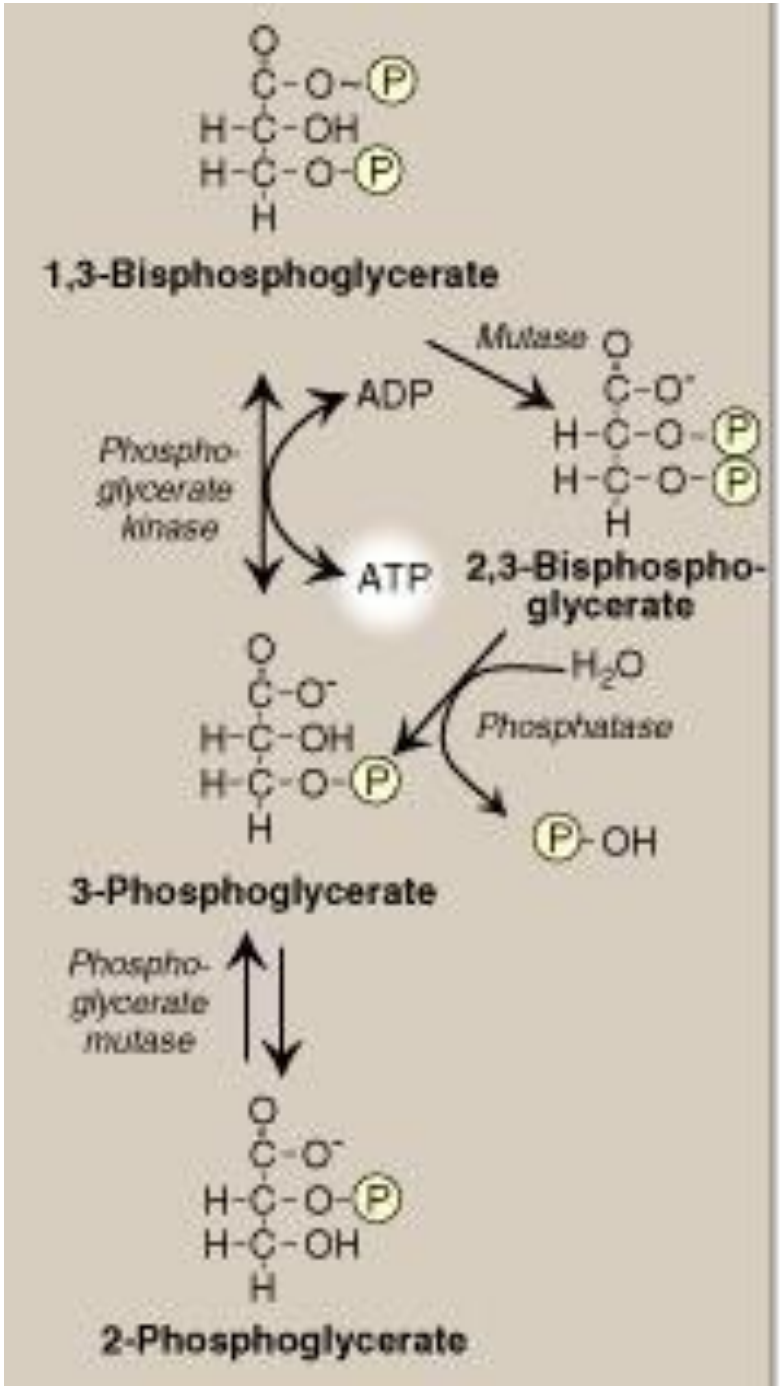
Synthesis of 2,3 bisphosphoglycerate in RBC

↑↑Oxygen delivery to tissues

By binding to deoxyhemoglobin reducing its affinity to O2 and increasing O2 release to tissues



- Glycolysis is major energy source as well as you have suger, some cells such as RBCs are depend on glycolysis as main source for ATP (RBCs need low energy)
- RBCs have some glycolytic modifications (some time)

في بعض الانزيمات بنستغني عن خطوة تحويل 1-3 bisphosphoglycerate → 3 phosphoglycerate بخطوتين بدل خطوة، يعني بدل ما نحولها مباشرة، بنروح بنمر بخطوتين لهدف وهاد الاشي نفس مبدأ لما يكون تحويلة ع الشارع.

- 1-3 bisphosphoglycerate will be converted to 2,3 bisphosphoglycerate by mutase and what exactly happene that P will be transported from C_1 to C_2, then the P on C_2 will be removed by phosphatase to produce 3 phosphoglycerate, the same product !! So why ?
- When the RBCs in the gas exchange site in tissue, here the hemoglobin bind to oxygen and it should release oxygen to go to tissues. And this is what exactly happen because of the low PO_2 in tissues ! Althoug the low PO_2 cause oxygen releasin by decresing the affinity of binding, there are probability to bind with deoxyhemoglobin

again !!

So, the 2,3 bisphosphoglycerate (hero) will bind to hemoglobin after oxygen releasing to prevent it from binding once again until it reach all tissues.

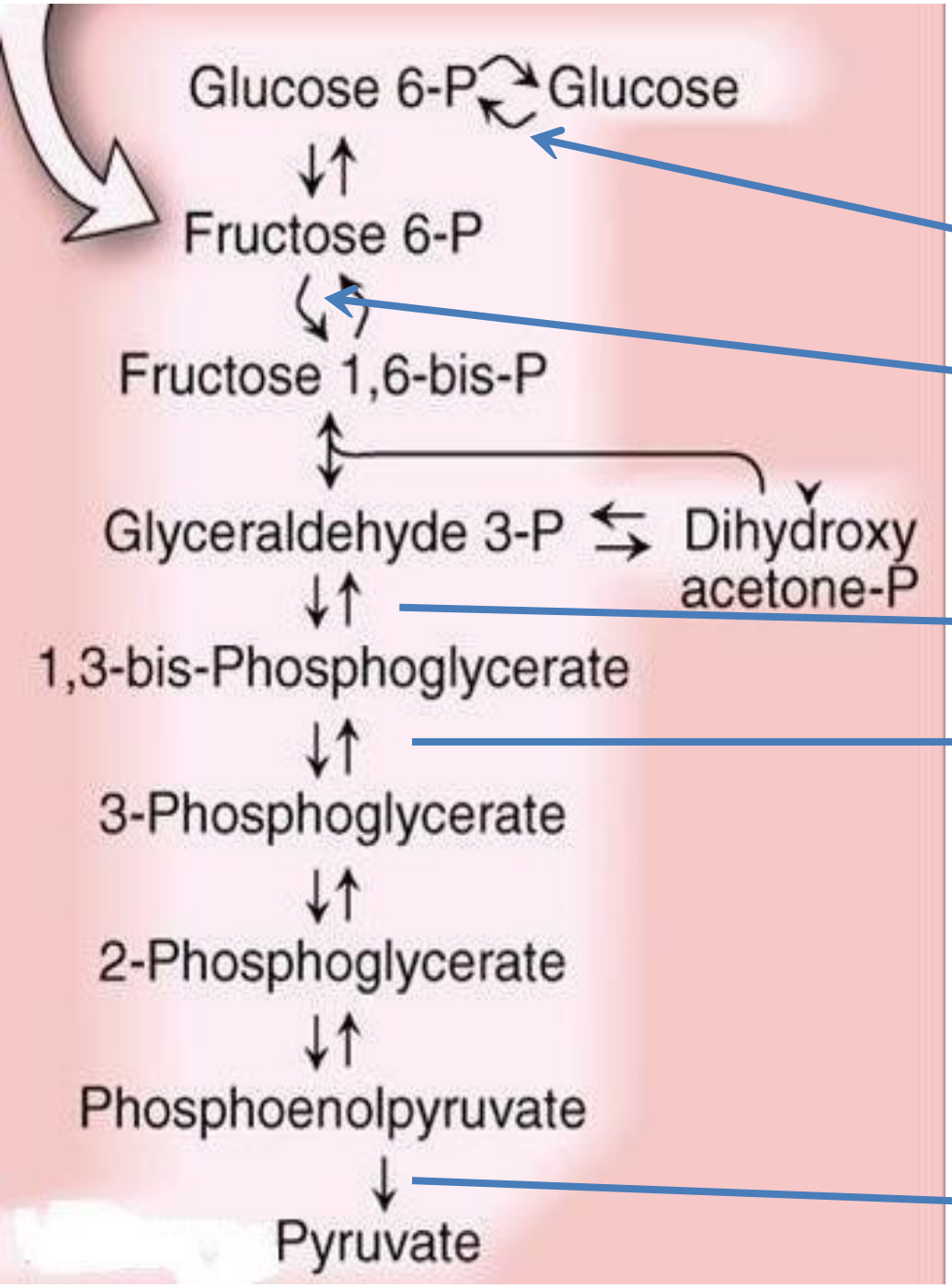
وهيك بنكون هنا وصلنا الـ oxygen والأمور تمام ، بتقدر تتخيل الـ 2,3 bisphosphoglycerate على إنه بطل على الـ هاد الطفل الـ hemoglobin حتى يهربوا جميع الأكسجينات.

هون الـ RBCs حتت جزء من الطاقة عشان مصلحة الأكسجين ، لأنه الطاقة اللي طلعت من تكسير رابطة P في كربونة 2 راحت هباءً منثورًا.

ومثل ما حكينا فوق هاي العملية تحس Sometime ، بيجي لما كانت الـ RBCs عند site of exchange at lung → لسه تحدث.

لا تنسوا أهل غزة من الدعاء.

