

وَقُلْ رَبِّ زِدْنِي عِلْمًا



RESPIRATORY SYSTEM

HAYAT BATCH

SUBJECT : Biochemistry

LEC NO. : 4

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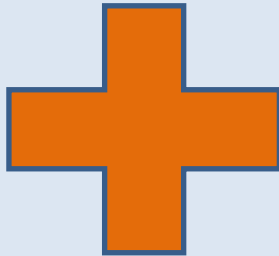
Role of hemoglobin in acid base balance

By

Dr. Wasaa Bayoumie El Gazzar

Hemoglobin

Heme



Globin

Globin

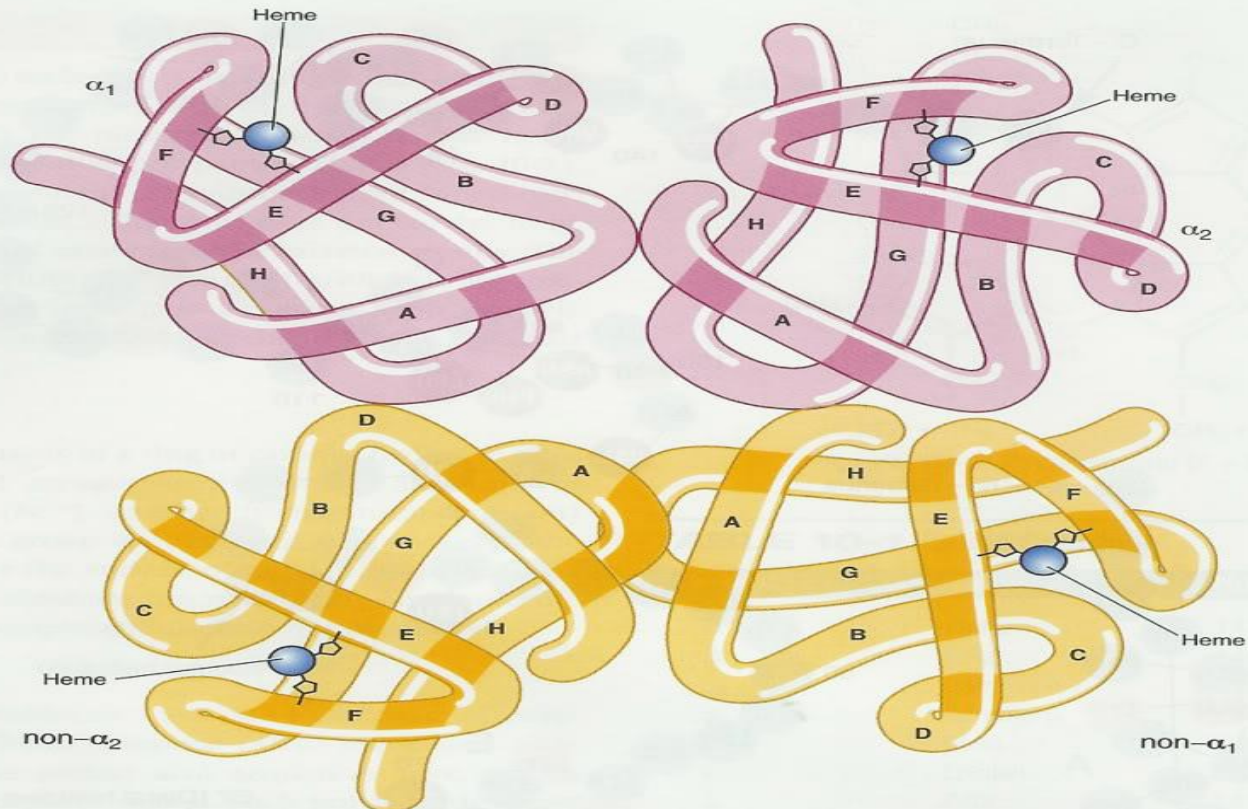


Figure 10-4 Complete Hb molecule. Heme is suspended between the E and F helices of the polypeptide chain. Pink represents α_1 (left) and α_2 (right); yellow represents non- α_2 (left) and non- α_1 (right).

Rodak, Hematology, third edition

Globin

- Tetramer : **4 polypeptide chains.**

2d (αβ)
2 (حماصة تا نية)

- Each polypeptide chain is formed of 7 or 8 helices which are termed A-B-C-D.....

↳ formed in the Secondary structure

- There are 4 types of the polypeptide chains that may enter in the formation of Hb (α - β - γ - δ).

