وَقُل رَّبِّ زِدْنِي عِلْمًا

RESPIRATORY SYSTEM

HAYAT BATCH

SUBJECT : Biochemistry

LEC NO. : 4

DONE BY : Yazan Allan

بسم الله الرحمن الرحيم

Role of hemoglobin in acid base balance

By

Dr. Walaa Bayoumie El Gazzar

قبل ما نبدأ بمحاضرتنا
باخر المحاضرة الماضية ضل سؤال ما حلته الدكتورة فبداية هاي المحاضرة تناقشنا فيه، هي السؤال للي مش متذكره 👇👇

((22-26)) ((35-45)) ((7.35-7.45))

واحد عنده ال ph تساوي 7.37 وال pCO2 يساوي 33 وال HCO3 تساوي 17 ايش هاي الحالة ؟

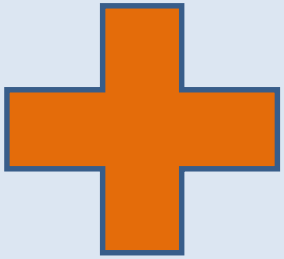
أ- compensated respiratory alkalosis

ب- metabolic acidosis with full comensation

طبعا الجواب هو خيار -ب- لانه حكينا احنا انه ال ph لازم يكون قريب لل alkalosis side بال compensated respiratory alkalosis اما هون بالسؤال كانت ال ph مايله باتجاه ال acidosis وغير هيك خلينا نتطلع على ال HCO3 قيمتها قليلة جدا اما ال pCO2 صحيح انها اقل من الطبيعي لكن مش قليلة كثير لانه احنا قللناها مشان نصلح النقصان بال HCO3 يعني تعتبر ضمن حالة ال compensation

اذا مش عارفين تحلوه وما فهمتو عالشرح لا سمح الله 🔪🔪 ارجعوا هون 👇 للدقيقة ٨:٣١
https://youtu.be/Ck7llsos3wQ?si=gNqa2_RR70Tl06pH

Hemoglobin

Heme  Globin

Globin

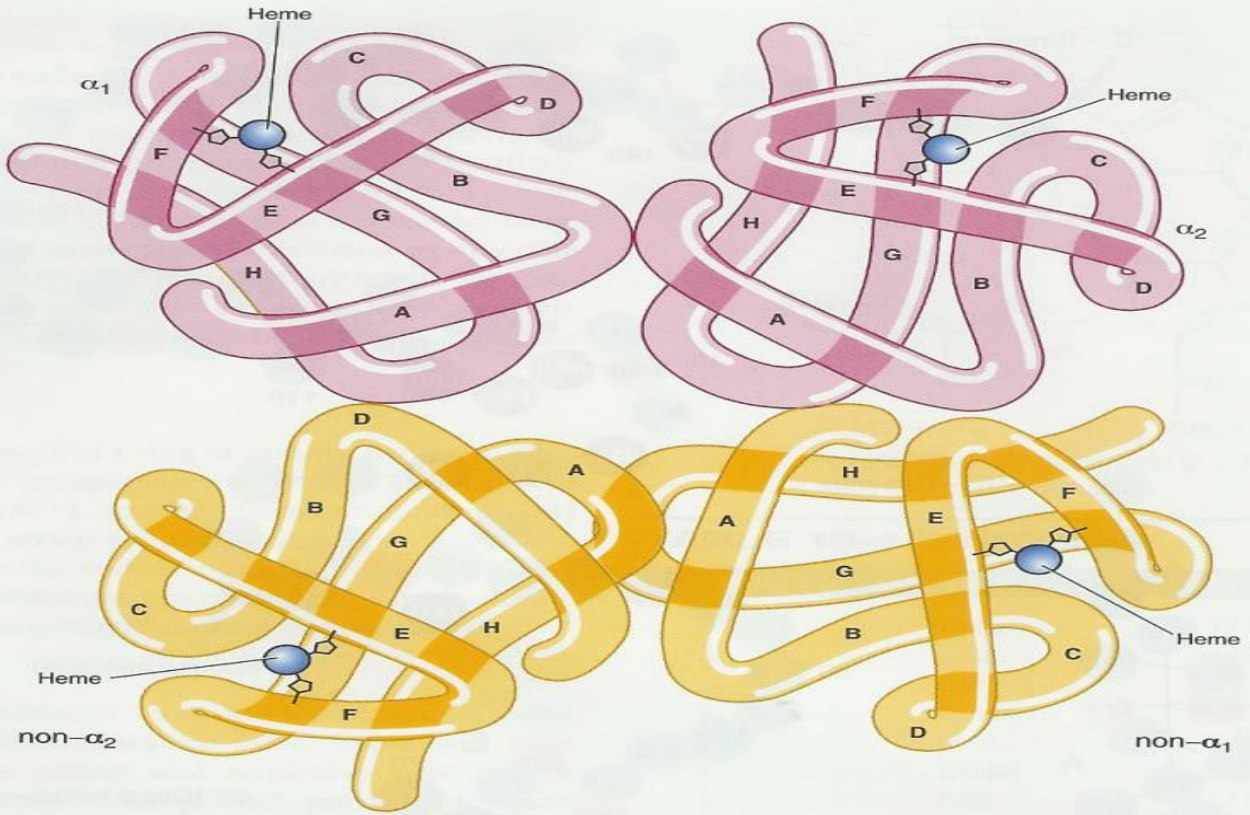


Figure 10-4 Complete Hb molecule. Heme is suspended between the E and F helices of the polypeptide chain. Pink represents α 1 (*left*) and α 2 (*right*); yellow represents non-α 2 (*left*) and non-α 1 (*right*).

Rodak, Hematology, third edtion

مراجعة سريعة (اخذناه بال HLS)

Globin

- Tetramer : 4 polypeptide chains.
- Each polypeptide chain is formed of 7 or 8 helices which are termed A-B-C-D…….
- There are 4 types of the polypeptide chains that may enter in the formation of Hb (α-β-γ-δ).

* most abundent Hb in adult is HbA 'a2b2'

كمان مراجعة

- α –chain → 141 amino acids

(α chain gene is on chromosome 16)

- β-γ-δ chains → 146 amino acids

(β-γ-δ chain genes are on chromosome 11)

- Hb is composed of 2 α and 2 either β , γ or δ

* يعني هو نا

بيتا غاما دلتا

- Hemoglobin A, the major hemoglobin in adults, is composed of 2 α chains and 2 β chains.

