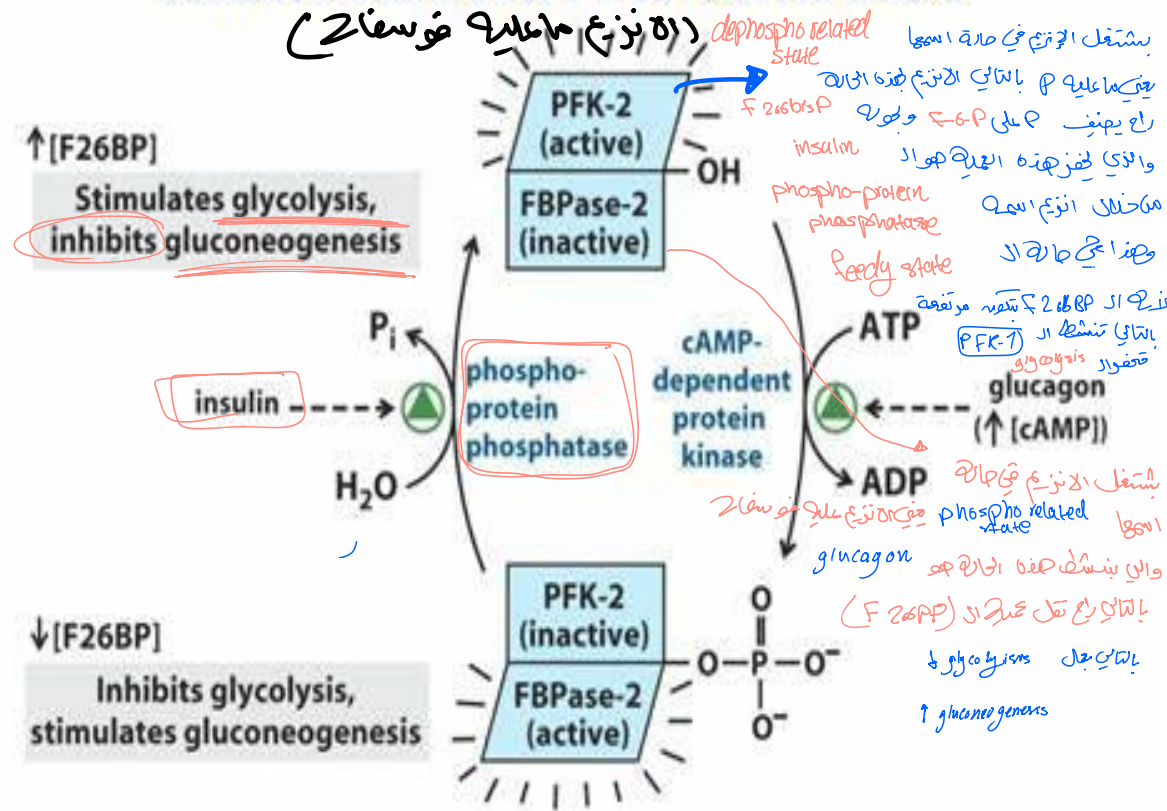
PFK2 allows for endocrine (insulin and glucagon) regulation of glycolysis

glycolysis → glucose
 gluconeogenesis → glucose

(In Liver mainly)



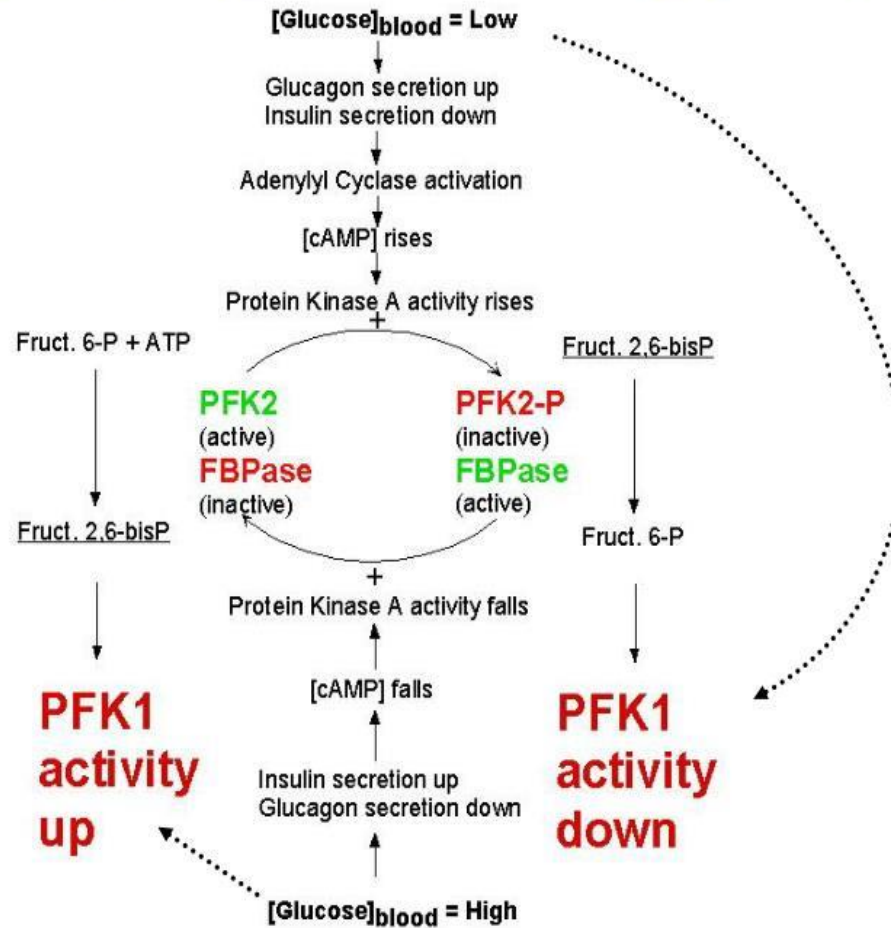
Insulin and glucagon levels affect the balance between PFK-2/FBPase-2



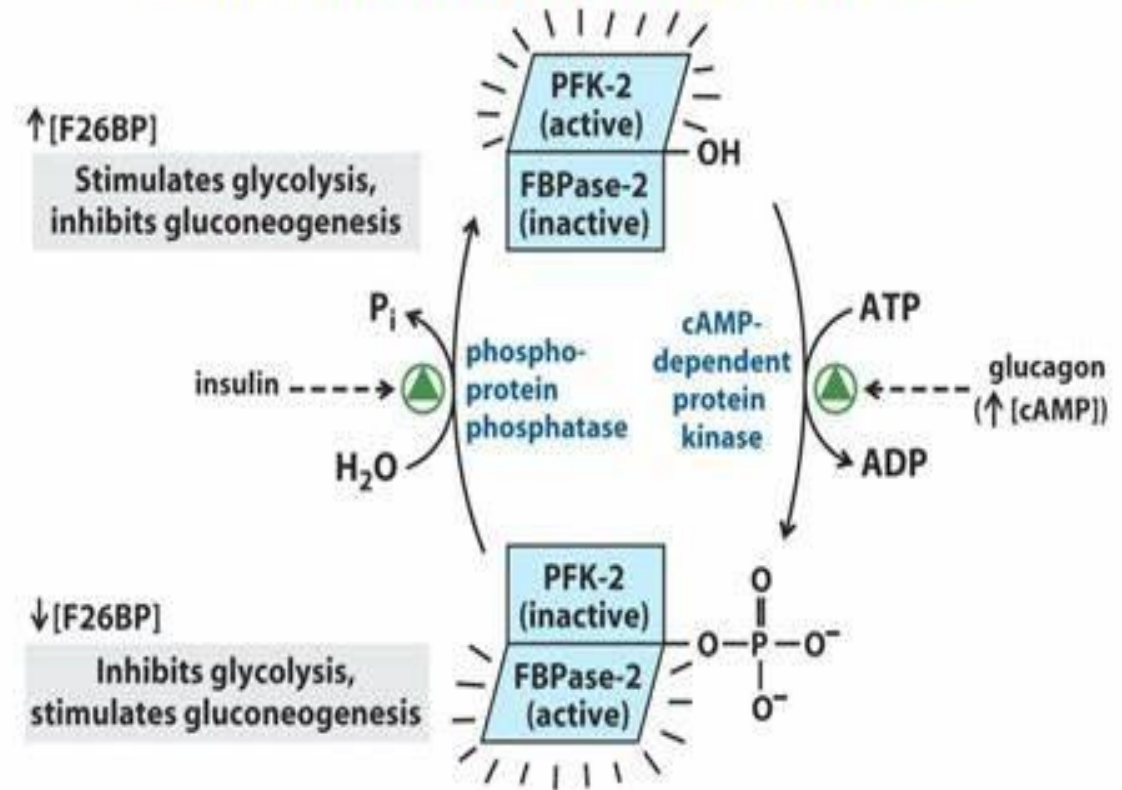
بالتالي تزيد عملية glycolysis
 حتى يتم حرق ال الجلوكوز الزائد