- 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** (*this means that there are several types of hemoglobin*)

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

(two identical dimers, $(\alpha\beta)_1$ and $(\alpha\beta)_2$)

- *Dimer: two chains*
- *In hemoglobin A, each dimer is composed of one alpha and one beta chains)*

(كل ديمر يتكون من هيموغلوبين من أكثر من نوعين من ال (Poly Peptide chain) مثلا: (Alfa + Beta + gamma) !!؟ الجواب (8)

- حبيب شو علاقة هاي الـ (chains) ببعضها؟ يعني شو علاقة شد (2 - Alfa with 2 - Beta) ؟

تذكر أنه الـ (Protein) له عدة (structures) :

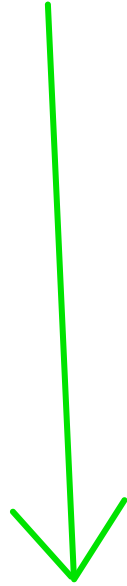
1- (Primary) : تكونه (chain)

2- (secondary) : ممكنه يكونه (helices or β -Blat+ sheets)

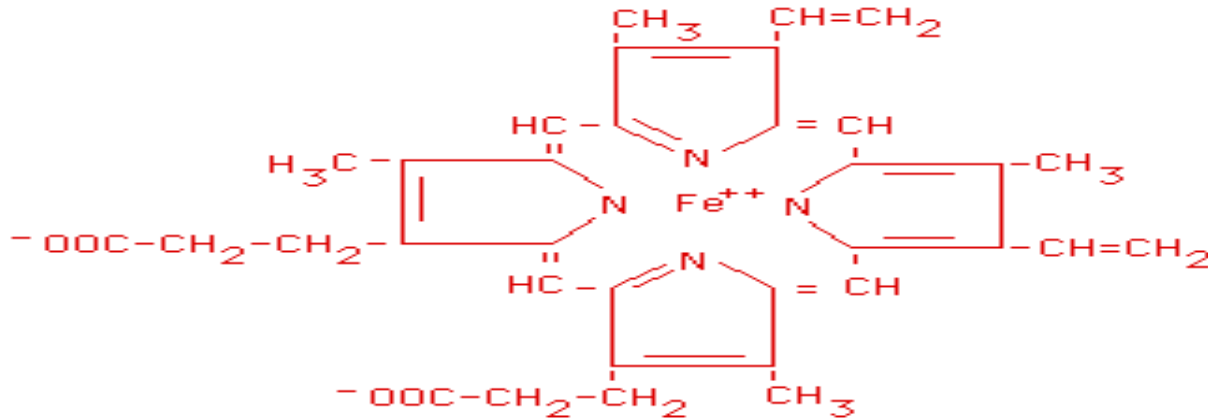
3- (tertiary) : (3D shape of Poly peptide chains)

4- (Quaternary) : تكونه للبروتينات التي تحتوي على أكثر من (Poly peptide chain)

وتدل على علاقة هاي الـ (chains) ببعضها زي الـ (Hb) واليوم بدنا نعوض شو هاي العلاقة



Heme



☀️ The iron atom of heme occupies the central position of the porphyrin ring.

☀️ Porphyrin ring: 4 rings → (Pyrrole ring) 4 (ring) ك

☀️ In Hb iron is in the ferrous state (Fe⁺⁺). (must be in the ferrous state)

☀️ Ferrous iron (Fe⁺⁺) has 6 valencies. (means that it can be connected to six different atoms or molecules)

☀️ Iron carries oxygen.

• حكيئا ال ferrous ion يرتبط ب 6 atoms or molecules شو
هم ال 6؟؟

اولا في عنا 4 rings المكونين لل porphyrin ring مرتبطين بال Fe
++

ثانيا ال O2 يرتبط بال Fe++

هيك صاروا 5

طيب شو السادس؟؟

رح نحكي عنه كمان شوي... ..