LuJaiN



Energy Need and Production

-ATP

-ATP

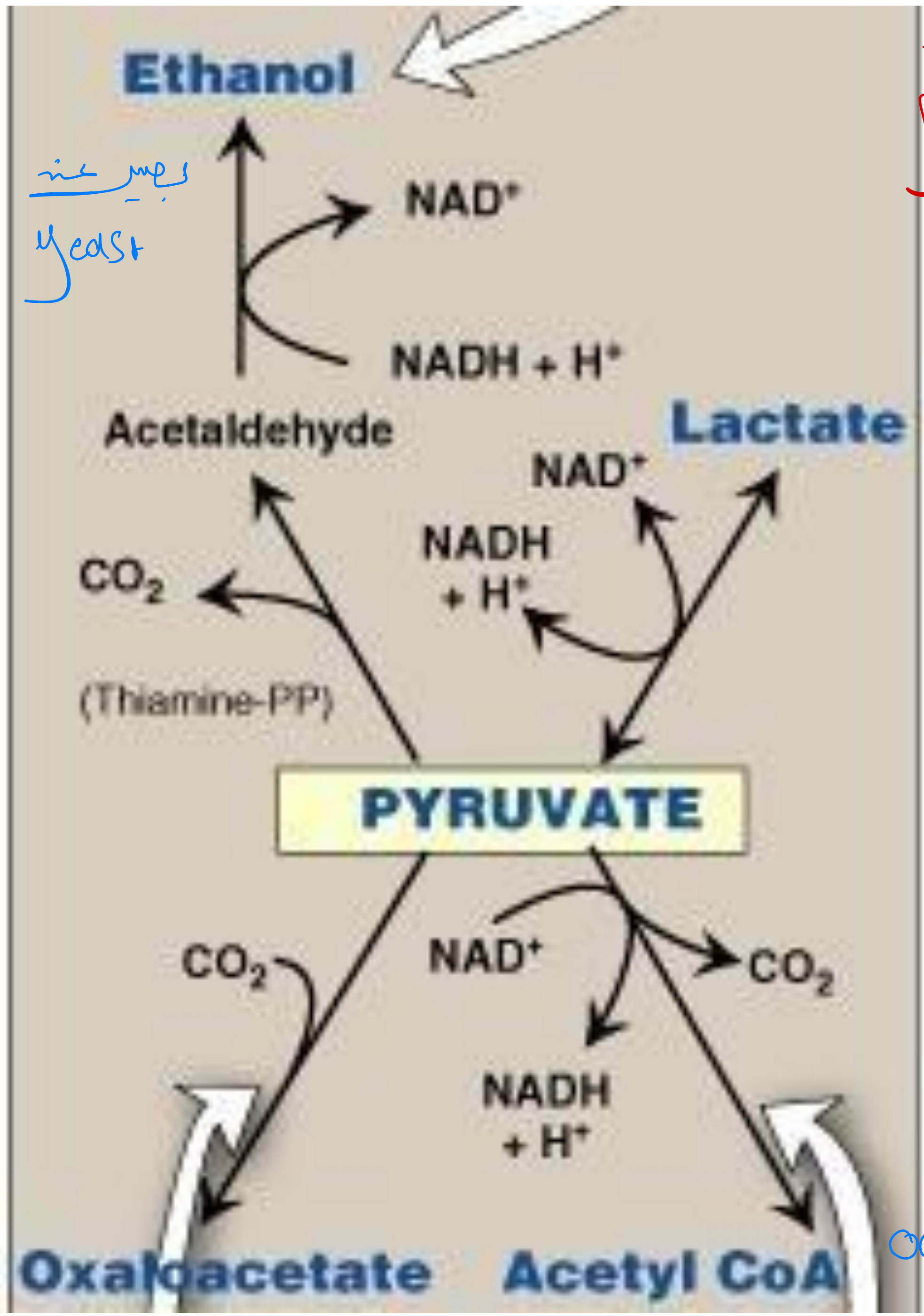
2 NADH

2 ATP

Is Oxygen needed?

No, Not Needed

2ATP



- اول معلومة مهمة ← pyruvate ① تأتي من أكثر من مصدر
- ثاني معلومة مهمة ← pyruvate ② يسلك أكثر من pathway
- ثالث معلومة مهمة ← ③ حالة الجسم لتحدد اول معلومتين

well fed — fasting — abnormalities

Pyruvate Fates

- الرسمة ح نفصل (لاحقاً)، بس نعلق عليها شوي

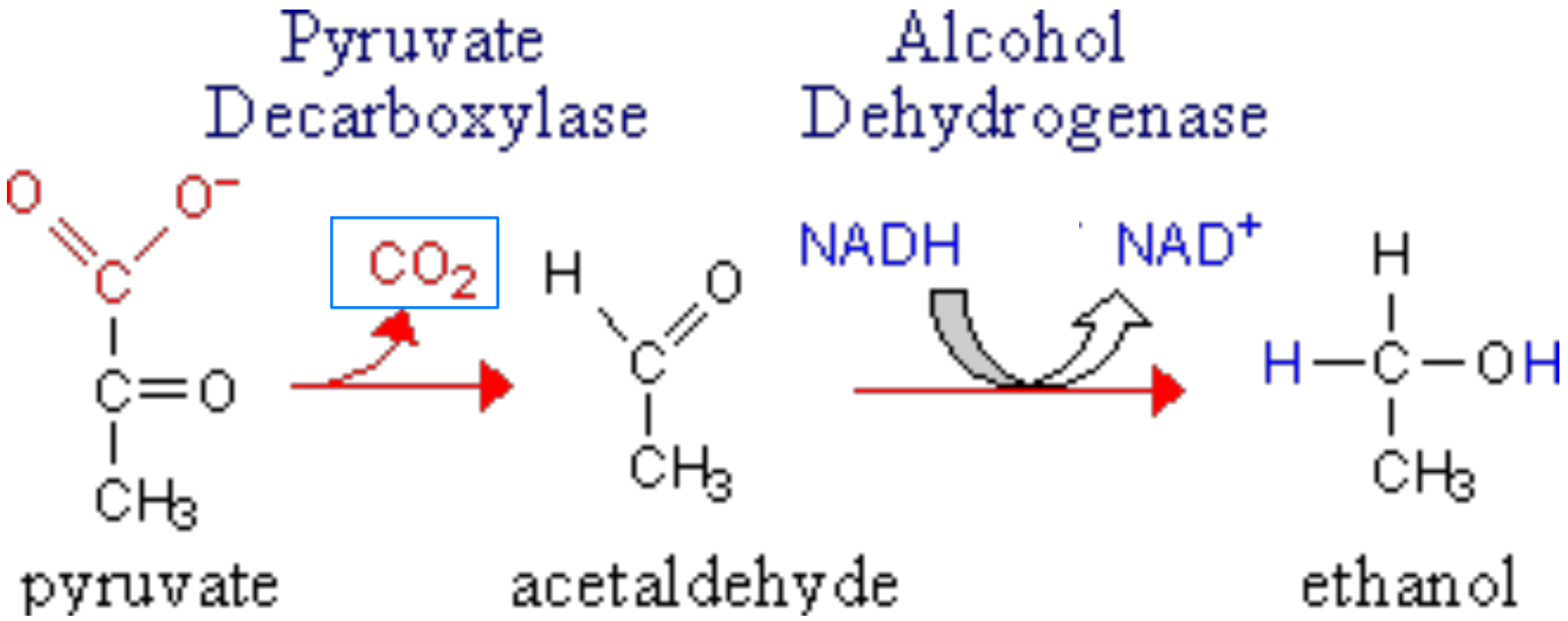
- pyruvate go into acetyl CoA in the well fed state → لما glu والأمور تمام

- pyruvate go into oxaloacetate in fasting state in order to begin glucogenisis path.

تعليق ع هاي النقطة ← pyruvate ① هون ما بكون اجا من glycolysis، لانه مش منطق اكون ب fasting وعندي glu ويصير ال glycolysis.