M. ELEYAN

PFK2 allows for endocrine (insulin and glucagon) regulation of glycolysis



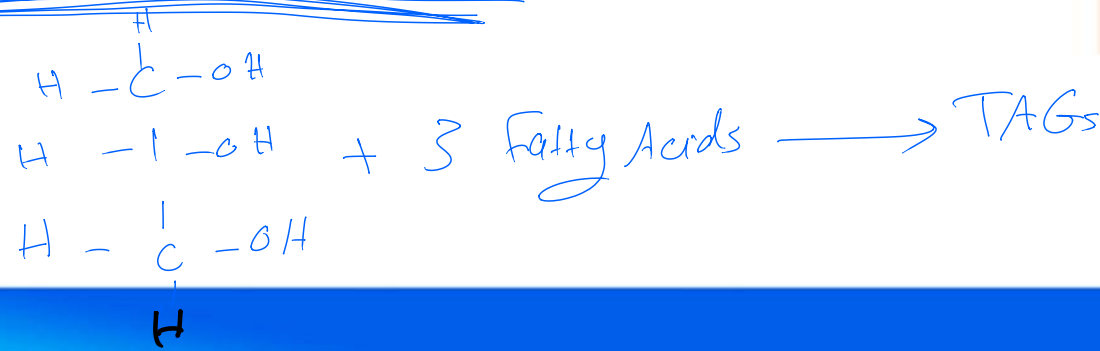
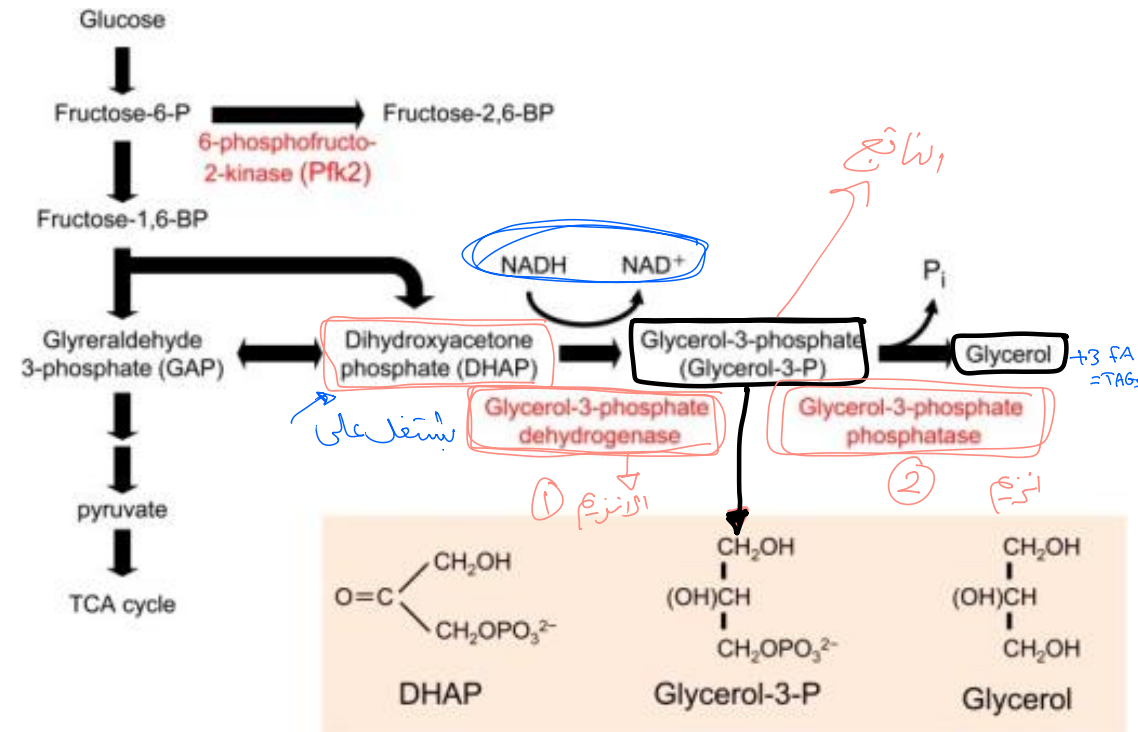
Insulin and glucagon levels affect the balance between PFK-2/FBPase-2



Dihydroxy acetone P04 (Substrate)

lipids
حلقه وصل حتى يتم تصنيع ال
carbohydrates من ال

- can be used in liver and adipose tissues to form **glycerol-3-PO4** which (Triacylglycerols) is used to form TAGs but, that occurs (conversion) أو تحويل إلى حاجات (conversion) with excessive glucose intake.

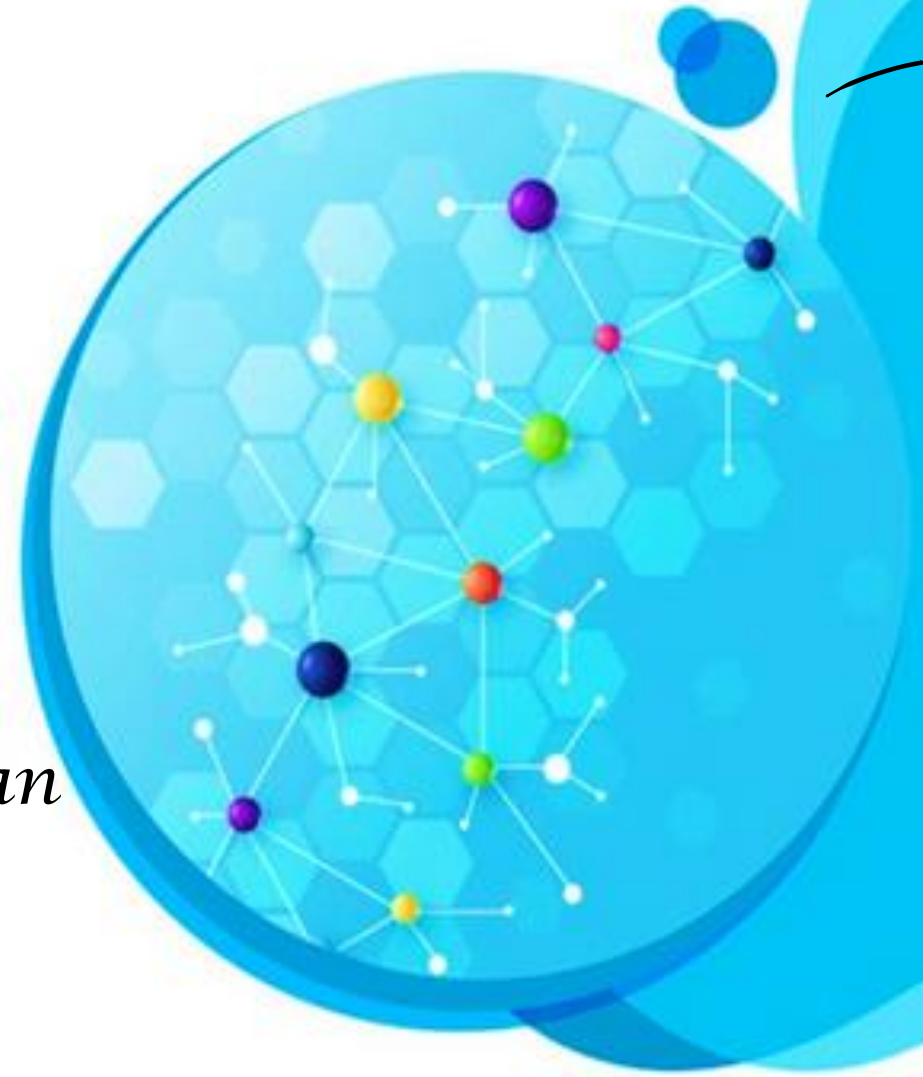


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Clinical aspects of glycolysis

خلل في ال

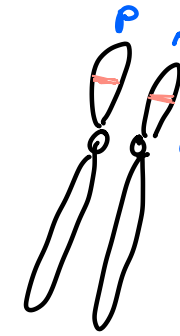
- There are many diseases associated with impaired glycolysis.
- They include:

① Pyruvate kinase deficiency.

② Hexokinase deficiency.

3. Lactic acidosis.

Pyruvate kinase (PK) deficiency



جبرار Pyruvate
تحوّل علی ۱/۱ autosomal (جبری)
فی ۱/۱ Paternal و ۱/۱ maternal
ظواهر خن نظری الورثی
لازم بقوه علی ۱/۱ Both alleles (P+M)

- PK deficiency is typically inherited as an autosomal recessive genetic disorder.
- PK deficiency causes decrease in the rate of glycolysis and decreased production of ATP.

↓ PK کمبود آید ال key enzymes ظواهر خن رفع قتل

	ATP produced	ATP, utilized	Net ATP
In absence of O ₂ (anaerobic glycolysis)	❖ 4 ATP by (Substrate level phosphorylation) a) 2ATP from 1,3 BPG. b) 2ATP from phosphoenol pyruvate	<u>2 ATP</u> a) glucose to glucose-6-p. b) fructose-6 to fructose 1,6 bis p.	2

In RBCs' [↑ بیشتر علی PK فو تا نه فی خلاصه
مراجعه انتاج 2 ATP

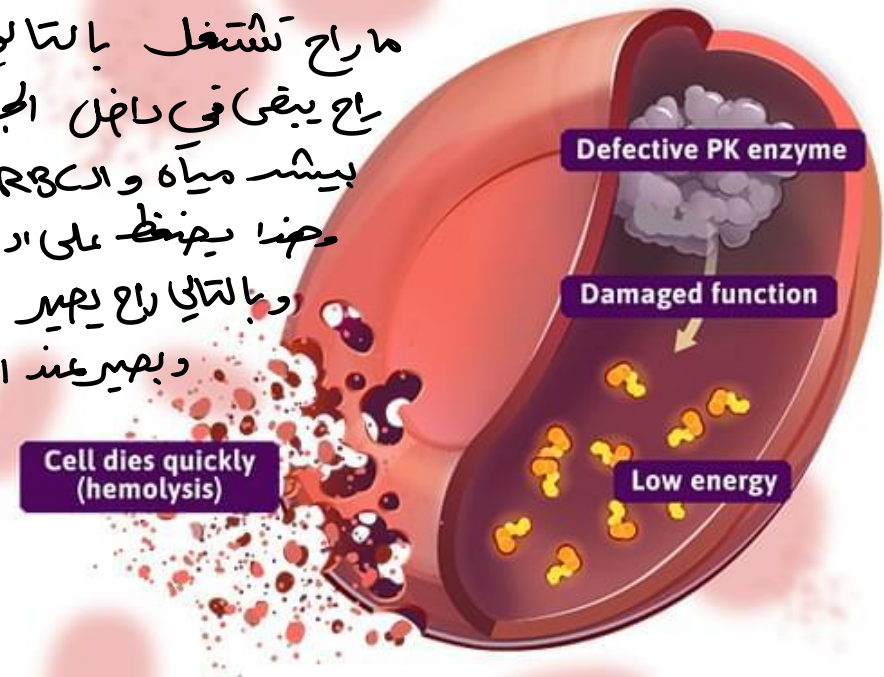
2 ATP = zero = وراجعه استهلاك 2 ATP

Pyruvate kinase (PK) deficiency

ATP is required for Na-K⁺ ATPase, which is important for stability of RBCs.