(two identical dimers, (αβ)1 and (αβ)2)

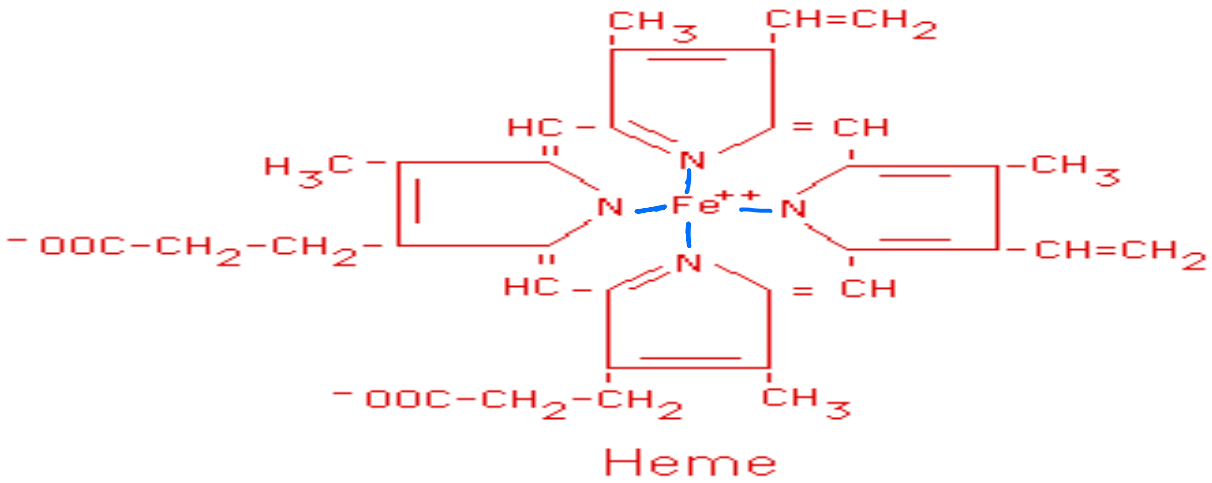
كل اللي حكينا مراجعة سريعة من ال HLS المفروض انه متذكرينه 😄🫠
بس احنا بدنا نعرف ايش علاقة ال chains ببعضيها، ايش علاقة ال2a بال2b
هاض اللي رح نحكي عنه اليوم

كنا اخذنا ب تركيب البروتين انه اله اشكال primary or secondary
stucture 'helicses or beta sheet' or tertiary structure اللي هو ال 3D
shape واخر شكل هو ال quaternary structure اللي بربط اكثر من chain
ببعض زي ال hemoglobin اللي بيحتوي على polypeptide chain 4

احنا بدنا نوصف علاقة ال alpha and beta chain ببعضيها

كل الفا ماسكة مع بيتا عاملة حاجة اسمها dimer، اصلا عندي ٢ بيتا و٢ الفا
يعني عندي 2dimer الاول aß1 الثاني aß2 وبكونو identical

Heme



Heme

- The iron atom of heme occupies the central position of the porphyrin ring. whith 4 pyrol ring bind with methine bridges
- In Hb iron is in the ferrous state (Fe^{++}) ***
- Ferrous iron (Fe^{++}) has 6 valencies. ability to bind in 6 different site
  4 with N ring and 1 with O2
  الموقع الاخير كمان شوي بنعرف مين بيرتبط فيه
- Iron carries oxygen.