اللهم صلِّ وسلم وبارك على محمد وعلى آلِهِ أصحابه أجمعين

Attachment of heme with globin chain

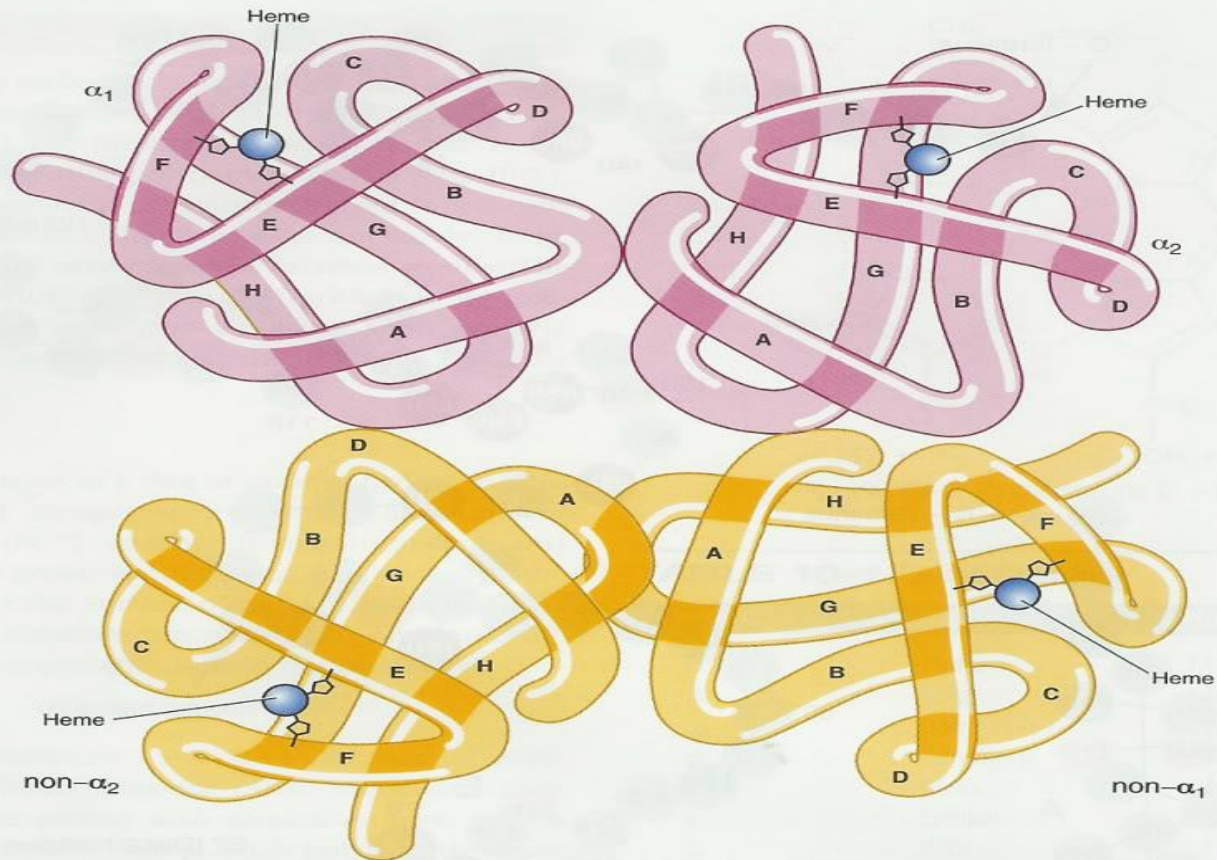
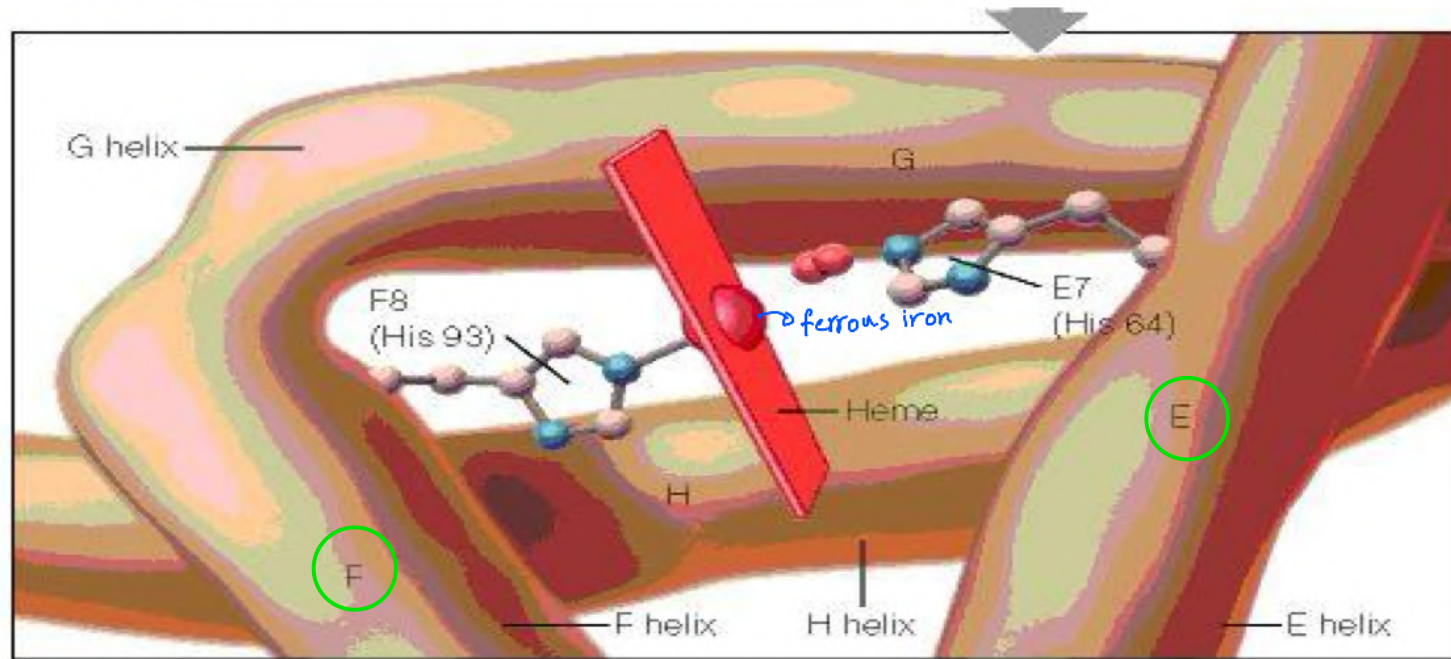


Figure 10-4 Complete Hb molecule. Heme is suspended between the E and F helices of the polypeptide chain. Pink represents α_1 (left) and α_2 (right); yellow represents non- α_2 (left) and non- α_1 (right).