- This leads to excessive hemolysis of RBCs, leading to hemolytic anemia.

في حال هذا المرض راجع يقل إنتاج
اد ATP بالتالي مفعلة او K^+ Na^+
ما راجع تشتغل بالتالي الموروث
راج بعض في داخل الجسم والى
بيش مياه وال RBC راج تنفخ
هنا يهبط على او membrane
وبالتالي راج يهبط hemolysis
وبصير عند المريض



Hexokinase (HK) deficiency

- **HK** results from a lack of the enzyme hexokinase, which is the first enzyme in the glycolytic pathway.
له معنى خلا فيه راع يودي الى عيانات كالهيمية او glycolysis
- **HK** shares a similar mechanism to PK deficiency in causing hemolytic anemia due to decreased ATP production in red blood cells (RBCs).
كمان راع يودي
↓ 2,6-bisphosphoglycerate
التحفي عليه او unloading لا تحفي الا RBCs
- HK deficiency is generally considered a rarer and more severe than PK deficiency.
لانه في البرايه

Lactic acidosis

- A condition characterized by a accumulation of lactic acid in the ^{في الدم} bloodstream, leading to a decrease in blood pH (acidity) and bicarbonate levels (HCO_3^-) and may lead to coma.

Bicarbonate Buffer
عباره عن جزئ من ال

راح تقلل لانخفاض قلوي
مادة فجزئ كبير مفادح يتم استهلاكه
ولو صارت حاجه فكله يبقون في Coma

Lactic acidosis

- Causes: It results from

1. Increased formation of lactate
2. Decreased utilization of lactate.

} accumulation of lactic acid

Lactic acidosis: Increased Lactate Formation:

1. **Severe Exercise**: During intense activity, muscle cells may rely more on anaerobic metabolism, producing excess lactate. } final producte
2. **Tissue Hypoxia (Oxygen Deprivation)**: Conditions like heart attack, respiratory failure, or severe anemia can deprive tissues of oxygen, leading to increased lactate production.

↑ lactic acid
Production

أعراض تؤدي إلى نقص O_2 في الأنسجة ←

Lactic acidosis: Decreased Lactate Utilization

→ hepatitis
→ cirrhosis

- **Liver Disease:** Liver dysfunction can impair lactate clearance, contributing to acidosis.

ما راح يتم تحويله لـ Pyruvate
تجمع فيه
accumulation

- It can convert lactate back into pyruvate through a process called the

Cori Cycle

Lactic acidosis: Certain Medications

- Phenformin: this medication, no longer widely used, can cause excessive anaerobic metabolism and lactate production.



Lactate

① Glycolysis in RBCs and ② muscles during exercise are the primary sources of lactate production.

Lactate Transport: Lactate diffuses from these tissues into the bloodstream.

ارتقاء

Fate Lactate

يقول د

1. Glucose formation: Lactate formed in muscles and RBCs may diffuse to the blood then to the liver.

عنه دهو :
تحويل جوكوزيه

- In the liver, lactate is converted to glucose by gluconeogenesis.
- Glucose may diffuse back to the blood, then to red cells or muscles to be used for production of energy.

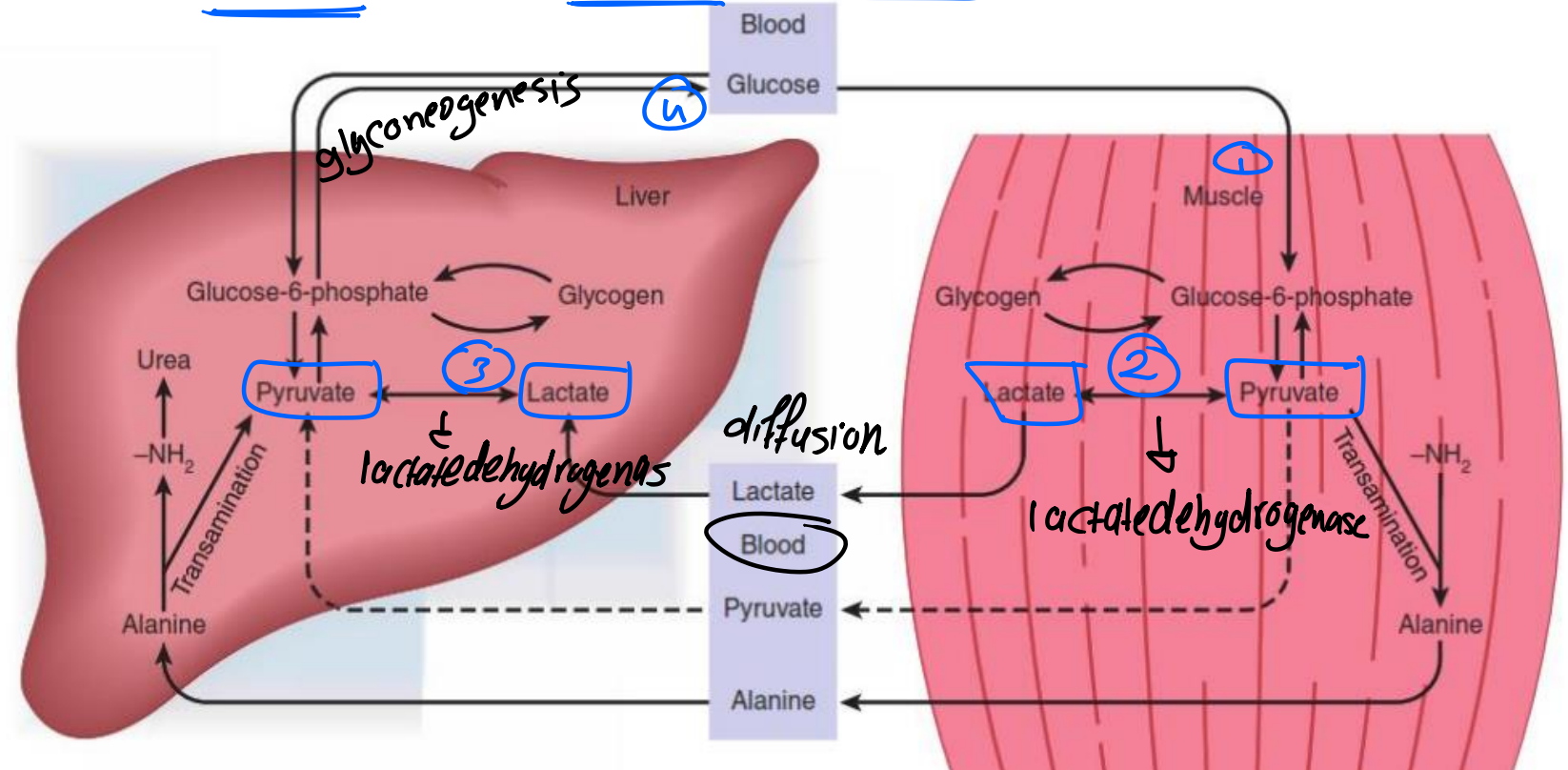
cori cycle سيقه

lactate-glucose cycle

Fate Lactate: Glucose formation: Cori cycle

- It is the conversion of glucose into lactate in peripheral tissues.

Followed by conversion of lactate into glucose in liver



Fate Lactate

The Rest of the muscle

2. Conversion into pyruvate.  If oxygen gets available, lactate is converted into pyruvate, which proceeds into Kreps cycle
3. Lactate is excreted in urine and sweat

Lactate dehydrogenase (LDH): The Crucial Enzyme

↔ قابل عكس لايكون

- **Function:** LDH is an essential enzyme that catalyzes the reversible conversion of lactate to pyruvate and vice versa.

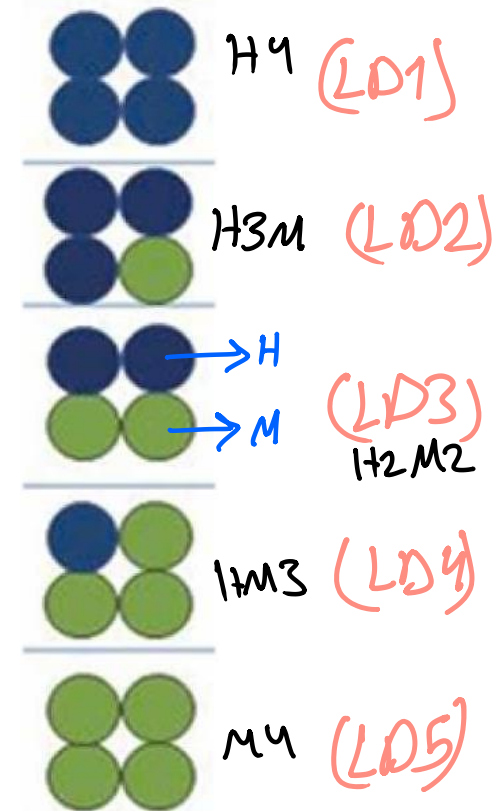
- **NADH Regeneration:** This reaction helps the re-oxidation of NADH+H⁺ into NAD⁺

↓
المادة في استقرار على ال
سلسلة التنفس

Lactate dehydrogenase (LDH): The Crucial Enzyme

→ catalyzing same reaction but different in amino acid sequences and found at different tissues

- Five LDH **isoenzymes** share a similar core structure but differ in their subunit composition.
- There are two main subunits: H (heart) and M (muscle).
- Different combinations of these subunits create the five isoenzymes (LD1-LD5).