Attachment of heme with globin chain

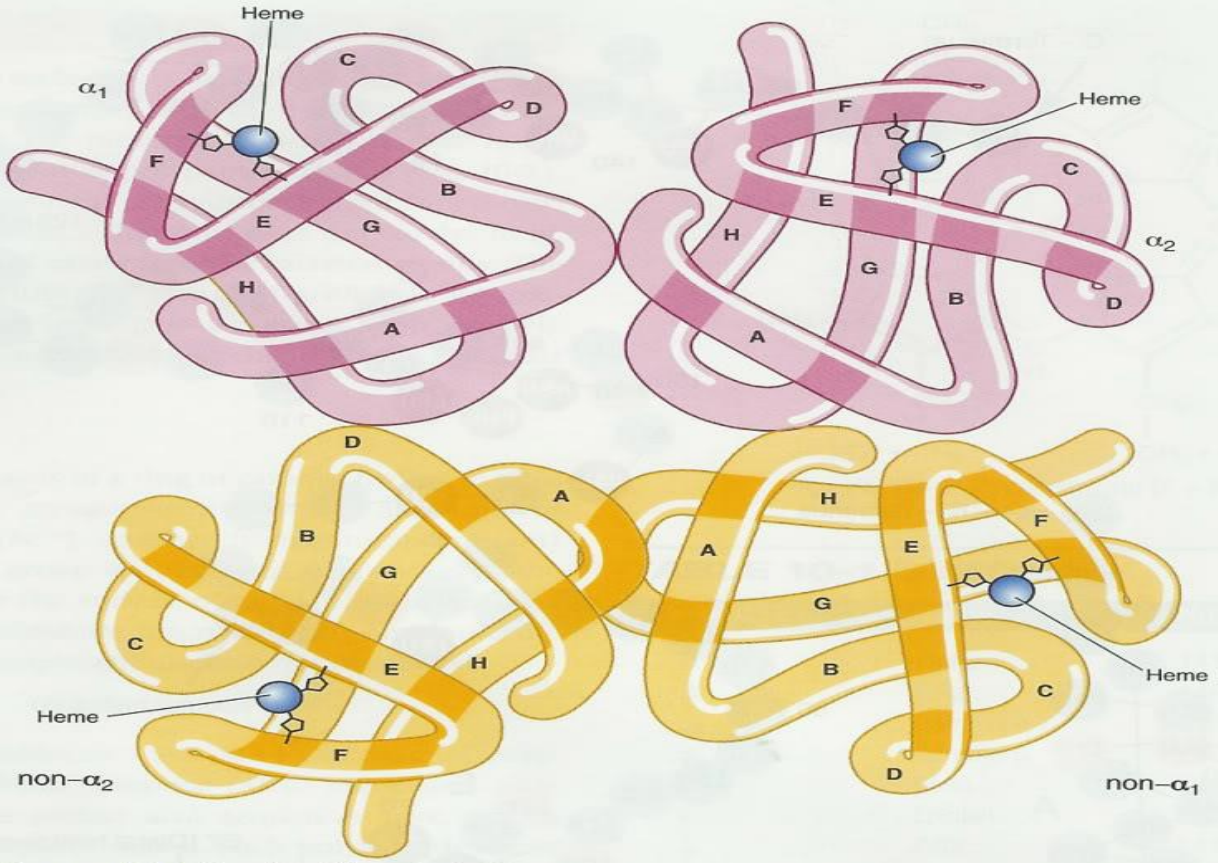
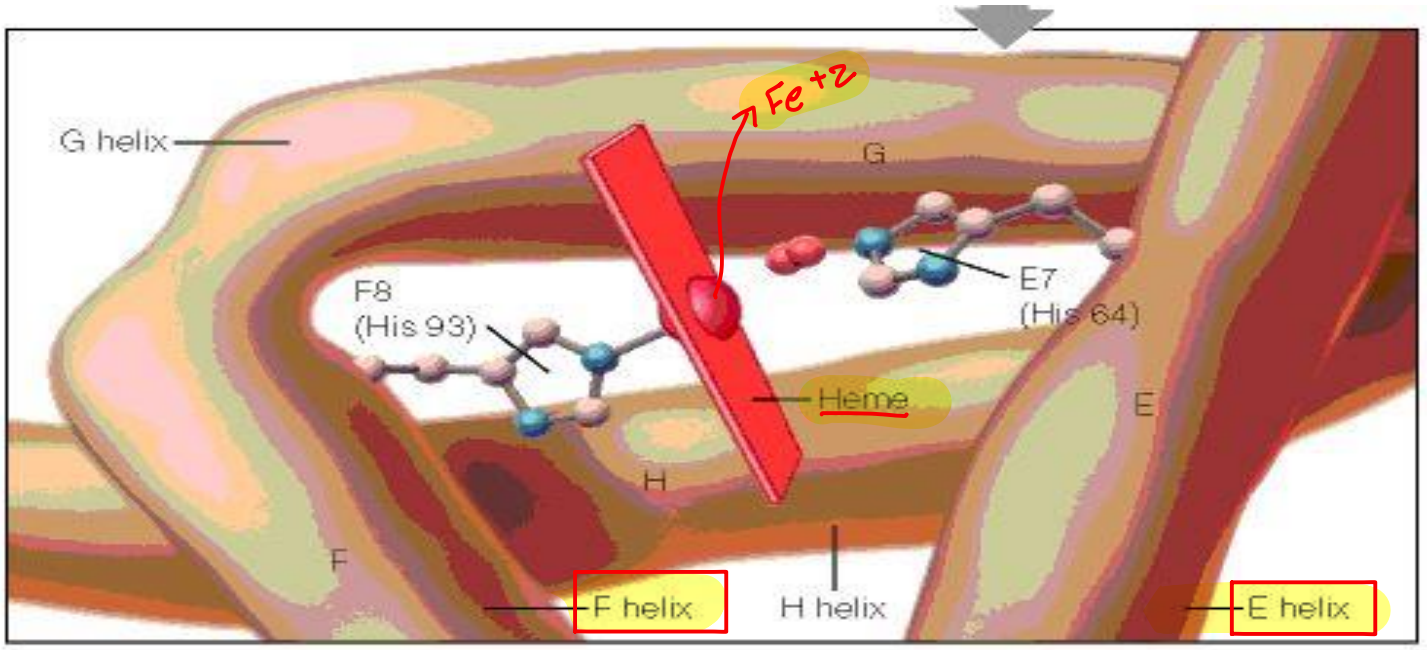


Figure 10-4 Complete Hb molecule. Heme is suspended between the E and F helices of the polypeptide chain. Pink represents α 1 (*left*) and α 2 (*right*); yellow represents non-α 2 (*left*) and non-α 1 (*right*).

Rodak, Hematology, third edtion

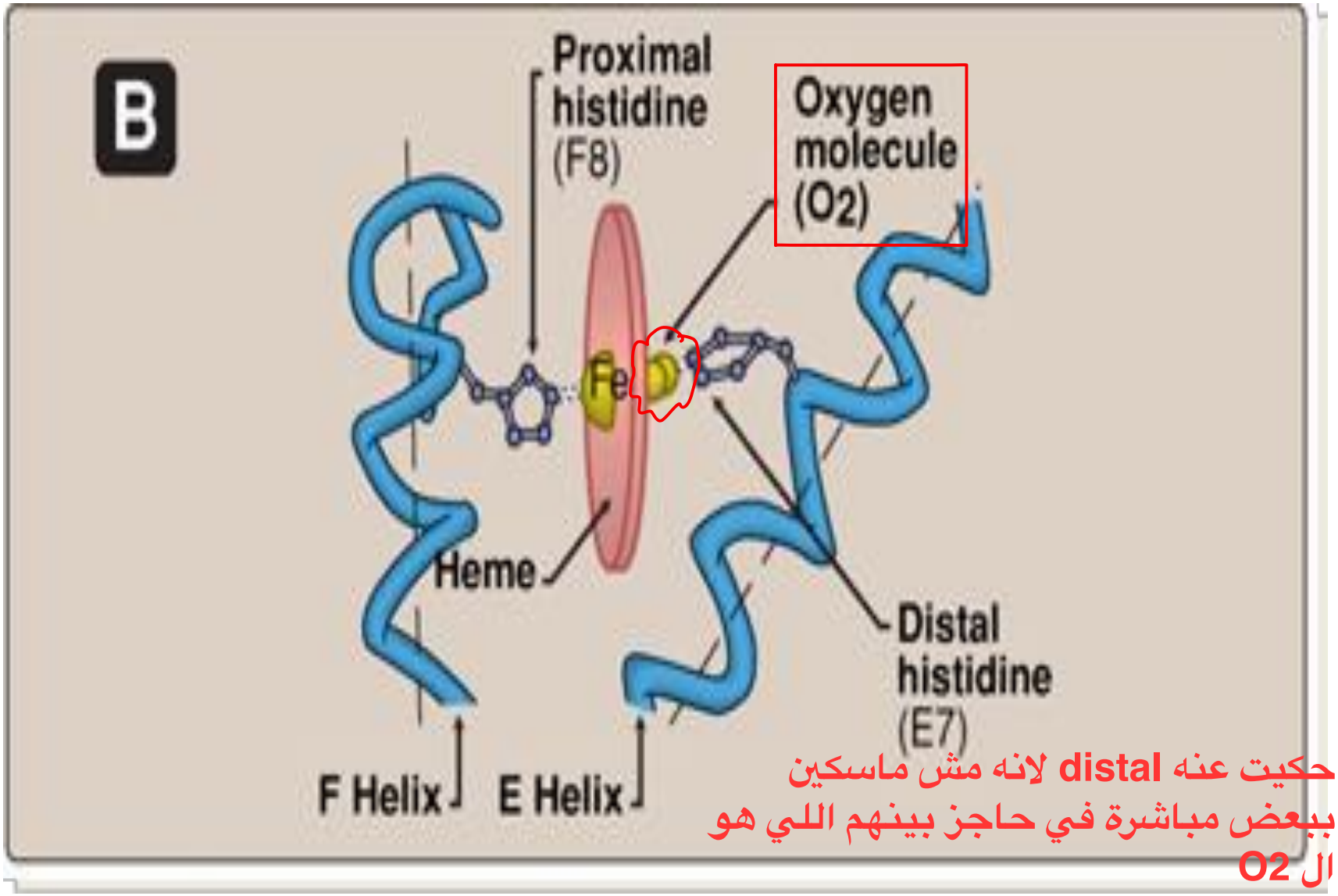
- **Each polypeptide binds a heme molecule at its center. (4 heme residues per Hb molecule)**