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



- ☀ Heme lies in a pocket (hydrophobic cleft) between E and F helices

- ☀ The red slide → porphyrin ring (Heme)
- ☀ The red ball → the ferrous ion
- ☀ Ferrous ion is connected to histidine which is attached to F helix. الجزيء السادس اللي يرتبط فيه

B

ايل (ربط السادسي)
بال (Amino Acid)

هونه اسمه
(histidine)

حبيب بشو بمك بالتزبط

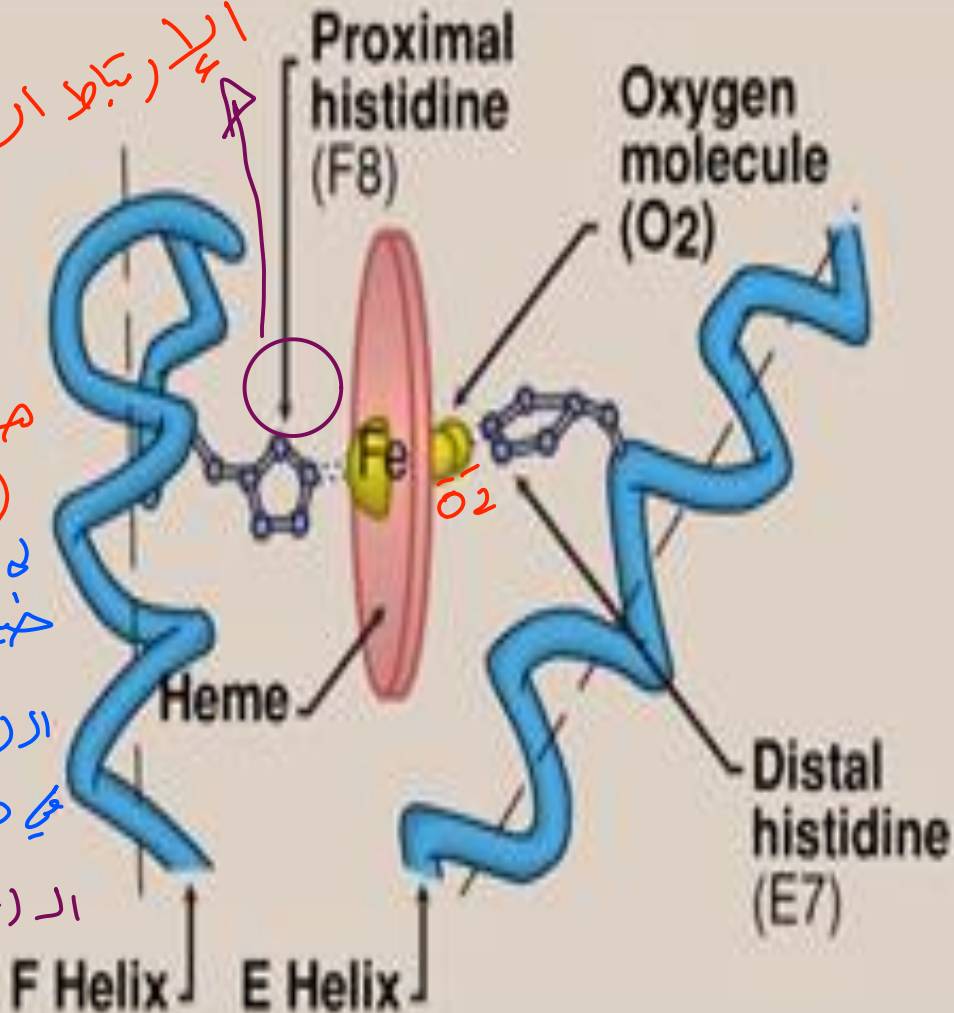
ال (Histidine) فيه (imidazole ring)

عج هذا ال (Ring) في (Nitrogen)

ال (ferrous iron) يرتبط بهذا ال (Nitrogen)

الموجود في ال (imidazole ring)

الموجود في ال (Histidine A.A)



انتبهوا أنه ال (Proximal Histidine) موجود بال (F-Helix)