② لما Pyruvate بدو يتحول ل glu في حالة fasting لازم اول اشي يتحول oxaloacetate

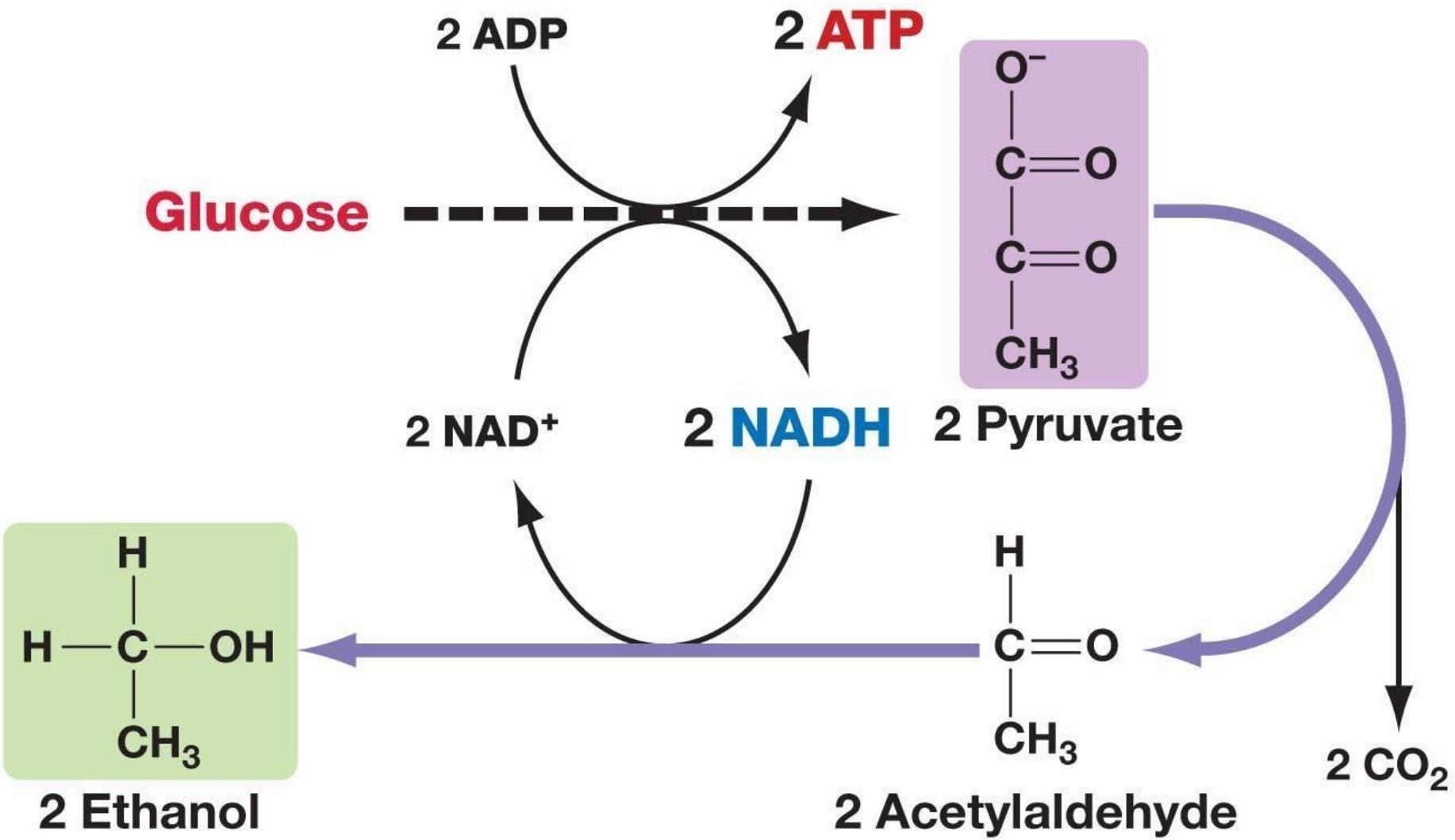
From Pyruvate to Ethanol



- Decarboxylation of pyruvate to acetaldehyde then reduce it to ethanol

١- كمثال على التفاعل خروج الأكسجين الذي يتفاعل بسبب CO_2

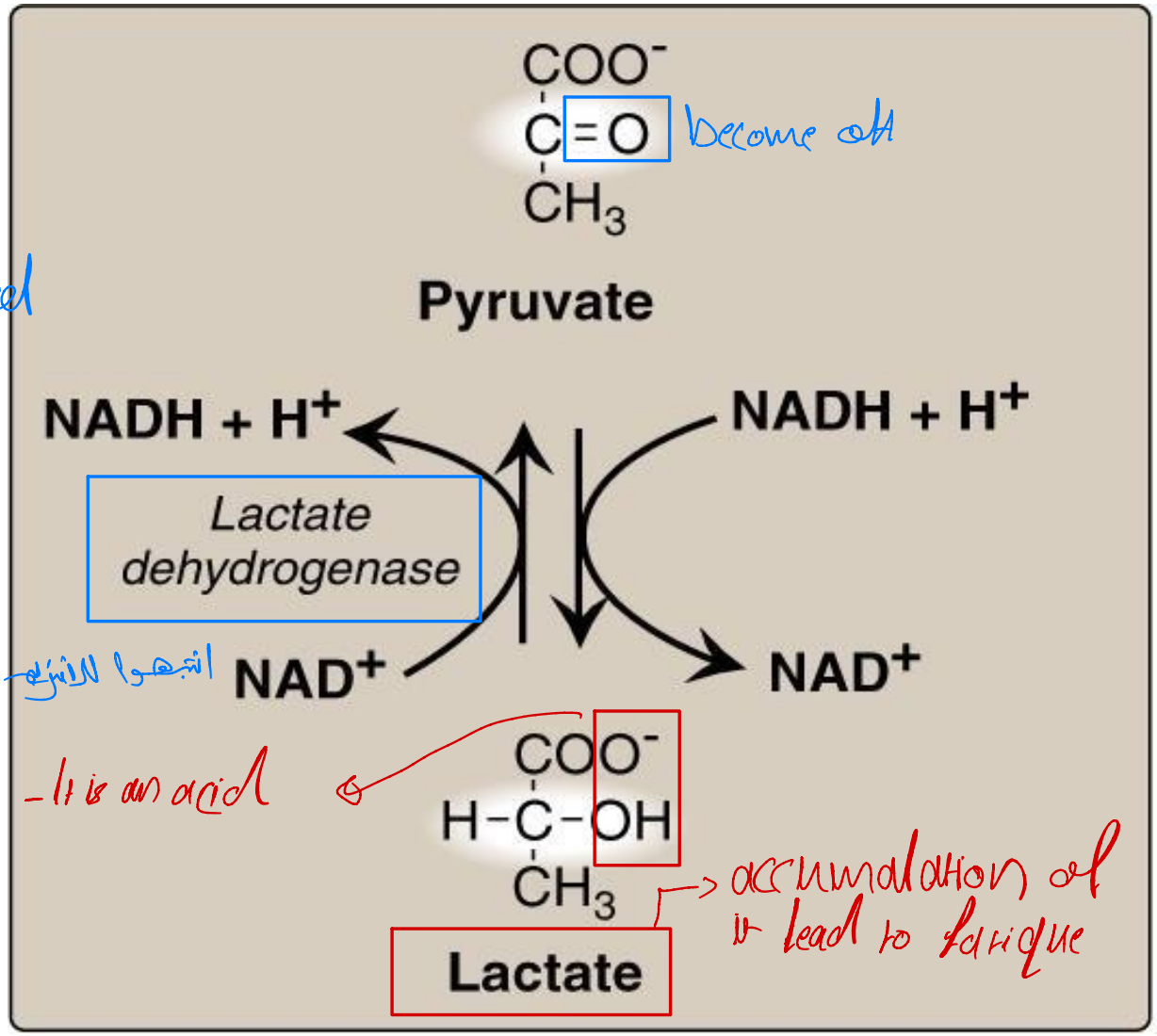
(b) Alcohol fermentation occurs in yeast.



From Pyruvate to Lactate

- It is a reduction reaction

So the NADH become oxidized to NAD^+ which we need in a lot of pathway.



$$\text{Pyruvate} + \text{NADH} \rightleftharpoons \text{Lactate} + NAD^+$$

When is Lactate Produced?

- Cells with low energy demand
- To cope with increased energy demand in rigorously exercising muscle, lactate level is increased 5 to 10 folds
- Hypoxia

  to survive brief episodes of hypoxia

• يُنتج lactate في هاي الحالة عشان نعيش مؤقتًا مدفعا

Clinical Hint: Lactic Acidosis

→ when the lactate accumulate.

- ↓ pH of the plasma → PH
- The most common cause of metabolic acidosis
  - ↑ Production of lactic acid
  - ↓ utilization of lactic acid

pyruvate

$$\text{Pyruvate} + \text{NADH} \rightleftharpoons \text{Lactate} + \text{NAD}^{+}$$

- Most common cause: Impairment of oxidative metabolism due to collapse of circulatory system.
  - Impaired O_2 transport
  - Respiratory failure → anarobic res.
  - Uncontrolled hemorrhage → loss of blood, less hemoglobin → less O_2 are transported → loss O_2 → anarobic respiration (shock).

Clinical Hint: Lactic Acidosis

- Direct inhibition of oxidative phosphorylation
- Hypoxia in any tissue
- Alcohol intoxication (high NADH/ NAD+)
- ↓ Gluconeogenesis
- ↓ Pyruvate Dehydrogenase
- ↓ TCA cycle activity
- ↓ Pyruvate carboxylase

سنتفصل كل نقطة منهم في السلايدز القادمة

_ Generally Alcohol metabolism ⇝ oxidation of Alcohol to an aldehyde which mean reduction of NAD^+ to NADH in Alcohol intoxication the ratio of $NADH/NAD^+$ will increased related to high conc. of NADH, And actually our bodies metabolism need NAD^+ more than NADH, for example TCA cycle will inhibited as a result for this high ratio which leaded pyruvate to convert to lactate.

_ We need gluconeogenesis in fasting state to convert pyruvate to glucose but if it (reduced) there will be accumulation of pyruvate which lead to lactate formation.

_ If pyruvate dehydrogenase activities reduced, the pyruvate will convert to lactate instead of acetyl CoA. ملاحظة بيصير oxaloacetate لأنو هدفنا بيصير بـ fasting، وعملية تكوين.

. well fed state بـ بيصير Acetyl CoA

_ As well as, reduce TCA cycle activities will lead to lactate formation.