- **Heme lies in a pocket (hdrophobic cleft) between E and F helices**

***

A B C D E F .... helices



حكيت عنه distal لانه مش ماسكين ببعض مباشرة في حاجز بينهم اللي هو ال O2

الموقع السادس لل ++Fe

- The iron of heme is coordinated with the nitrogen of the imidazole ring of one histidine in the F helix this histidine is called the proximal histidine

- The other histidine residue in the E helix is called the distal histidine (lies near the heme but is not bonded to it). (1) It stabilizes binding of oxygen to heme and (2) destabilizes binding of carbon monoxide. ***

هسا بدنا نحكي عن علاقة ال polypeptide

- The 2 polypeptide chains of each dimer are **tightly** held together, mostly by **hydrophobic bonds.**

strong

- Each dimer is held relatively **loosely** to the other dimer, mostly by **ionic and hydrogen bonds.** This allows movement of the 2 dimers relative to each other, a process that occurs during oxygenation and deoxygenation.

اما علاقة ال 2dimer ببعضيهم

weak

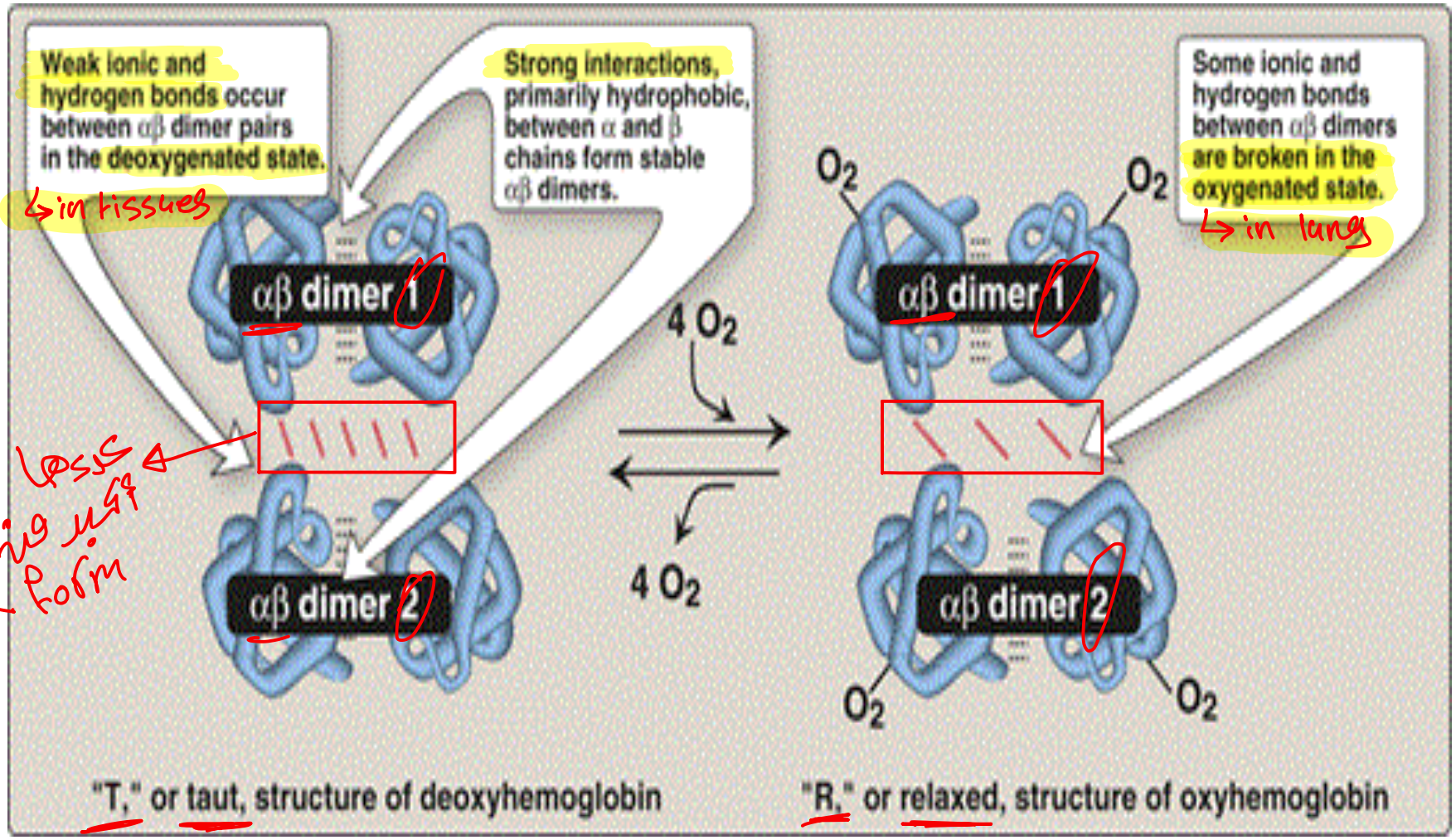
- Thus 2 forms of Hb can be recognized:

1- The "T" form (Hb)

→ taut / tense

2- The "R" form (Hb)

يعني اذا زادت قوة ال ionic & hydrogen bond of dimers <-- تكون حركة ال 2dimers بين بعض اقل ، وبخلي ال Hb بحالة ال T form


Weak ionic and hydrogen bonds occur between αβ dimer pairs in the deoxygenated state.
Strong interactions, primarily hydrophobic, between α and β chains form stable αβ dimers.
Some ionic and hydrogen bonds between αβ dimers are broken in the oxygenated state.
αβ dimer 1
αβ dimer 2
4 O2
4 O2
O2
O2
O2
O2
"T," or taut, structure of deoxyhemoglobin
"R," or relaxed, structure of oxyhemoglobin

نيجي لاهم موضوع وهو ارتباط ال O2 م ' ع ال Hb

its facilitated by previous binding of other oxygen molecules

شو يعني هاي الجملة

عندي 4molecule of O2، اول وحدة هي بس تيجي تمسك بال Hb بتكون صعبة ،بس اللي بساعد بالارتباط هو ال Po2 عند الرئتين عالي فبساعد بشكل كبير، وبمجرد ما ارتبطت اول ذرة O2 بصير الموضوع اسهل بالنسبة للثانية واسهل ذرة برتبط هي الاخيرة

لدرجة انه

The affinity of Hb for the last oxygen molecule is about 300 times greater than for the first oxygen molecule. (cooperative binding kinetics).

- **When the first oxygen molecule is bound to hemoglobin, it leads to conformational changes of the hemoglobin, thus facilitating the binding of the other oxygen molecules to the hemoglobin.**

Binding of oxygen to Hb

- The ease with which an oxygen molecule binds to a certain Hb molecule depends upon whether other oxygen molecules are bound to it.
- Binding of oxygen to Hb is facilitated by previous binding of other oxygen molecules **(cooperative binding kinetics).**
- The affinity of Hb for the last oxygen molecule is about 300 times greater than for the first oxygen molecule.

- This pulls the proximal histidine towards the porphyrin ring and is accompanied by deprotonation of the imidazole ring of histidine and of N-terminal amino groups in the peptide chain.
- This leads to rupture of salt bonds between globin chains, and Hb changes from the T to R state, increasing its affinity for oxygen.
- This is sometimes called **heme-heme interaction.**

- **The "T" form (Hb):**

  - This is the taut (tense) form of hemoglobin. The polypeptide chains are difficult to move relative to each other because of the presence of more ionic bonds between the 2 dimers.

  -It is stabilized by protonation due to increased number of charged groups, increasing ionic bonds.

  -This occurs when CO_2 is added to the blood by the tissues increasing $[H^+]$ in red cells. It is stabilized by deoxygenation, which leads to protonation of Hb.

  يعني عند ال tissues

  عشان بعدها احول ال co2 ل H2CO3

  -It has a lower affinity for oxygen.

لو بتتذكر، المرة الماضية حكينا انه ال
bicarbonate buffer system can buffer any acid except H2CO3o

قبل المحاضرة 2

معلومة مهمة انه ال **bicarbonate system** بعمل **buffer** لكل ال**acid** ما عدا ال **carbonic acid** هذا ال **hemoglobin** وال **oxyhemoglobin** بعالجولي اياه

H2CO3

24

هون لازم تركز

- The bicarbonate system is the most efficient for the buffering of all acids added to the blood, other than carbonic acid, because:

A- It is present at a higher concentration than the other buffers.

B- The ratio **BHCO3/H2CO3**, which determines the pH of the system (20:1 at pH 7.4), can be readily corrected by respiration. This is because H2CO3 can be rapidly converted to CO2, by the help of the enzyme **carbonic anhydrase,** and disposed of by the lungs. ***

Thus, if an acid is added to the blood, it converts the BHCO3 to H2CO3, decreasing their ratio below 20:1. the blood pH decreases, and acidosis occurs.

المحلهلون

This rapidly stimulates respiration, leading to loss of CO2 through the lungs and decreasing H2CO3. the ratio BHCO3/H2CO3 increases to 20:1 and the blood pH becomes 7.4.

- **The "R" form (Hb):**

-This is the relaxed form of Hb. There are less ionic bonds between the two dimers, and the polypeptide chains are more free to move relative to each other.

-It is stabilized by deprotonation due to decreased number of charged groups, decreasing ionic bonds.

-This occurs at the lungs when CO_2 is lost from the blood. It is stabilized by oxygenation, which leads to deprotonation of Hb.

-It has a higher affinity for oxygen.

Allosteric properties of Hb

- The ability of Hb to reversibly bind oxygen is affected by:

1-The pO2 (through heme-heme interactions as described before)

حكينا اول ذرة بتمسك بصعوبة وبعدين بصير اسهل

2-The pH of the environment

3-The pCO2

4-The availability of 2,3-bisphosphoglycerate.

- These are collectively called allosteric effectors (allos=other, steros=site) because their interaction at one site on the Hb molecule affects the binding of oxygen to heme groups at other locations on the molecule.

الCO_2 مسك ف مكان بعيد ما اله علاقة بال iron بس اثرت بال binding of O_2

Carbon dioxide

- Some of the CO_2 (15%) delivered by the tissues to the blood is carried by the terminal amino groups of Hb in the form of carbamate.

$$Hb\text{-}NH_2 + CO_2 \longrightarrow Hb\text{-}NH\text{-}COO^- + H^+$$

This gives Hb a negative charge, increases the formation of ionic bonds, which stabilizes the T-form. The affinity of Hb for oxygen decreases, helping delivery of oxygen to the tissues.

pH (The Bohr Effect):

- Most of the CO_2 delivered by the tissues to the blood is converted to H_2CO_3 in the red blood cells. H_2CO_3 liberates hydrogen ions, which protonate the N-terminal amino groups of the α-subunits and the C-terminal histidine of the β-subunits, stabilizing the T-form.
- The affinity of Hb for oxygen decreases, helping delivery of oxygen to the tissues. The reverse occurs at the lungs.