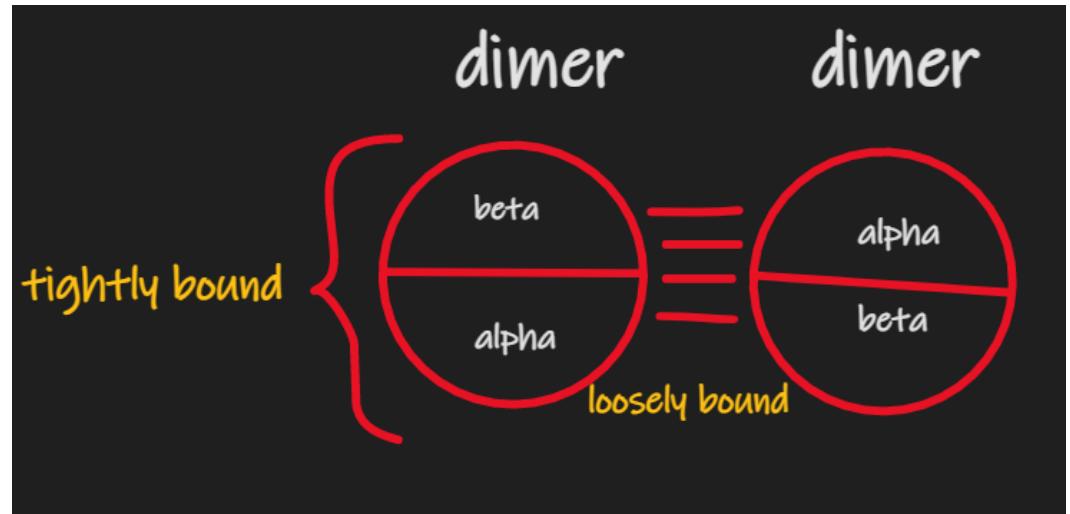
☀️ The iron of heme is coordinated with the nitrogen of the imidazole ring of one histidine in the F helix this histidine is called the proximal histidine (ماسك في الحديد على طول).

☀️ The other histidine residue in the E helix is called the distal histidine (lies near the heme but is not bonded to it). ^{helps} It stabilizes binding of oxygen to heme and destabilizes (prevents) binding of carbon monoxide.