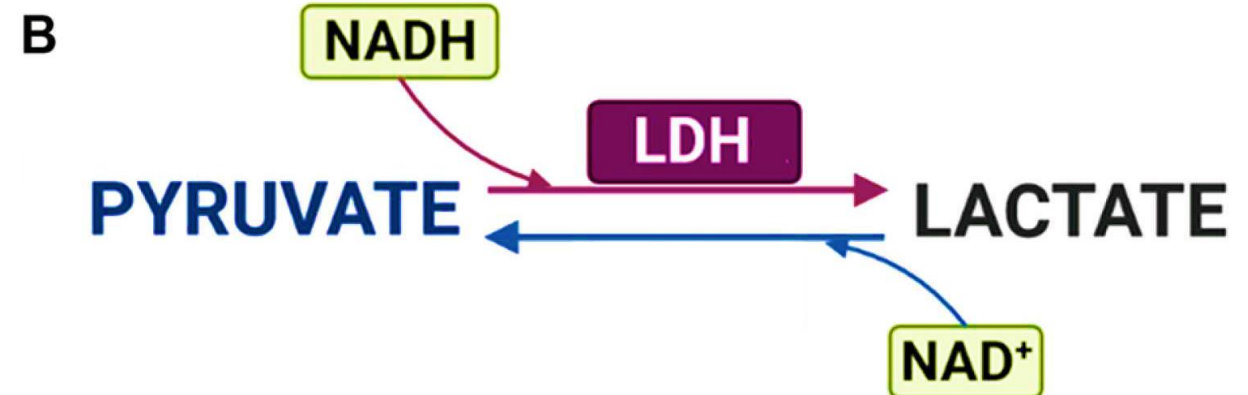
↑ elevation
 اذ ۱ صافنی
 راح صافنی اثری

Lactate dehydrogenase (LDH): Medical importance

- Estimation of the activity of
lactate dehydrogenase enzyme in
plasma helps the diagnosis of
heart and liver diseases.

A

Isoenzyme	Subunits	Tissue localization
LDH-1	H4	erythrocytes cardiac muscle
LDH-2	H3M	
LDH-3	H2M2	lymphatic tissue, brain, platelets, malignant tissue
LDH-4	HM3	liver skeletal muscle
LDH-5	M4	



معياراً (في المختبر)

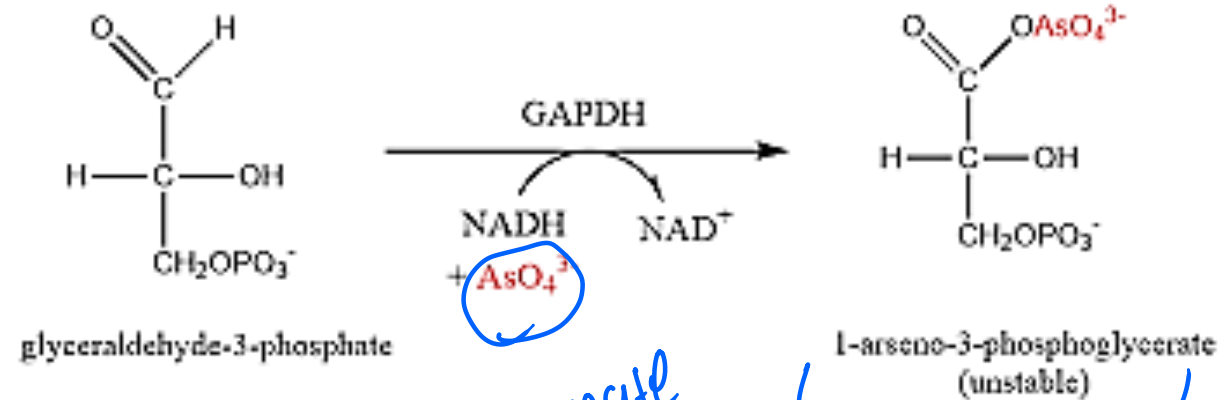
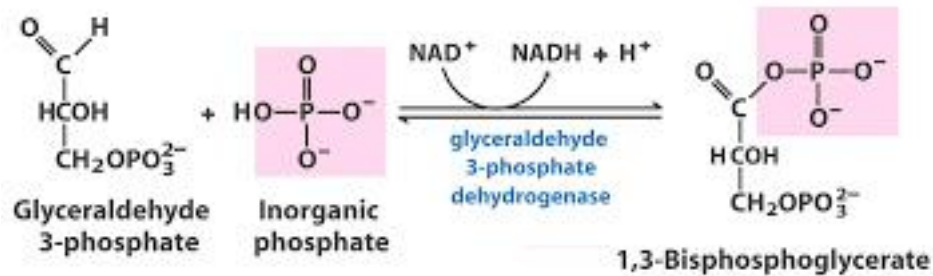
In vitro inhibition of glycolysis

In vivo (في الجسم)

inorganic phosphate و التي تشارك في
المرحلة الثانية

1- Arsenate: by competing with inorganic phosphate in the reaction:

glyceraldehyde-3 -p $\rightarrow$ 1,3 bisphosphoglycerate



Arsenate

glycolysis

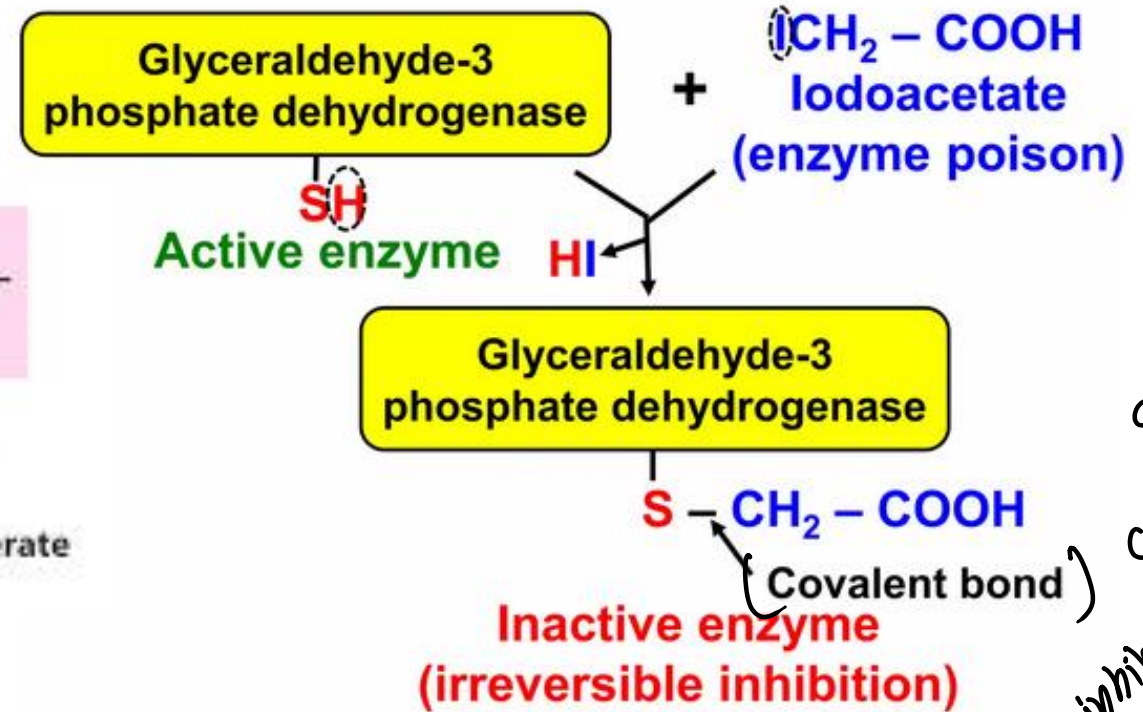
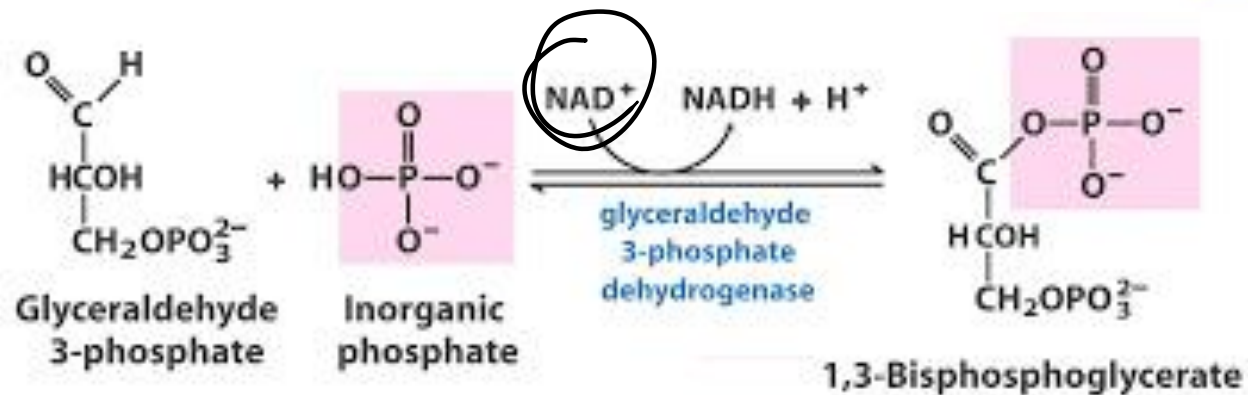
1-arseno-3-phosphoglycerate (unstable)

يضع ! كما ان عيبه هو

In vitro inhibition of glycolysis

2- Iodoacetate: by inhibiting glyceraldehyde-3-p dehydrogenase.

Example



الإنزيم أصبح
Covalent Bond
inhibition دائم

In vitro inhibition of glycolysis

گلیکولیسس کا توقف

3. Fluoride: Inhibits enolase enzyme.

- **Sodium Fluoride:** Clinically, sodium fluoride (NaF) is the most common form of fluoride used to inhibit glycolysis by adding it to the blood before measuring blood glucose.