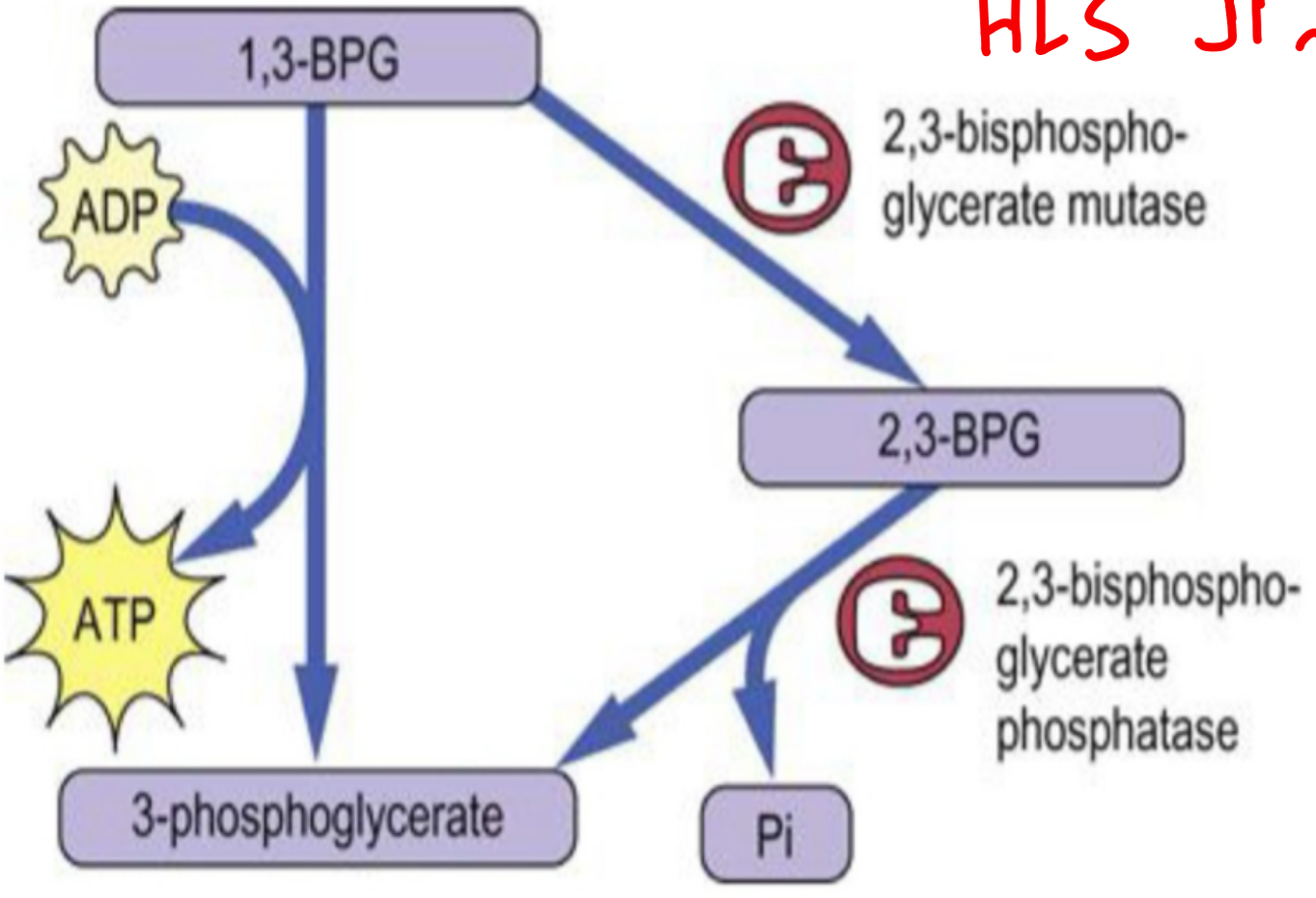
$$Hb\text{-}O_2 + H^+ \longrightarrow Hb\text{-}H^+ + O_2$$

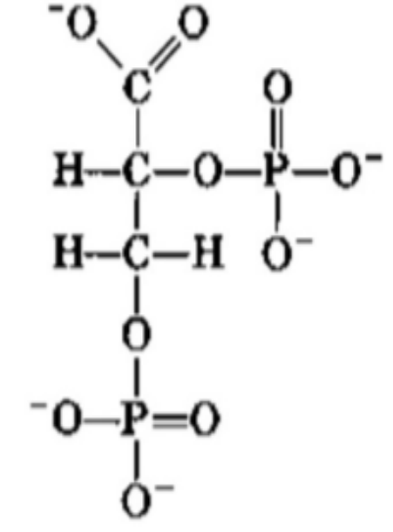
- The influence of pH and pCO_2 to facilitate oxygenation of Hb in the lungs and deoxygenation at the tissues is known as the **Bohr effect.**

2,3- Bisphosphoglycerate

- The 2,3-bisphosphoglycerate (BPG) molecule carries 5 negative charges and is derived from oxidation of glucose (glycolysis) in red cells.
- It binds to a positively charged pocket in Hb between the 2 β chains (small cavity in the center of the four Hb subunits)
- Binding favors the T- form of Hb, reducing affinity for oxygen and helping delivery of oxygen to tissues.
- BPG increases in red blood cells in cases of chronic anemia and in hypoxia. This helps delivery of oxygen to tissues.