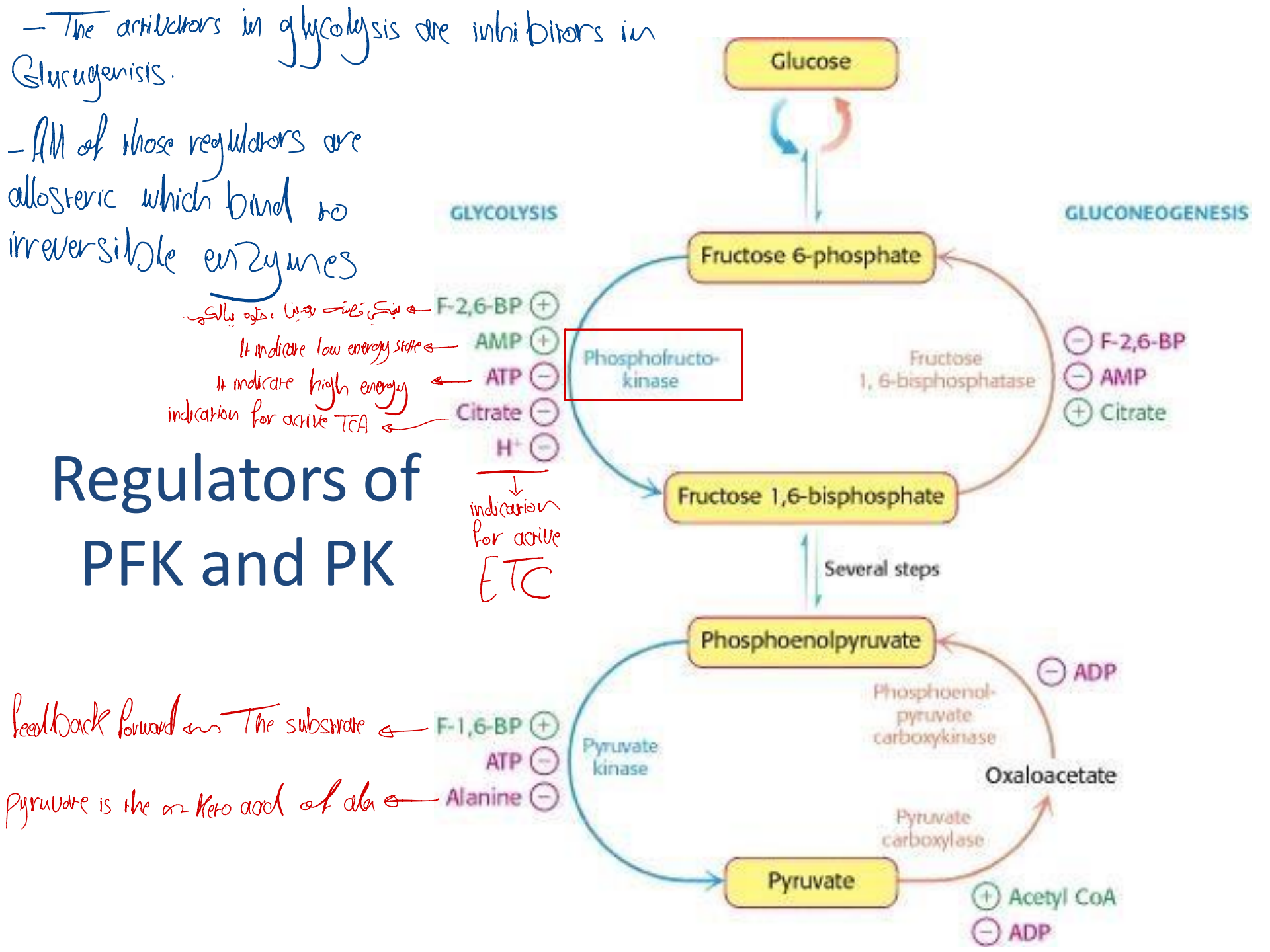
_ Reduced pyruvate Carboxylase which convert pyruvate to oxaloacetate will lead to lactate formation. يوضح هون زمنا باتجاه lactate مش acetyl CoA لأنه كل بـ fasting state، يعني لما glu بيمشي الـ glycolysis و TCA cycle

Regulation of Glycolysis

- The activators in glycolysis are inhibitors in Glucogenisis.

- All of those regulators are allosteric which bind to irreversible enzymes

Regulators of PFK and PK



It indicate low energy state

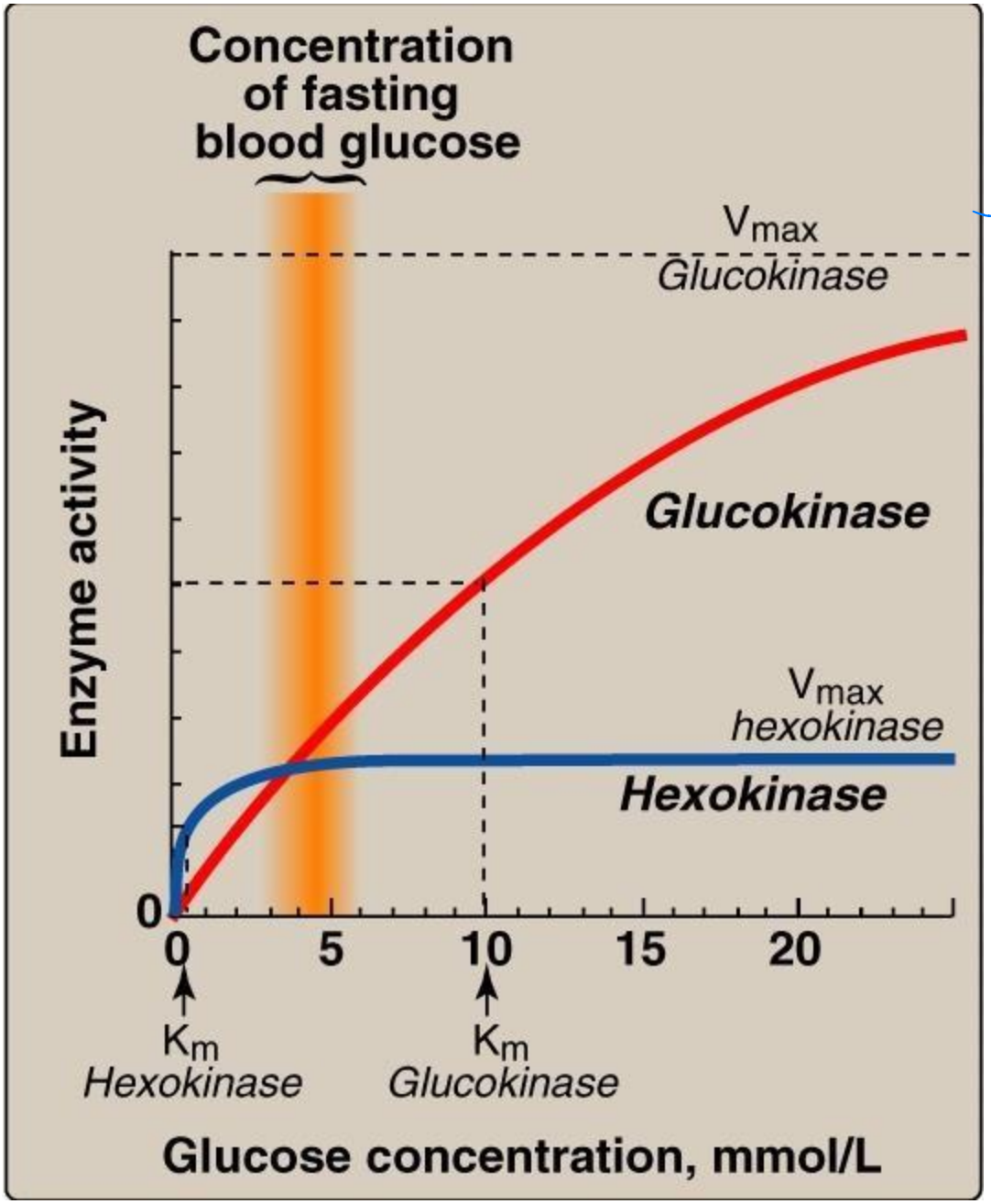
It indicate high energy

indication for active TCA

indication for active ETC

Feedback forward on The substrate

Pyruvate is the α-keto acid of ala



- The Vmax for hexokinase is much lower than glucokinase.