فلورائیڈ کا اضافہ



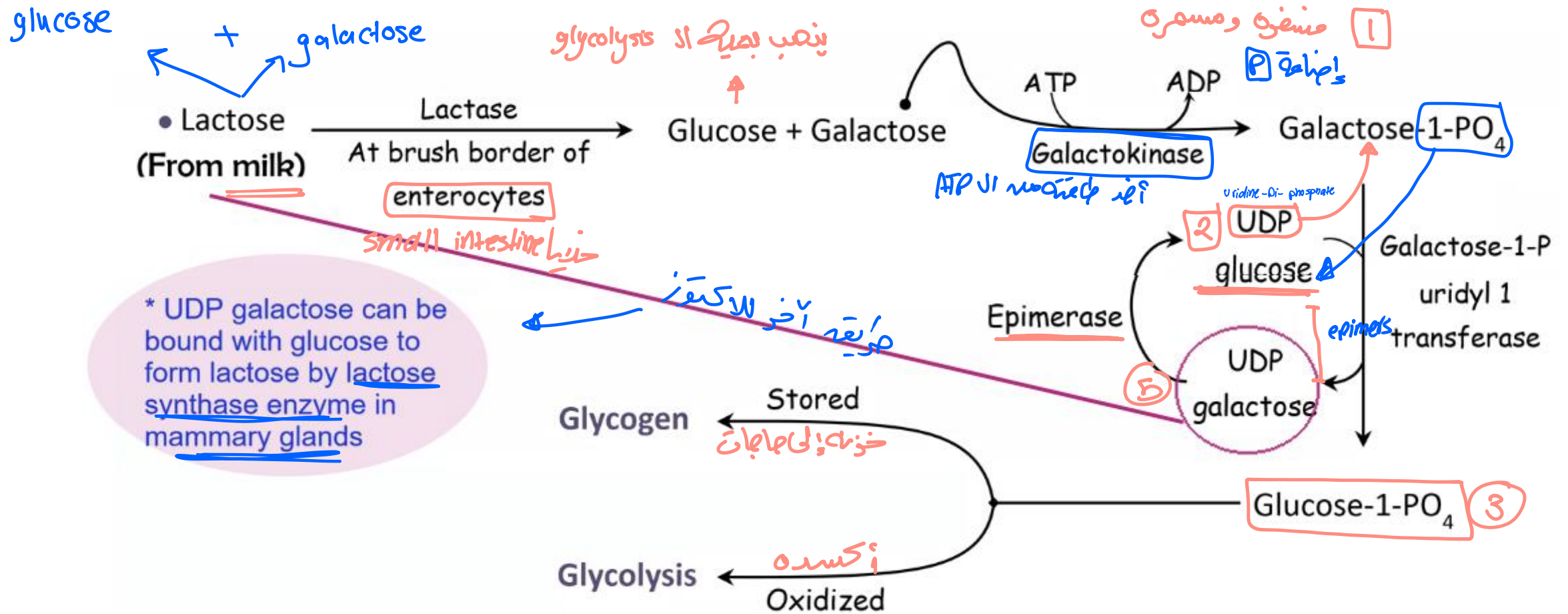
Medical Biochemistry
Carbohydrate Metabolism

Asst. Prof. Mohammed Hasan Eleyan

Faculty of Medicine

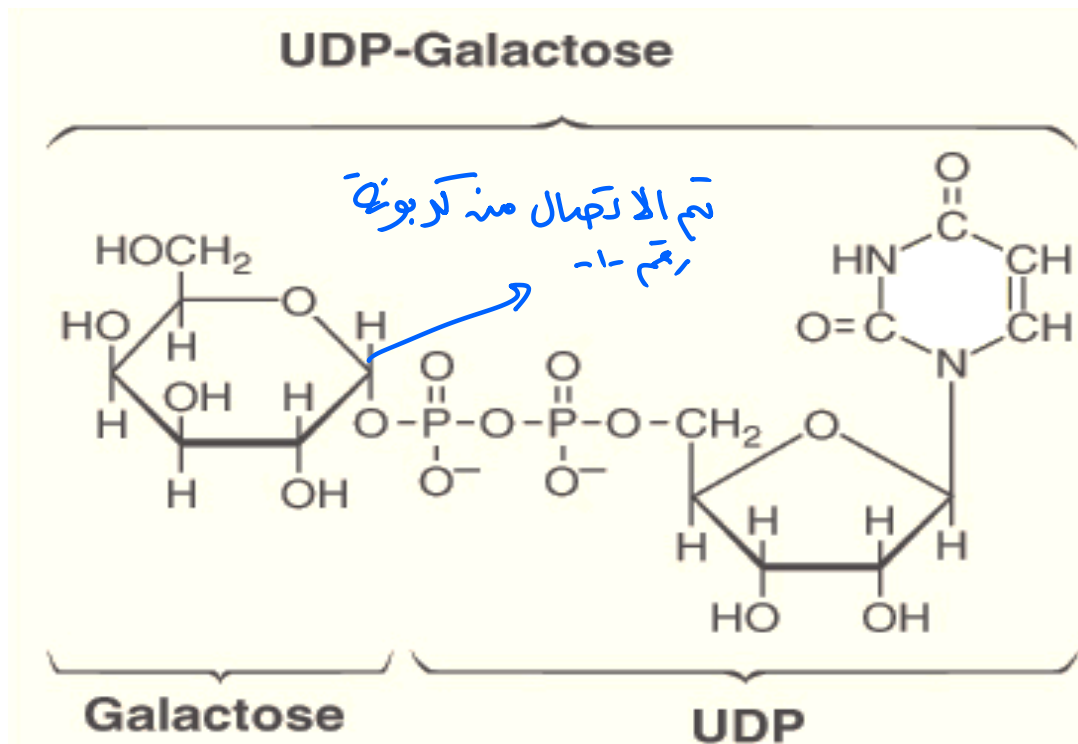
Al-Azhar University-Gaza

Galactose metabolism pathway (primarily in the liver).

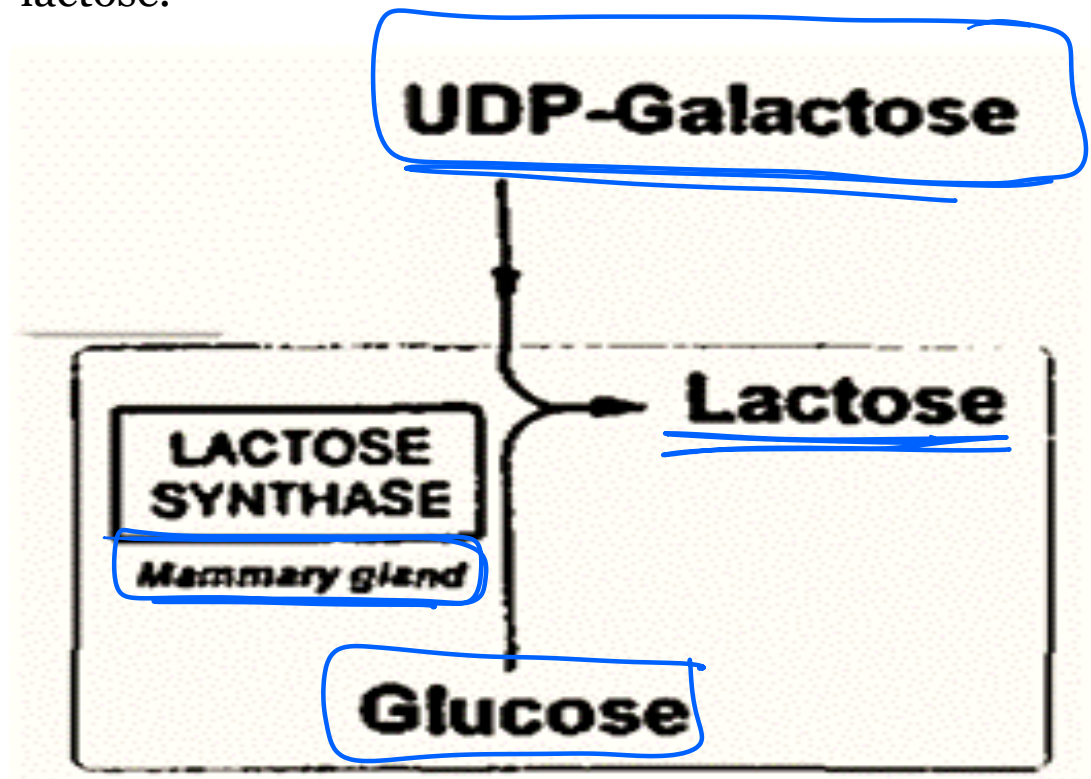


In mammary gland and lactose synthesis

Structure of UDP-galactose. UDP = uridine diphosphate.



UDP-Galactose reacts with a molecule of glucose in the presence of lactose synthase enzyme to form lactose.



Lactase deficiency

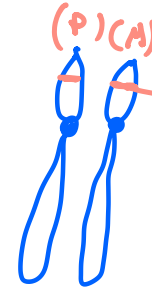
intolerance

لازيم اللاكتوز
lactose intolerance

- It also known as lactose intolerance & is a deficiency of lactase enzyme which digest lactose.