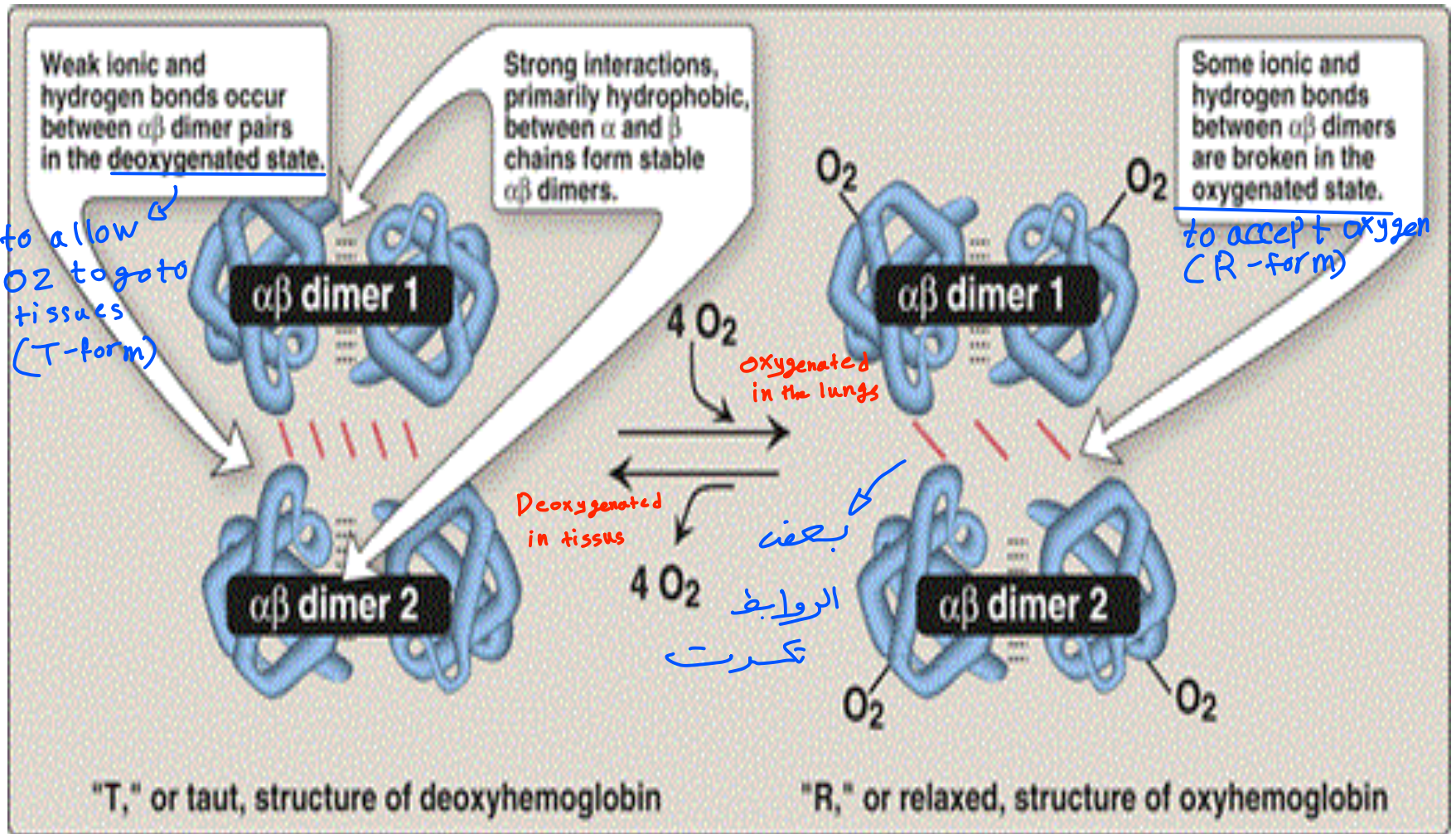
C O

↳ (Affinity of -CO- in high concentration is very high to binding with heme, but we need O₂ not CO, distal histidine allows binding of O₂, and prevents binding of CO)

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



- 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.
- Thus 2 forms of Hb can be recognized:
 - The "T" form (Hb) (*tense*) → can't move normally (Deoxygenated Hb)
 - The "R" form (Hb) (*relaxed*) → able to move normally (Oxygenated Hb)






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**).

• يعني لو جزيء O2 واحد ارتبط بالهيموغلوبين هاد الاشئ رح يسهل ارتباط باقي جزيئات الاكسجين للهيموغلوبين

- *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.*
- The affinity of Hb for the last oxygen molecule is about 300 times greater than for the first oxygen molecule.

الهم نصرا وفرجا قريبا   

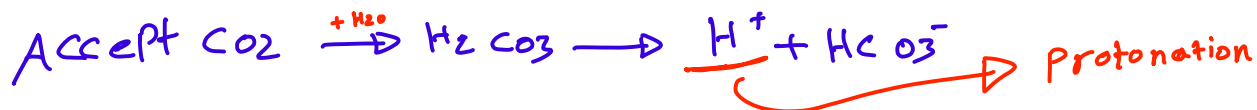
- This pulls the proximal histidine towards the porphyrin ring and is accompanied by deprotonation (loss of H⁺) of the imidazole ring of histidine and of N-terminal amino groups in the peptide chain.
- This leads to rupture of salt (*ionic*) bonds between globin chains, and Hb changes from the T to R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

- The “T” form (Hb): → *in the tissues*

- This is the ^{مشدود} 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 CO₂ is added to the blood by the tissues increasing [H⁺] in red cells. It is stabilized by deoxygenation, which leads to protonation of Hb.



-It has a lower affinity for oxygen.

عند الـ (tissues) الـ (Hb) بعمل تفتين :
1) Deoxygenation / 2) Protonation

— آنا بيحب الـ (O₂) بس بوخذ (CO₂)

- The "R" form (Hb): → in the lungs

T-form : Tissue

R-form : Respiratory organ (Lungs)

-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 CO₂ is lost from the blood. It is stabilized by oxygenation, which leads to deprotonation of Hb.

* The partial pressure of the oxygen is high in the lungs → higher reactivity with hemoglobin.

-It has a higher affinity for oxygen.

عند ال (Lung) ال (Hb) يجعل :

1) OXYgenation / 2) Deprotonation

Allosteric properties of Hb

قدرة ال (Hb) أنه يملك ويفلت

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

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

- ✓ The partial pressure of O₂ is high in the lungs → increased reactivity of O₂ → higher affinity of O₂ to hemoglobin → binding of the first O₂ to hemoglobin → facilitating the binding of other O₂ molecules to hemoglobin by converting the hemoglobin from the tense form to the relaxed form.

2-The pH of the environment

- ✓ When CO₂ enter the red blood cells, it is converted to H₂CO₃ by carbonic anhydrase enzyme. H₂CO₃ is an acid which means that it is a proton donor, thus increasing the protonation of hemoglobin → hemoglobin stays at tense form → low affinity of O₂ to hemoglobin
T-form Hb

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.

Carbon dioxide

- Some of the CO₂ (15%) delivered by the tissues to the blood is carried by the terminal amino groups of Hb in the form of carbamate.



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 CO₂ delivered by the tissues to the blood is converted to H₂CO₃ in the red blood cells. H₂CO₃ 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. الكلام الأحمر ما بهم الدكتور
- The affinity of Hb for oxygen decreases, helping delivery of oxygen to the tissues. The reverse occurs at the lungs.