- لما نأكل وجبة أول ما نأكل كلها يكون مستوى السكر عالي وبيشتغل ينزل لمستوى معين

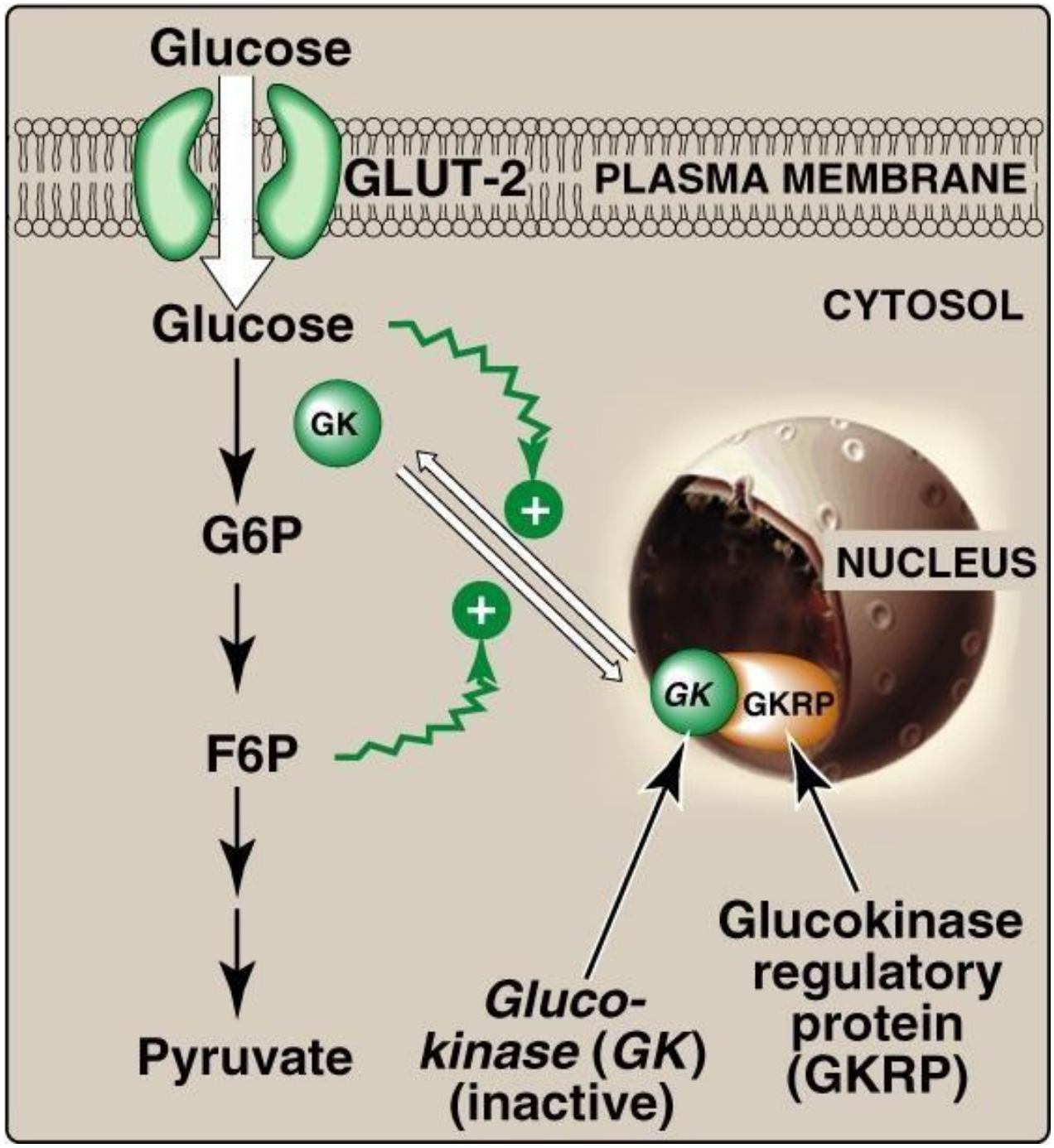
Glucokinase and Hexokinase Activity

→ fasting blood sugar يعني

وغالبًا ما بيلزم ينزل عن كذا علشان

الشخص يغيب عن الوعي.

Hexokinase more active than Glucokinase.

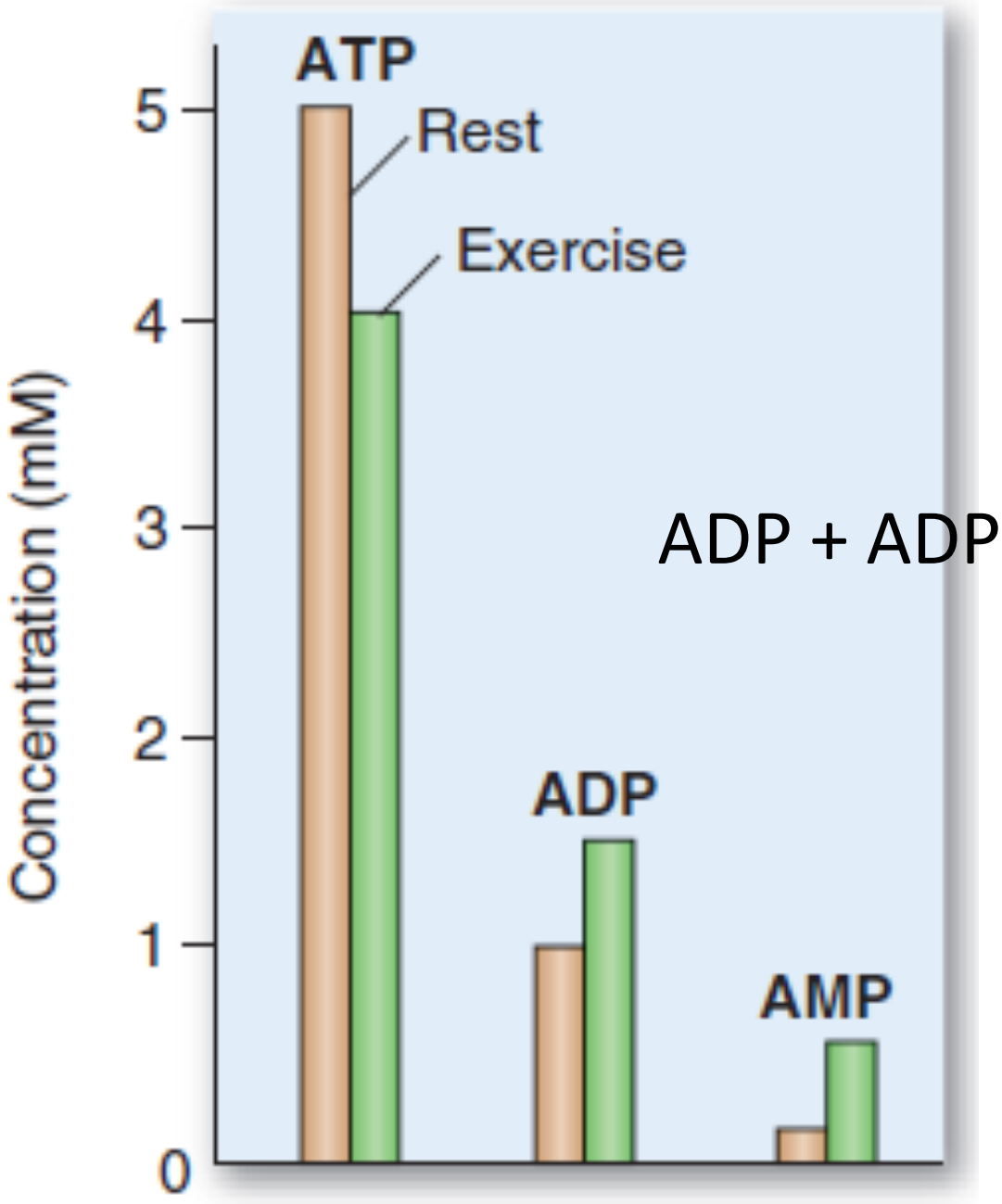


Glucokinase Regulation

- whenever the conc. of glu. is relatively low, the glucokinase is sequester in nucleus where it bound to a regulatory protein GKRP

after we eat food with glucose the glucose will activate the dettachment of glu. kinase from GKRP.

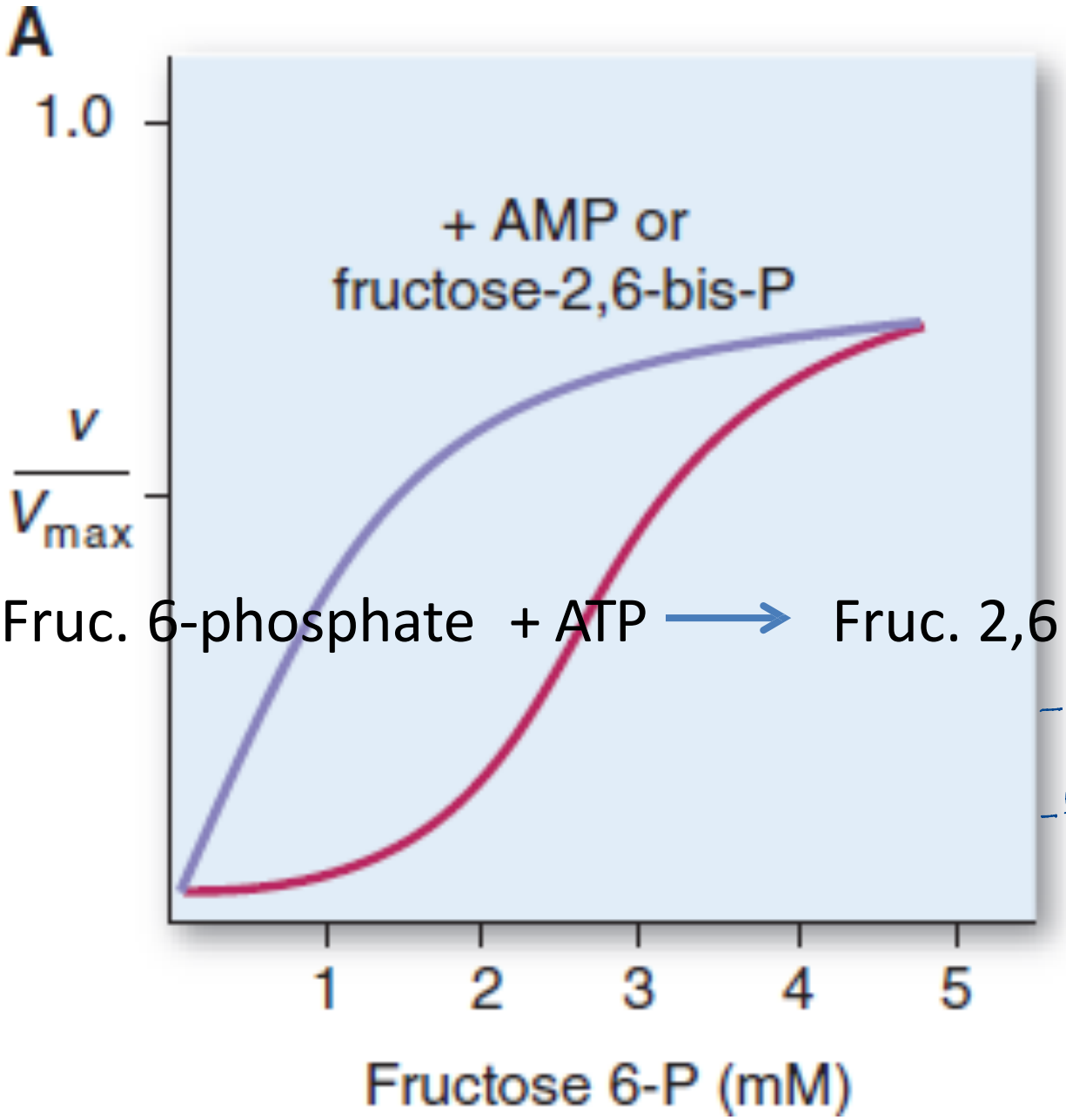
- whenever the conc. of fructose 6 phosphate increases it will inhibit the glu. kinase by activating the sequestrion which mean (حبس)