→ glucose

disaccharidase enzyme



الجين موجود على كروموسوم رقم 2 - مفعلة يهبط في جوف الرحم على M+P

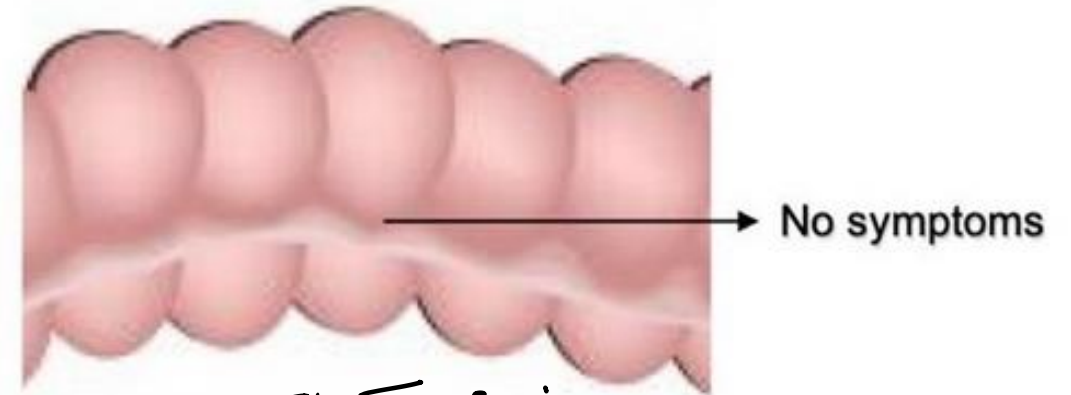
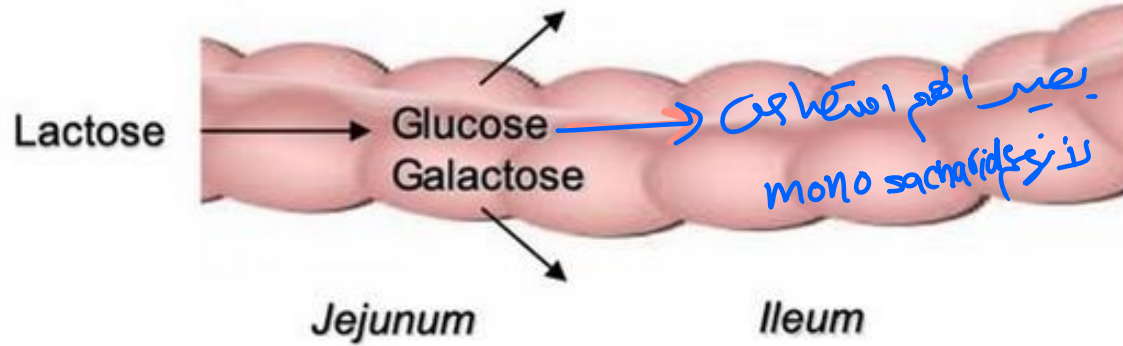
- It may be Congenital or Acquired.

- Hereditary (autosomal recessive) mostly in Asians and Africans. (1^{ry} cause) or 1^{ry} type

- Acquired after gastroenteritis due to enterocytes destruction. 2^{ry} cause. or 2^{ry} type

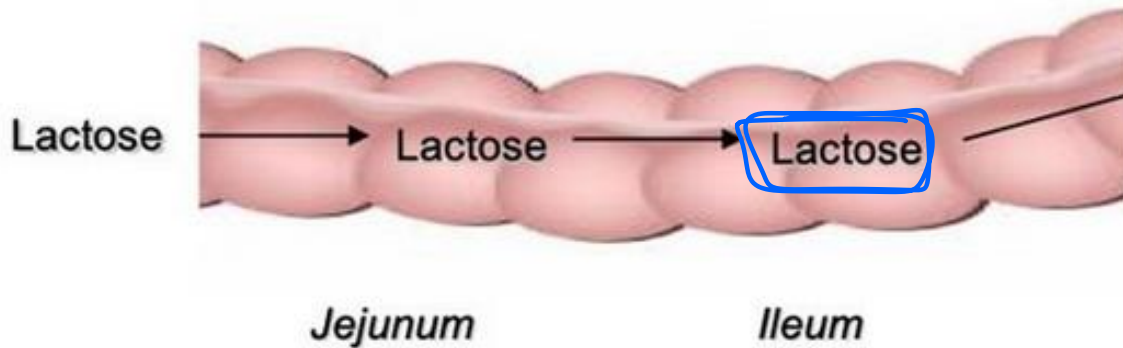
lactase enzyme → destruction

Lactase persistence

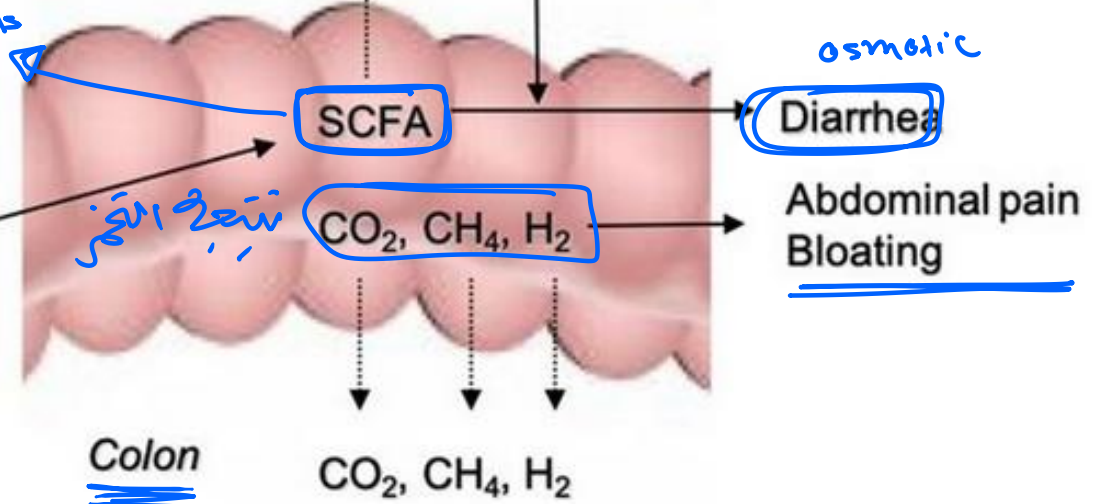


Handwritten notes in Arabic and English: 'osmotic' (تشنج) and 'fermentation' (تخمير).

Lactase non-persistence Lactose maldigestion



Handwritten note in English: 'short chain fatty Acids' (أحماض دهنية قصيرة السلسلة).



Lactase deficiency

- The presence of lactose in intestine causes:
 - Increased osmotic pressure: So water will be drawn from the tissue (causing dehydration) into the large intestine (causing diarrhea).
 - Increased fermentation of lactose by intestinal bacteria and produce CO₂ gas (distention and abdominal cramps).
 - Investigation: +ve H₂ breath test after lactose administration.
- Treated by removing lactose from diet (free lactose milk) or lactase pills.

يتم إعطاء المريض كمية من اللاكتوز ولو كان مريضاً باللاكتوز
راح يهضم متواجداً في الـ intestine بالتالي راح يطبع H_2 و CO_2
ويتم قياس كمية الغاز الموجودة في النفس ومن خلاله نعرف إذا كان
المريض أم لا

adult

children

Galactosemia:

Definition: It is increase blood galactose concentration due to inability to metabolize galactose.

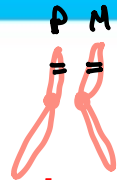
• Causes: Inherited enzyme deficiency of:

خس طرائق في ذراع

1. Galactokinase.
2. Galactose-1-P uridyl 1 transferase.
3. Epimerase.

Galactokinase deficiency (autosomal recessive (AR))

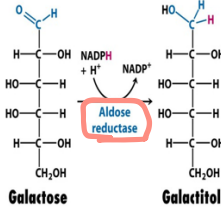
اسم المرض



نقصية الجين مغروبي

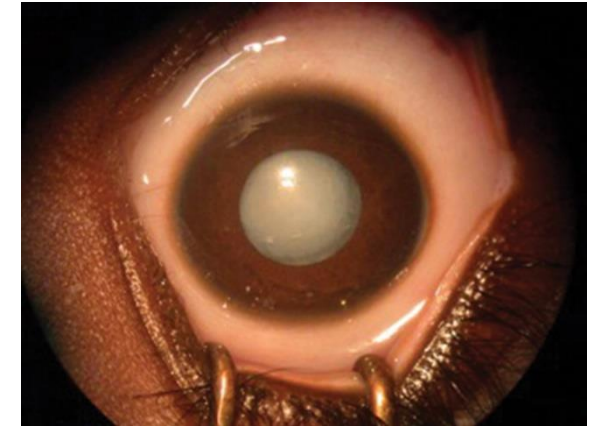
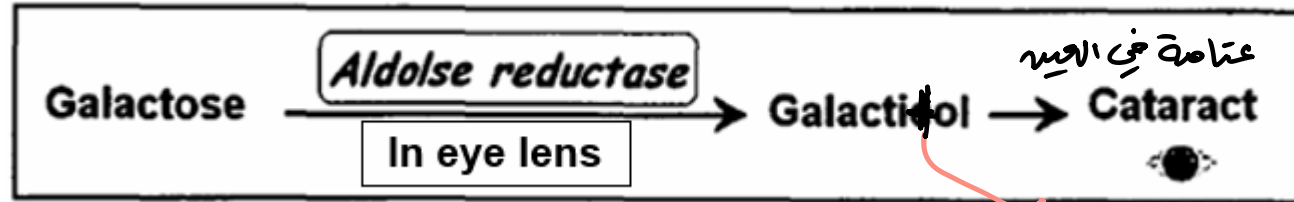
2- Sugar alcohols:

- Galactose is reduced to galactitol (dulcitol)
- It has a sweet taste but is not as sweet as sucrose.
- Galactitol is used as a sugar substitute in some food products, particularly in sugar-free and reduced-calorie foods.
- Additionally, it has applications in the pharmaceutical and medical fields.

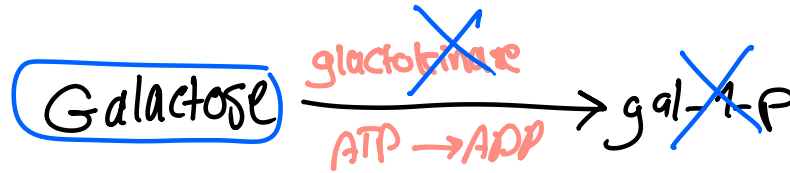


M.ELEMAN

- Classic galactosemia: Benign galactosemia due to accumulation of unphosphorylated galactose which can leave cells again (not trapped yet).
- Early cataracts in child due to high galactitol in eye lens.