تذكير فى ال HLS



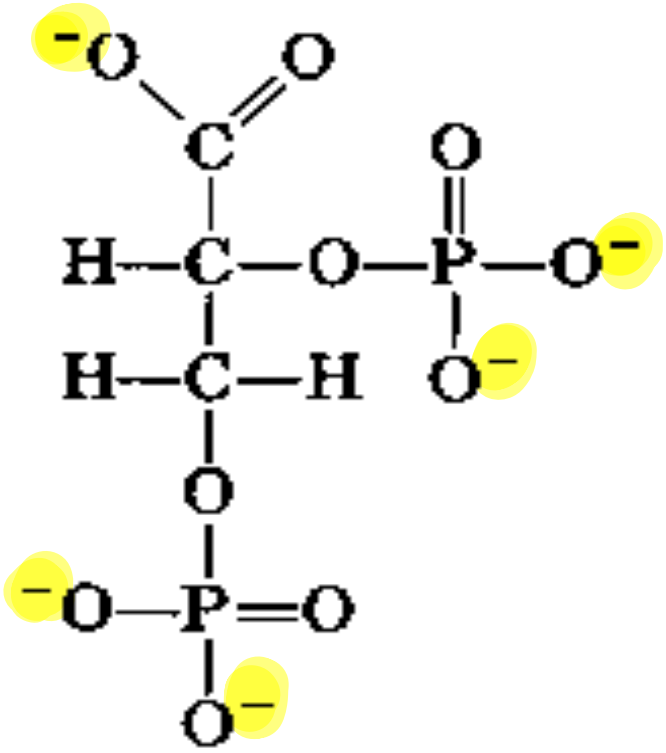


2,3-Bisphosphoglycerate

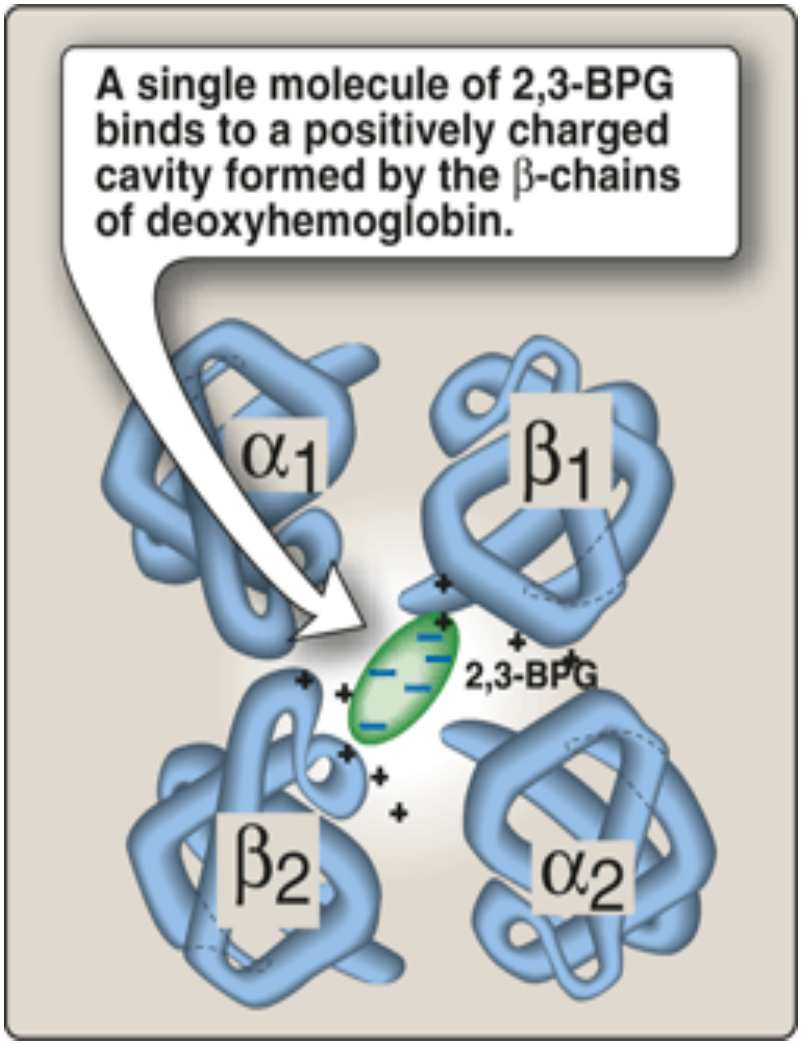
(اسما)

- This pathway discovered by Rapoport-Lubring and called Rapoport-Lubring cycle.
- About 15 to 25% of the glucose utilized in red cells is utilized through BPG shunt.