Regulation by ATP and AMP

ADP + ADP $\rightleftharpoons$ ATP + AMP

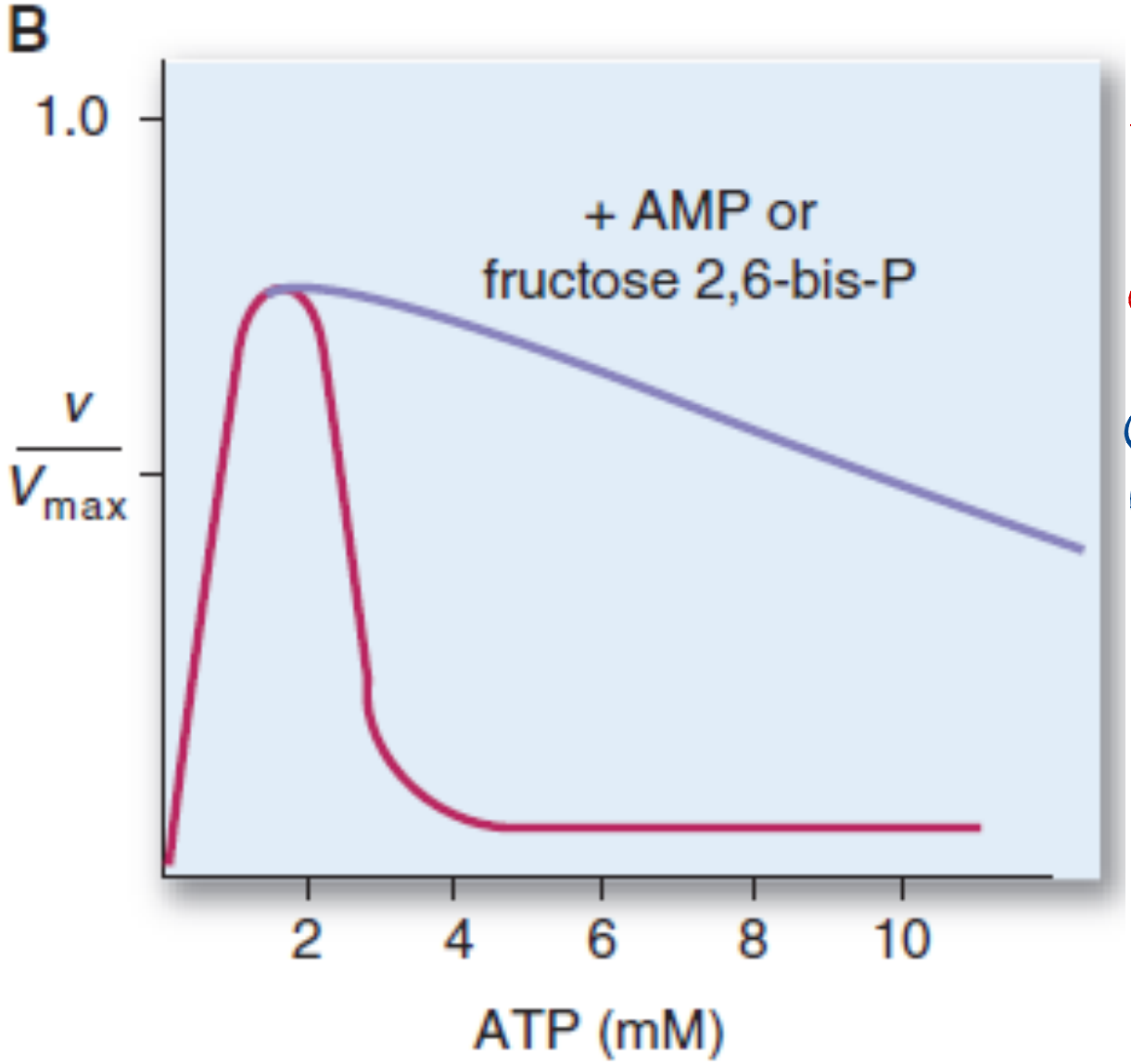
Regulation of PFK by Fructose 2,6-bisphosphate



Fruc. 6-phosphate + ATP → Fruc. 2,6 bisphosphate + ADP

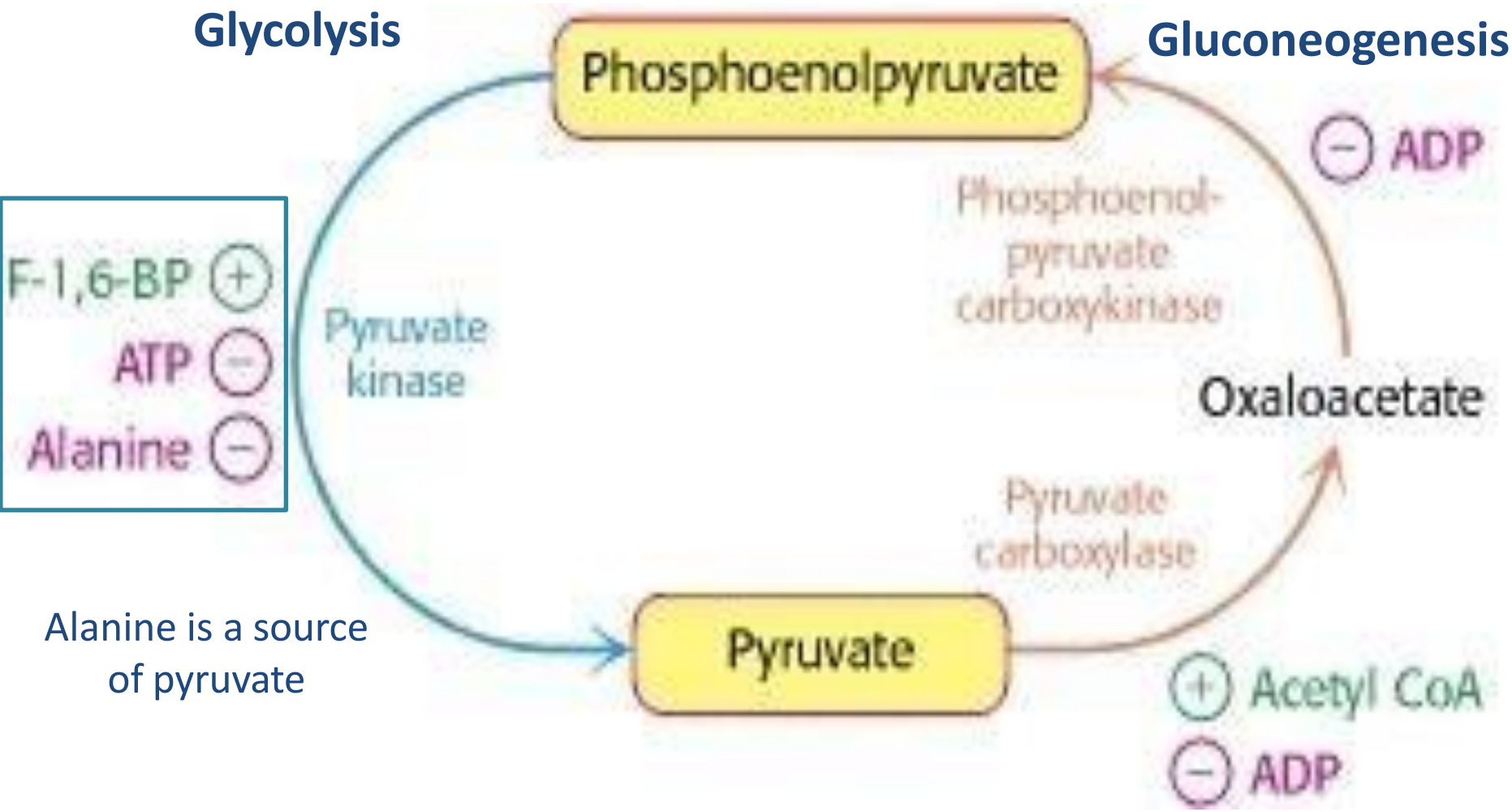
- Red curve is without activator (AMP)
  sigmoidal
- purple curve is with activator (AMP)

How about the other substrate?