طالما ما صار له عتمة
ومسرة بقدر يدخل العين
ويخرج منها بدون مشاكل



كحول : راع يسبب
العتاء في داخل الـ lens
بالتالي يغير
في العين cataract

M.ELEMAN

αααααααα

Galactose-1-P uridylyltransferase deficiency (AR)

رشته‌های گلیکوزید و glucose-1-P در آنزیم گالاکتوز-1-P یوریدیل ترانسفرهز

- Malignant galactosemia (severe consequences) due to accumulation of phosphorylated galactose, which is trapped inside cells and leads to osmotic destruction of tissues. So early onset:

- Cataracts
- Liver cirrhosis
- Lethargy, vomiting and diarrhea on lactose ingestion
- Hyperurecemia due to phosphate trapping & decrease purine salvage

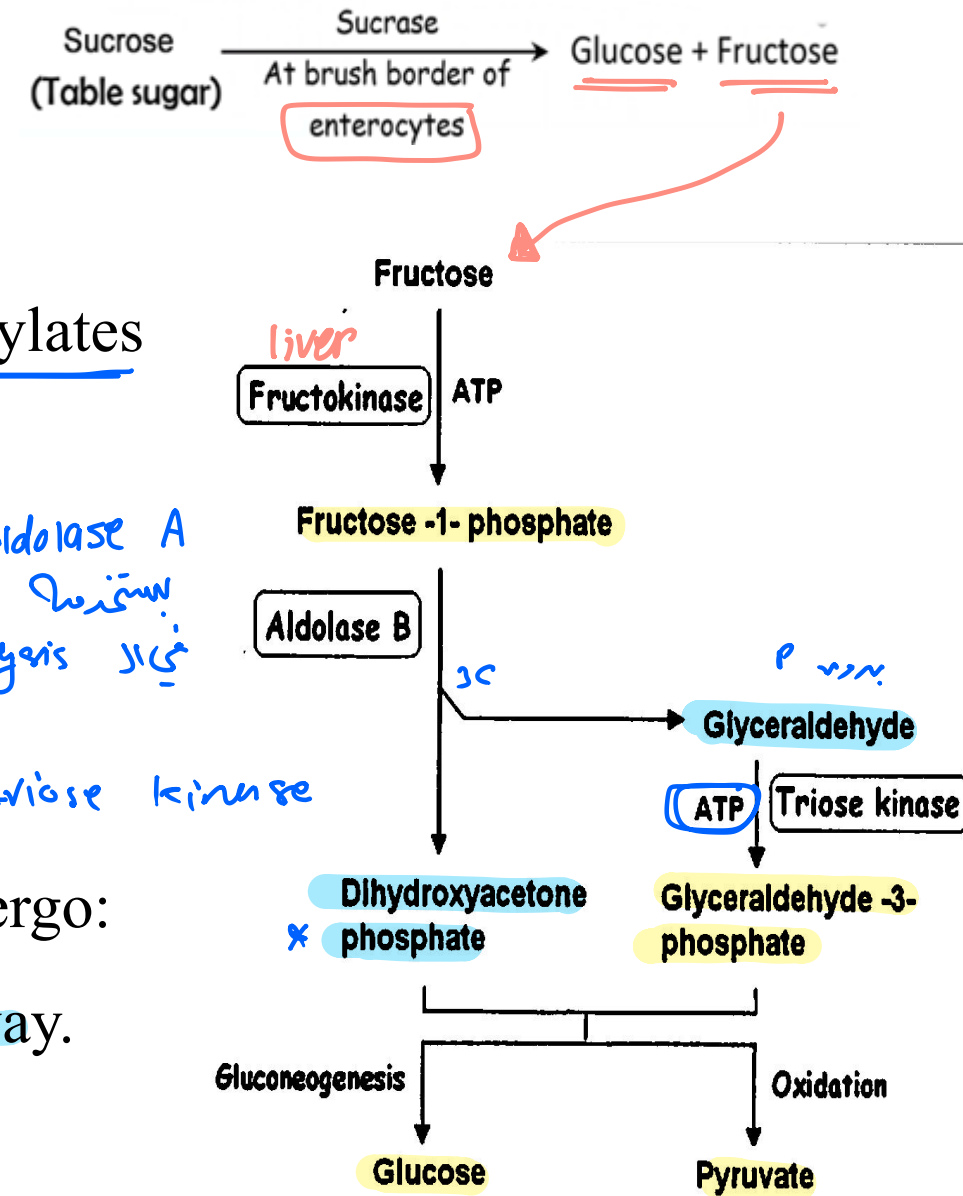
بند از recycling عصاره پورین و
نیاز به فوسفات و الفوسفات با فعل منفی
التهاب راجع به سبب و uric acid با تاتی بهر
swelling
hyperurecemia
Purine → uronic acid
salmon

Pathway نیاز به فوسفات و تاتی بهر

- Treatment: Galactose free diet (Soy based milk formula which has sucrose instead of lactose).

Metabolism of fructose: In the liver:

1. Liver contains fructokinase enzyme, which phosphorylates fructose into fructose-1-phosphate. *trapping*
2. Fructose-1-phosphate by aldolase B enzyme gives Dihydroxyacetone phosphate + glyceraldehyde. *aldolase A*
glycolysis
3. Glyceraldehyde gives glyceraldehyde-3-phosphate. *triose kinase*
4. Glyceraldehyde-3-p + Dihydroxyacetone-p may undergo:
 - a) Glucose formation (gluconeogenesis): main pathway.
 - b) Oxidation to pyruvate (glycolysis).



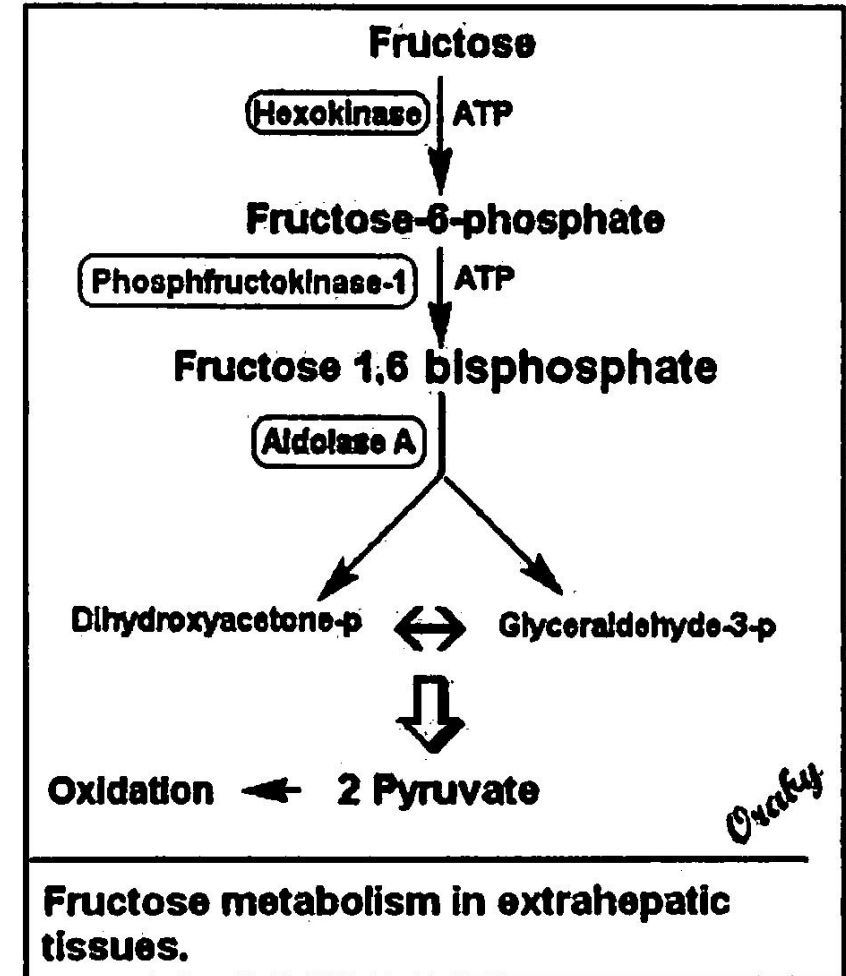
Metabolism of fructose in liver.

غیر الیور
liver

Metabolism of fructose: In extra-hepatic tissues:

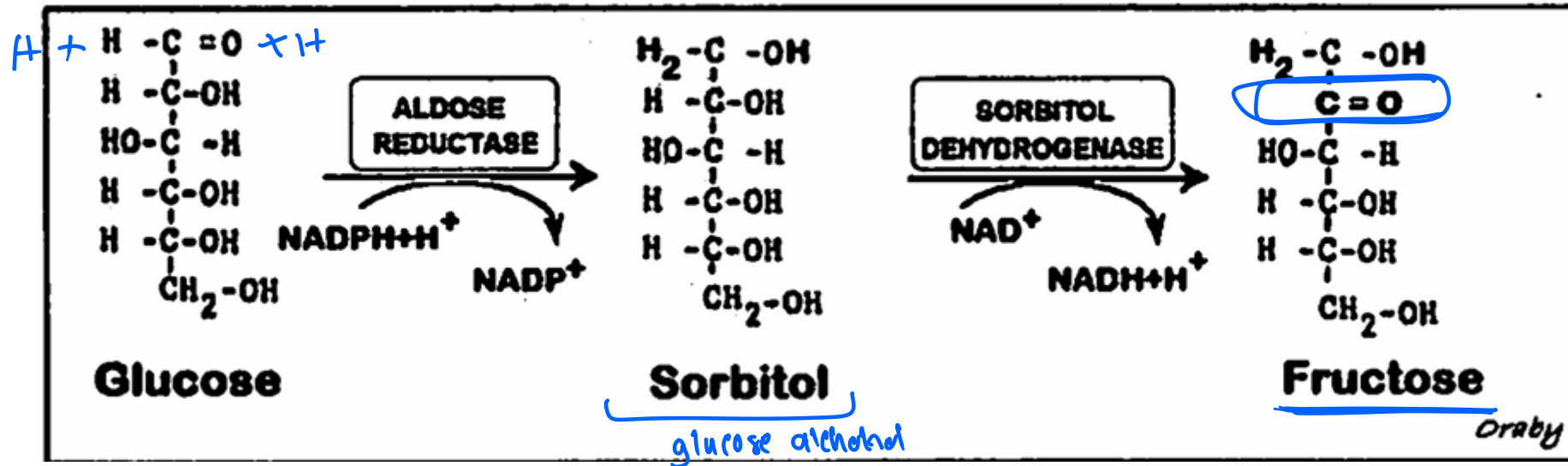
- Because fructokinase is not available in muscles and adipose tissue, fructose is metabolized by hexokinase and other enzymes into pyruvate (oxidation).