- The influence of pH and pCO₂ to facilitate oxygenation of Hb in the lungs and deoxygenation at the tissues is known as the **Bohr effect.**

2,3- Bisphosphoglycerate *(with two phosphate groups)*

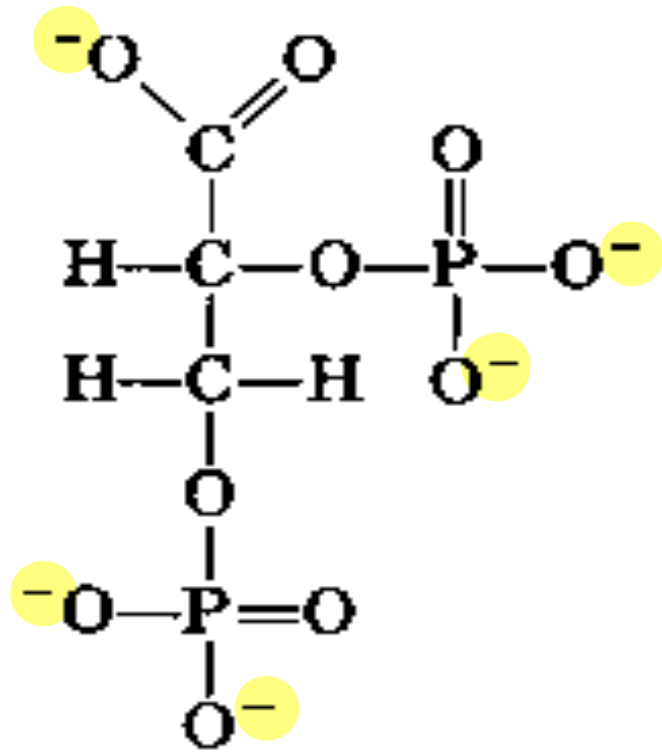
- The 2,3-bisphosphoglycerate (BPG) molecule carries 5 negative charges and is derived from oxidation of glucose (glycolysis) in red cells.
- It binds to a positively charged pocket in Hb between the 2 β chains (small cavity in the center of the four Hb subunits)
- Binding favors the T- form of Hb, reducing affinity for oxygen and helping delivery of oxygen to tissues. *(facilitating the separation of O₂ from hemoglobin)*
- BPG increases in red blood cells in cases of chronic anemia and in hypoxia. This helps delivery of oxygen to tissues.

①

②

سبحانه الله بزيد بهزول المرضيه عثمانه يساعده في تسليم

او (O₂) لل (tissue) بسرعة



2,3-Bisphosphoglycerate

↳ have five negative charges

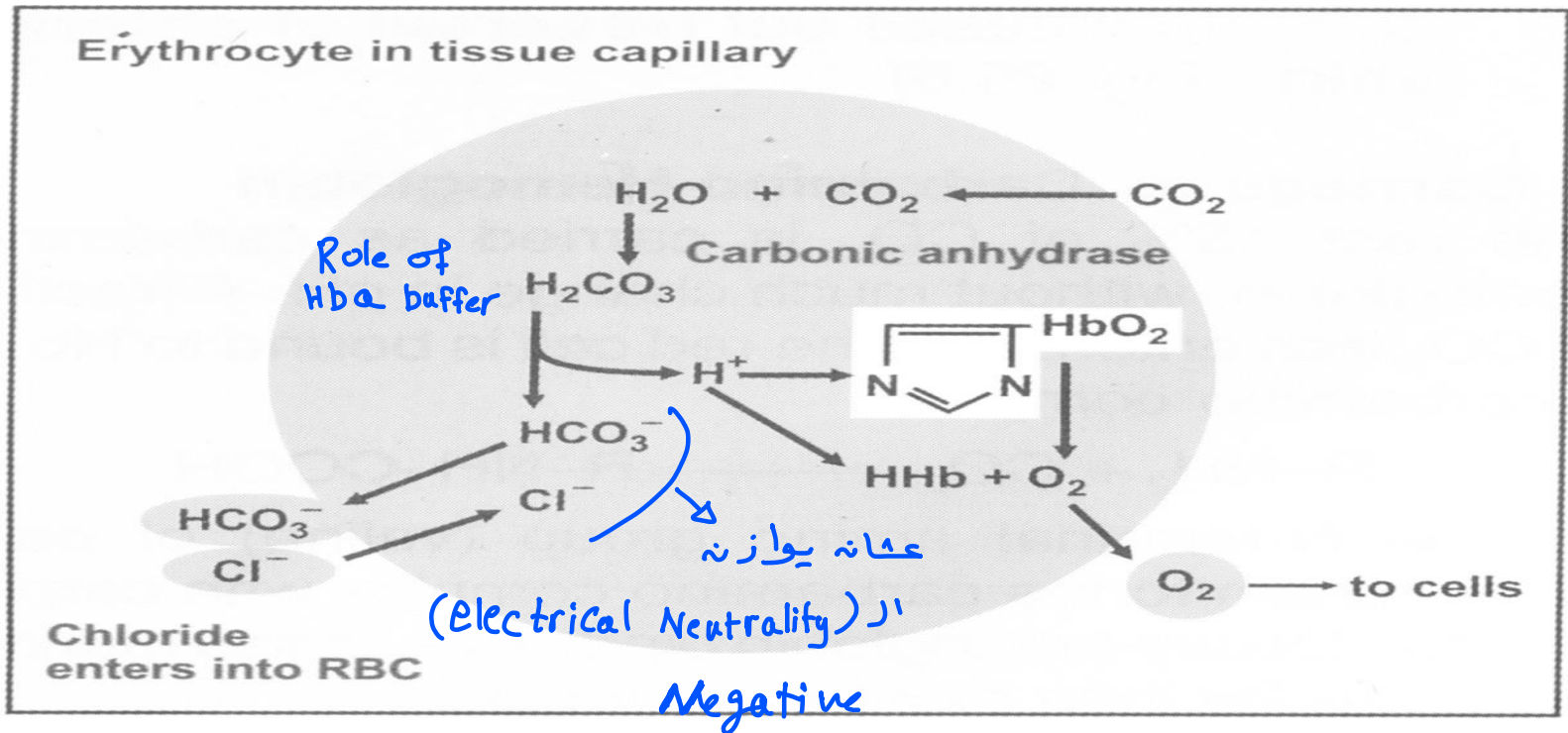
A single molecule of 2,3-BPG binds to a positively charged cavity formed by the β -chains of deoxyhemoglobin.