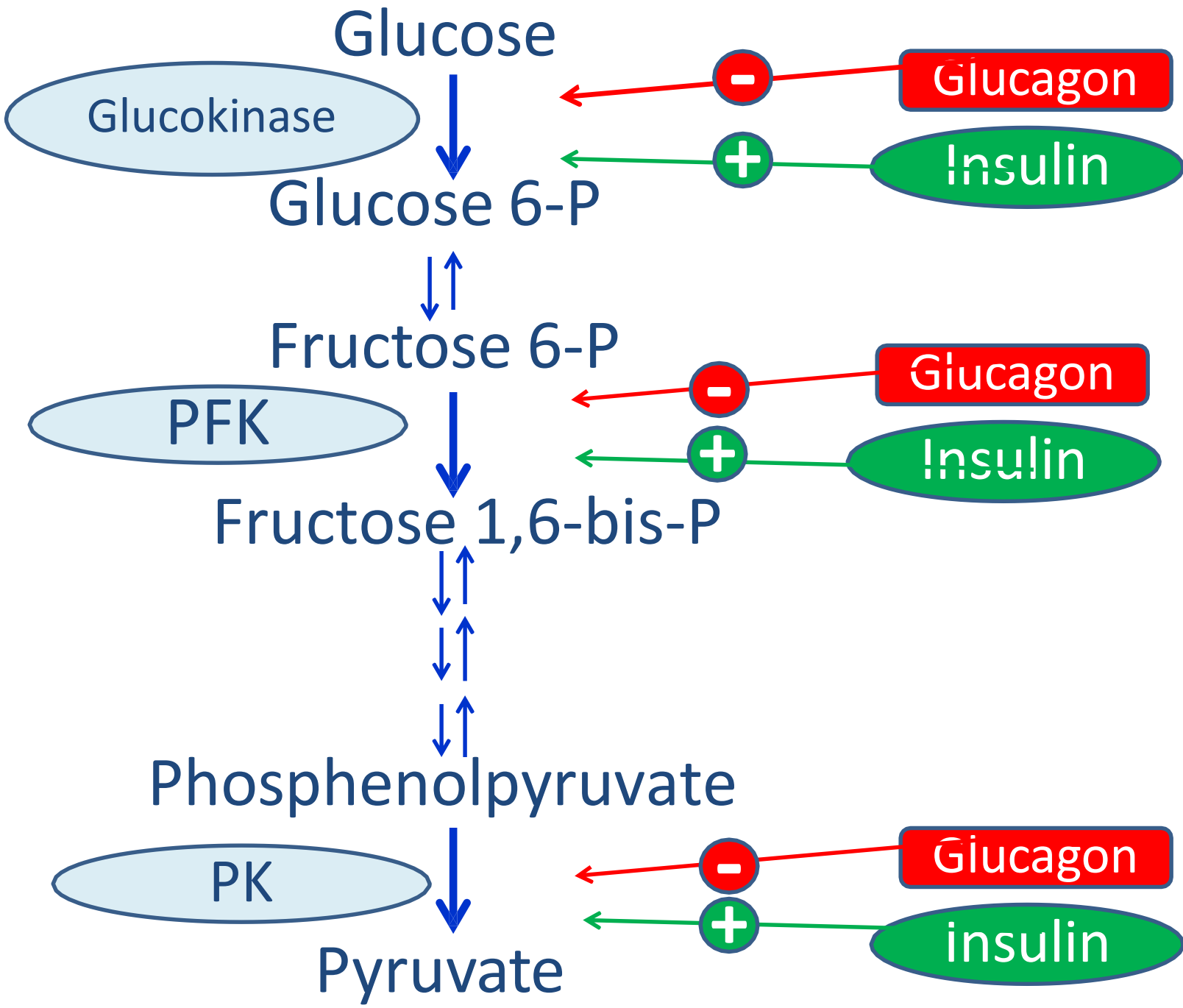
- In the red curve ATP play role as a substrate. but when we have conc. of ATP it will play role as an inhibitor as in purple curve.