5 negative charged



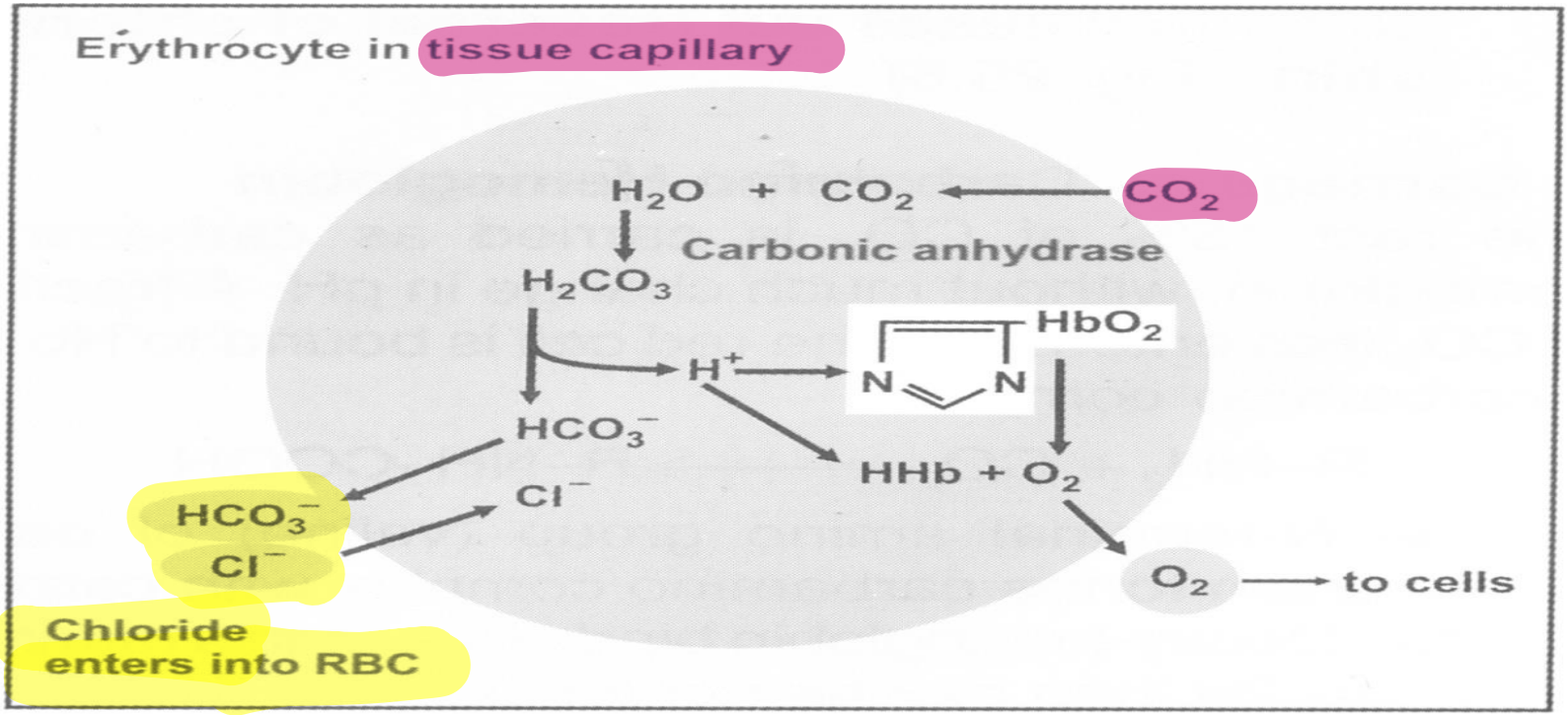
2,3-Bisphosphoglycerate



بكون قليل بعينات الدم المخزنة في بنك الدم

- BPG decreases in red blood cells upon storage of blood, reducing delivery of oxygen to tissues.
- This can be prevented by adding inosine to the blood collection medium, which keeps the level of BPG normal in red blood cells.

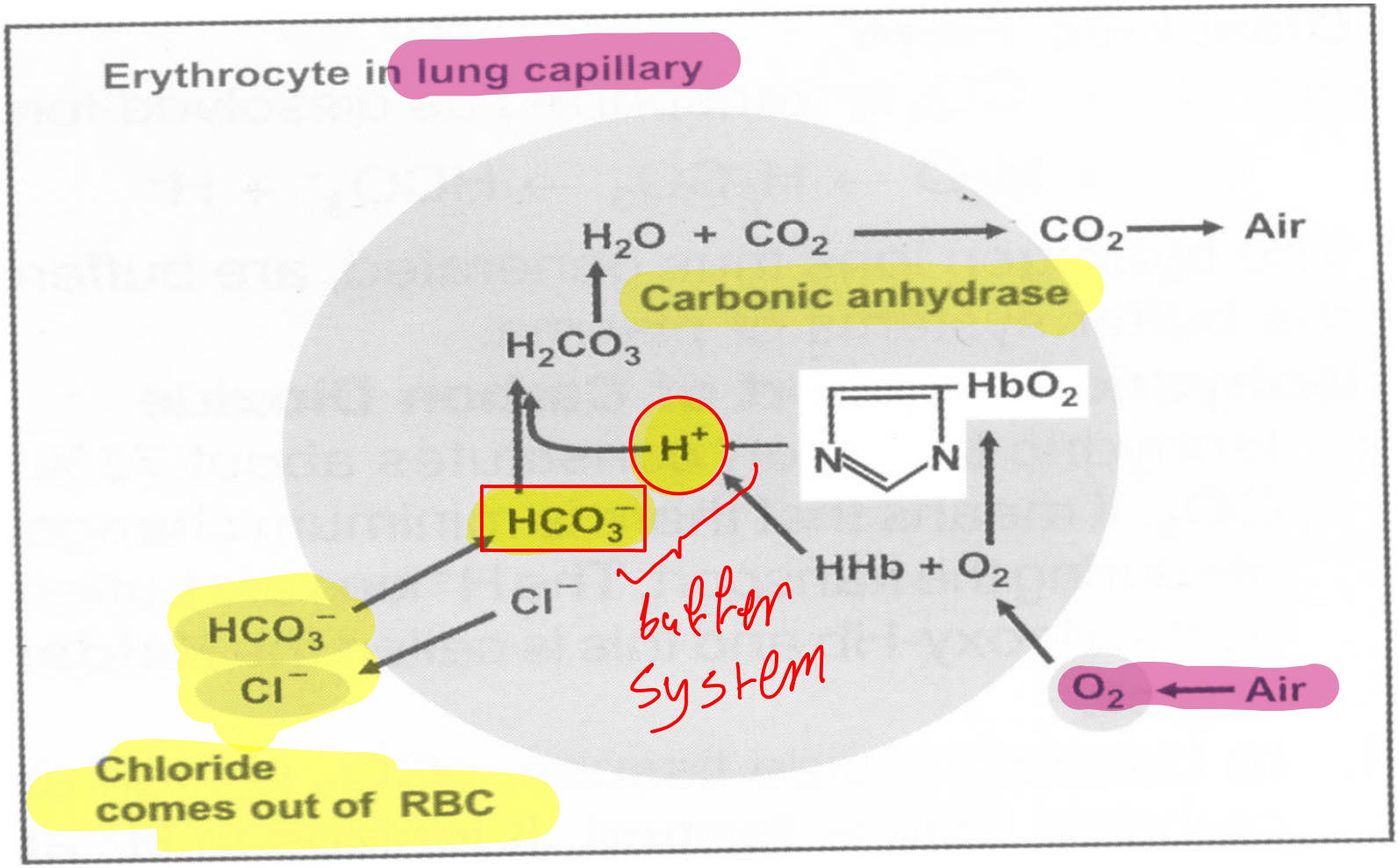
انا محتاج لل BPG عشان تسهل وصول ال O2 لل tissues
فما بزبط افقده
بنضيف ال inosine على وحدات الدم فبمنع خسارة ال BPG



The chloride shift

When CO2 is taken up, the HCO3- concentration within the cell increases. This would diffuse out into the plasma. Simultaneously, chloride ions from the plasma would enter in the cell to establish electrical neutrality. This is called chloride shift or Hamburger effect.

ملخص للمحاضرة



تم بحمد الله