- BPG decreases in red blood cells upon storage of blood (المقصود اكياس الدم في بنوك الدم), reducing delivery of oxygen to tissues. (حبة الواحد بر ينقل دم بلزوه BPG و 2 نضابنعمد)
- This can be prevented by adding inosine to the blood collection medium, which keeps the level of BPG normal in red blood cells.

اللهم هب لأهل غزة عطاء يفوق

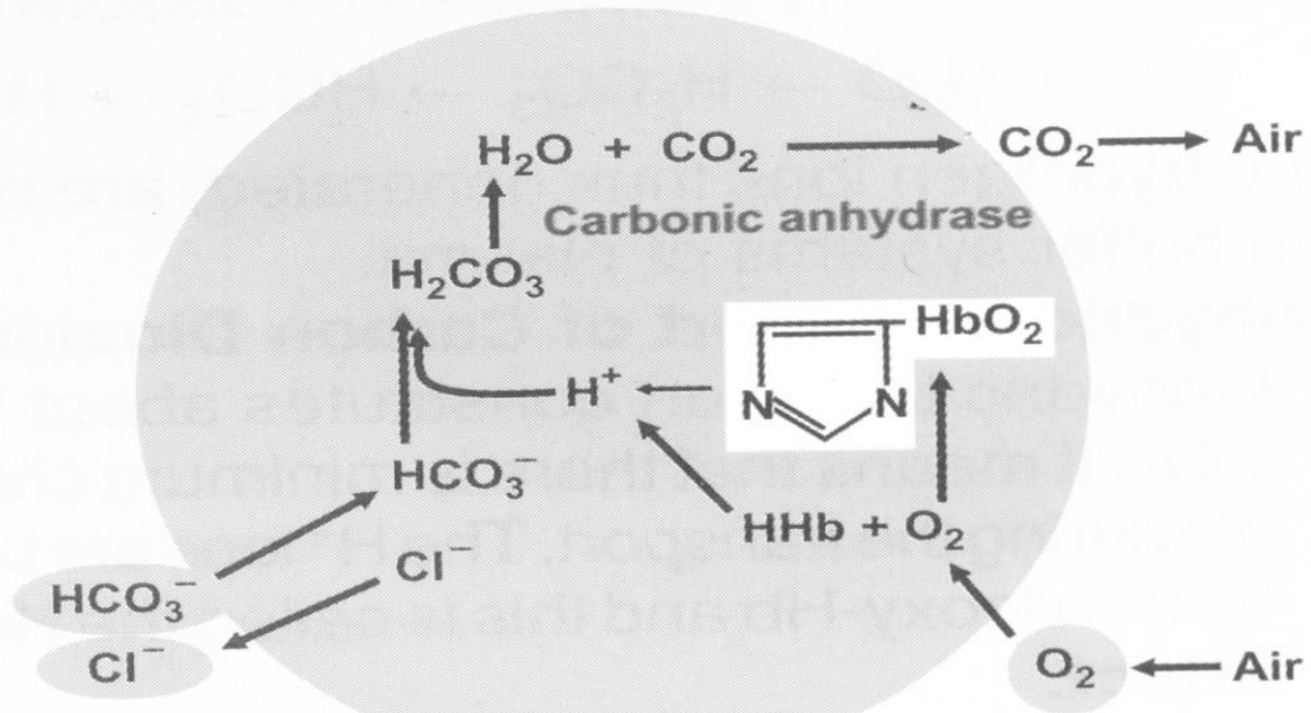
البلاء وفرجا ينسيهم الشقاء 🇵🇸🙏



The chloride shift

When CO_2 is taken up, the HCO_3^- 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.

Erythrocyte in lung capillary



Chloride comes out of RBC

— دعاء بعد المذاكرة —

اللهم

إنني أستودعك ما قرأت
وما حفظت وما تعلمت،
فرده لي عند حاجتي إليه
إنك على كل شيء قدير
وحسبنا الله ونعم الوكيل.