Regulation of Pyruvate Kinase

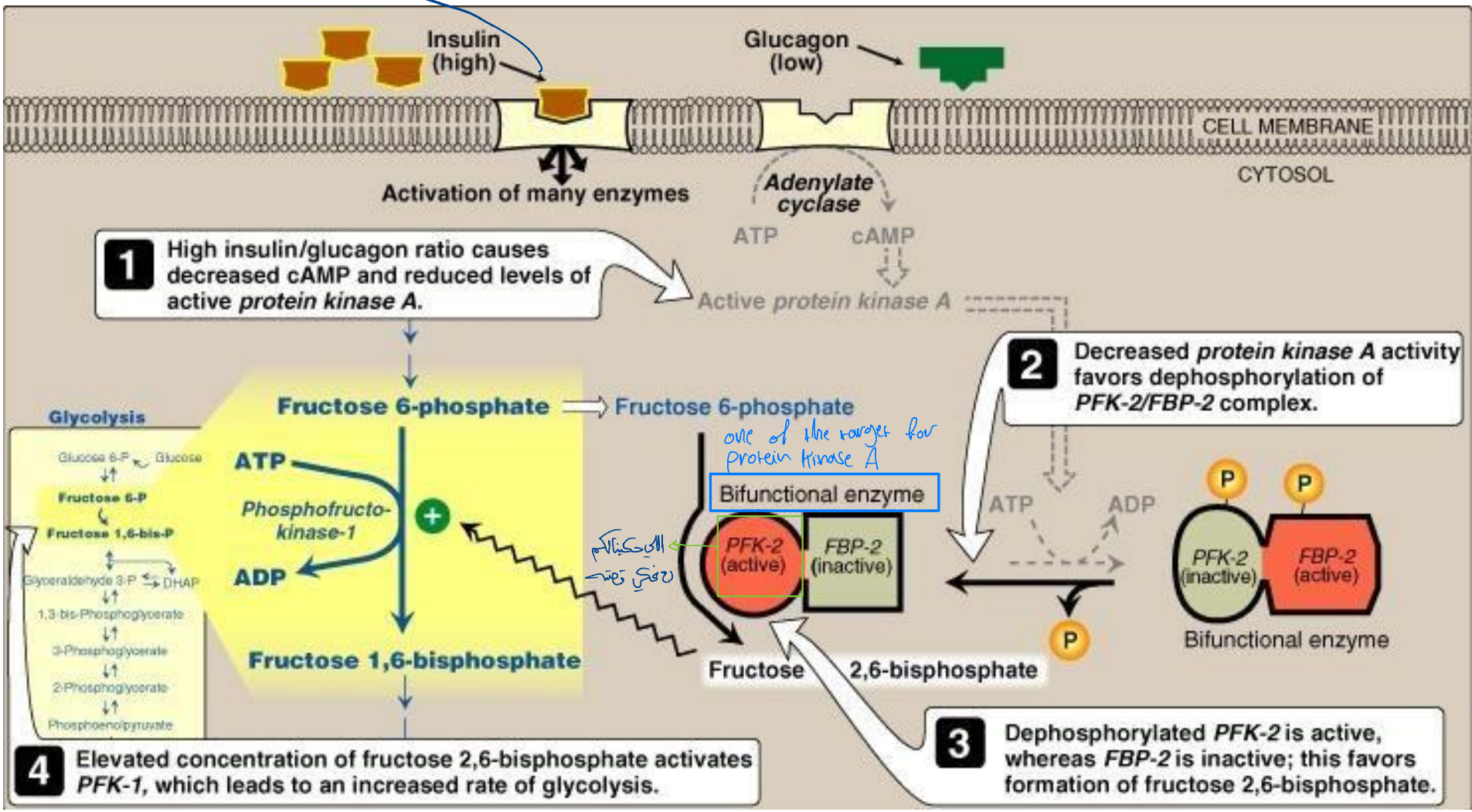


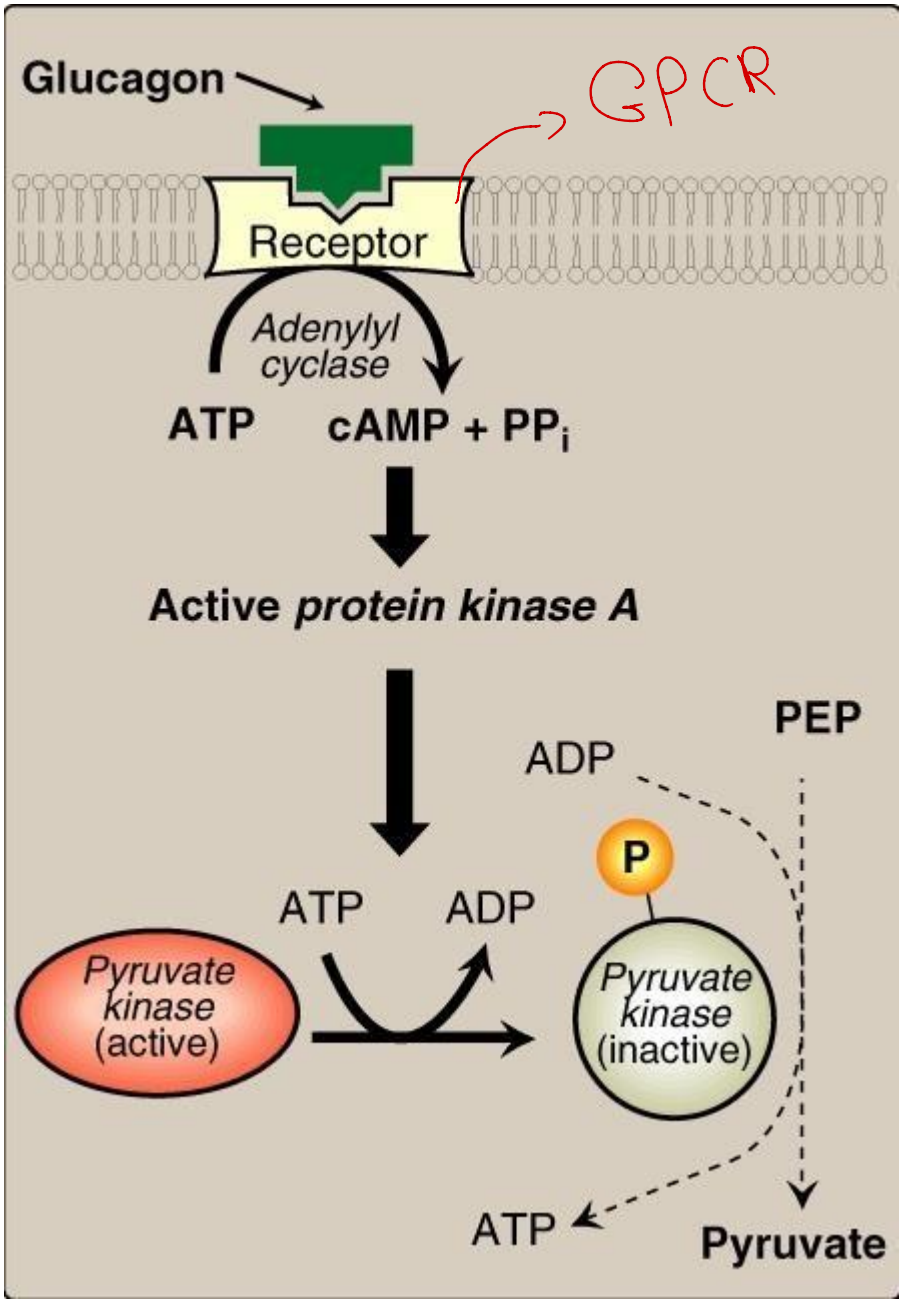
Alanine is a source of pyruvate

Hormonal Regulation



Hormonal Regulation of Phosphofructokinase





Hormonal Regulation of Pyruvate Kinase

Clinical Hint: Pyruvate Kinase Deficiency

– The most commonly enzyme affected by mutations.

- The most common among glycolytic enzyme deficiencies
- RBCs are affected
- Mild to severe chronic hemolytic anemia
- ATP is needed for Na+/K+ pump ➔ maintain the flexible shape of the cell

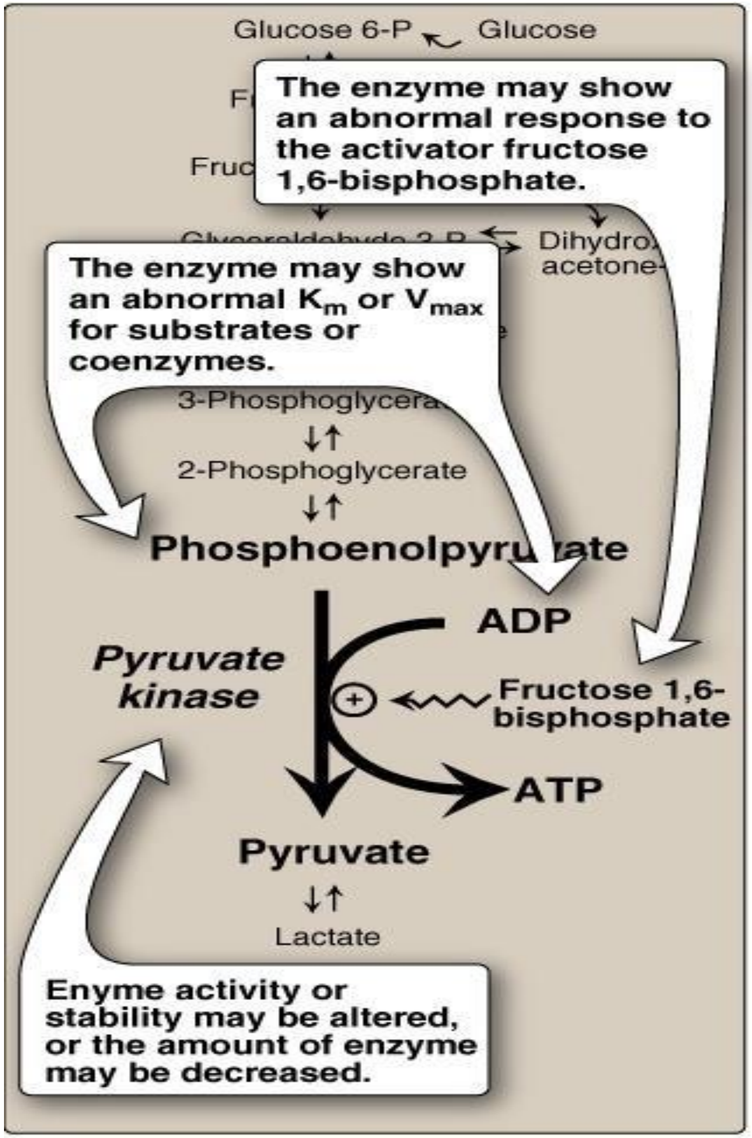
(راح يجي منها سؤال)

~> The shape mean the function, so they become premature → بيموتوا قبل 120 يوم

- Low ATP ➔ premature death of RBC

~> * عشان هيك بصير انحلال فيه كأنه عنده انيميا.

- Abnormal enzyme; mostly altered kinetic properties



Alterations observed with various mutant forms of pyruvate kinase

External Inhibitors of Glycolysis

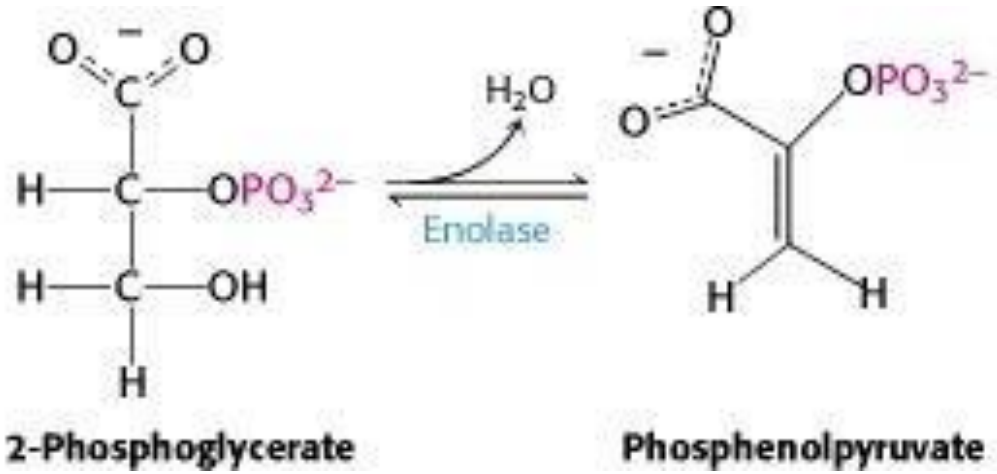
- inhibitors from outside our bodies

Inorganic Inhibitors of Glycolysis

Fluoride

- Fluoride inhibits Enolase

https://youtu.be/bplSIA1m8HM?si=-NDgws-thGrdPeZP



Fluoridated water → ↓ bacterial enolase →

Prevention of Dental Carries

Inorganic Inhibitors of Glycolysis

Arsenic Poisoning

عنصر الزرنيخ

- Pentavalent Arsenic (Arsenate)

  competes with phosphate as

  as a substrate for GA3PDH

- ↓ ATP synthesis → يقلل تصنيع ATP

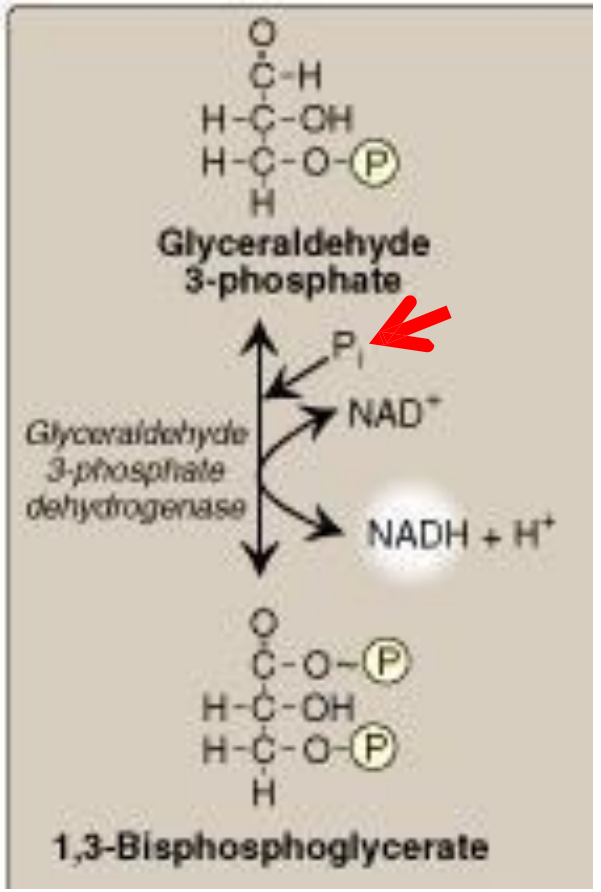
- Trivalent Arsenic (Arsenite)

  Forms stable complex with -SH

  of lipoic acid ⇝ خطير جدًا

- ↓ Pyruvate Dehydrogenase
- ↓ α ketoglutarate Dehydrogenase

➔ Neurological disturbances.....**DEATH**



Lujain Ahmad