غیر الیور
liver
بہت زیاد



In the testis (seminal vesicle), lens, peripheral nerves and renal glomeruli:

- Glucose is converted into fructose through sorbitol formation:



- Fructose is the main nutrient for sperms. *کافیه من یقین*
- Deficiency of fructose in semen correlates with male Infertility.

Genetic disorders of fructose metabolism:

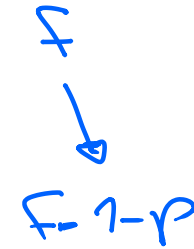
Fructose metabolized
extra hepatic
by hexokinase

Fructose is keto sugar $\therefore$ aldofructose in lens inactive

- Essential fructosuria: (Benign) high fructose in urine

بیماری کی صفت است

- Cause: Due to deficiency of fructokinase enzyme (AR).



- Effect: Not serious condition. The excess accumulated fructose is lost in urine (fructosuria).

Hereditary fructose intolerance.

- Cause: Due to deficiency of aldolase-B enzyme (AR).

swelling
osmosis

- This leads to accumulation of fructose-1-phosphate leading to damage of liver and kidney tissues (Liver and kidney failure).

X di hydroxy acetone phosphate
X glyceraldehyde

- Treatment: Fructose free diet

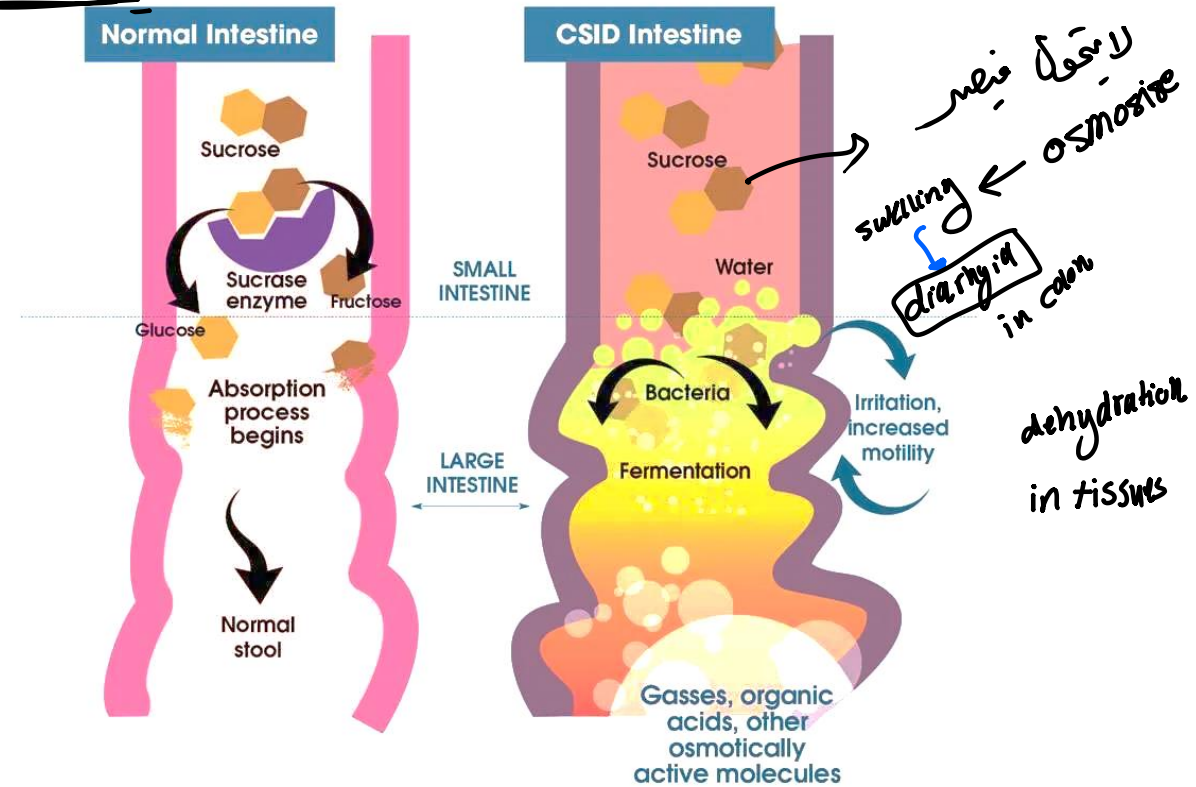
لا يظفر عند الأطفال ولا يفرغوا

حليب عياره في lactose

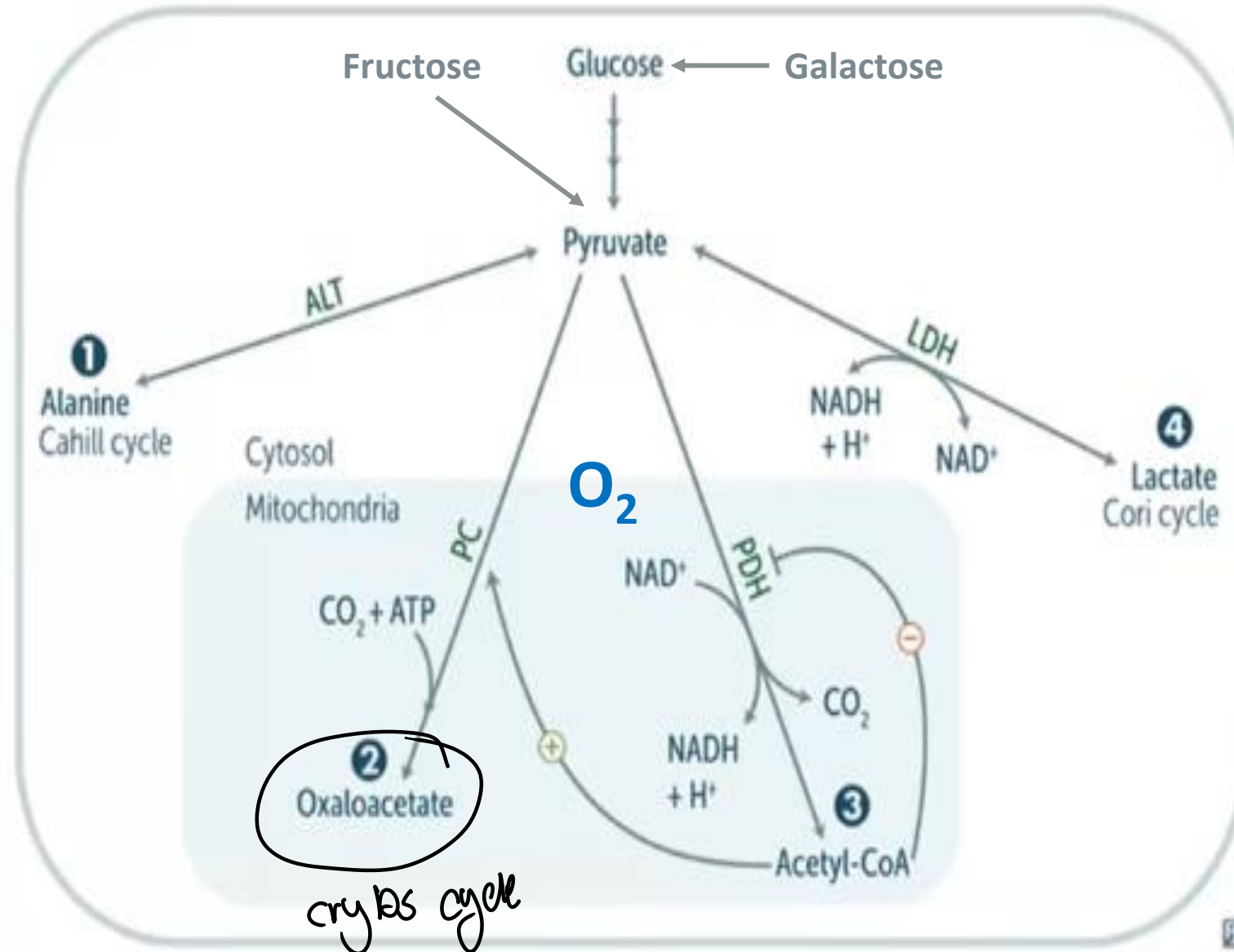
Sucrase deficiency:

تظهر عند ال new borns
↑ القرحة بـسبب

- A rare condition, showing the signs and symptoms of lactase deficiency.
- It occurs early in childhood



Pyruvate metabolism



Functions of different pyruvate metabolic pathways (and their associated cofactors):

- 1** Alanine aminotransferase (B_6): alanine carries amino groups to the liver from muscle
- 2** Pyruvate carboxylase (B_7): oxaloacetate can replenish TCA cycle or be used in gluconeogenesis
- 3** Pyruvate dehydrogenase ($\text{B}_1, \text{B}_2, \text{B}_3, \text{B}_5$, lipoic acid): transition from glycolysis to the TCA cycle
- 4** Lactic acid dehydrogenase (B_3): end of anaerobic glycolysis (major pathway in RBCs, WBCs, kidney medulla, lens, testes, and cornea)

Thanks

Thanks