Structure & Function of Hemoglobin

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Editing File

Objectives:

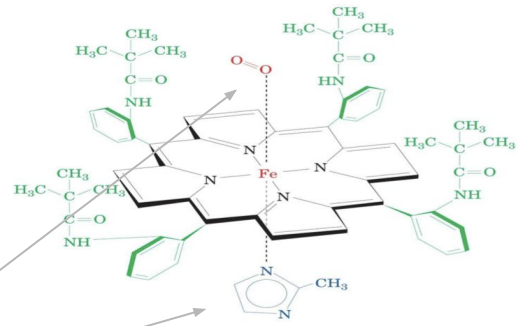
- The structure and function of hemoglobin.
- The factors affecting oxygen binding to hemoglobin.
- Examples of normal and abnormal hemoglobin structures.

Hemoglobin (Hb)

- Oxygen transport function
- Contains heme as prosthetic group
- A hemeprotein found only in red blood cells
- Heme reversibly binds to oxygen

The heme group:

- A complex of protoporphyrin IX + ferrous (Fe^{2+})
- Fe^{2+} is present in the center of the heme
- Fe^{2+} binds to four nitrogen atoms of the porphyrin ring
- Forms two additional bonds with:
  - Oxygen
  - Histidine residue of globin chain



The heme group: Fe^{2+}– porphyrin complex with bound O_2

The iron molecule must be in the ferrous state (Fe^{2+}) When the Heme group contains ferrous iron, the iron is able to bind to 6 molecules:

- 4 Pyrrole nitrogens of the porphyrin ring
- 1 Histidine of the globin chain
- 1 Molecular O_2 3+

In case the iron was in the ferric state (Fe^{3+}), it can only make five bonds, so it cannot bind to oxygen. This is the case in Met-hemoglobin. "Abnormal hemoglobin"

Types of Hb

Normal

Form	Chain composition	Fraction of total hemoglobin
HbA	$\alpha_2\beta_2$	90%
HbF	$\alpha_2\gamma_2$ (Gamma)	< 2%
HbA_2	$\alpha_2\delta_2$ (Delta)	2% - 5%
HbA_{1c}	$\alpha_2\beta_2$-glucose	3% - 9%

Abnormal:

Unable to transport O^2 due to abnormal structure

1- Carboxy Hb	CO replaces O_2 and binds 220X tighter than O_2 (in smokers)
2- Met Hb	Contains oxidized Fe^{3+} (~2%) that cannot carry O_2
3- Sulf Hb	Forms due to high sulfur levels in blood (irreversible reaction)

Hemoglobin A (HbA)

Major Hb in adults

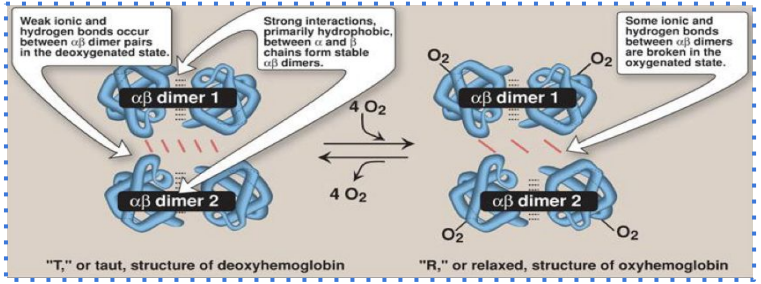
Composed of four polypeptide chains:
↳ Two a and two β chains

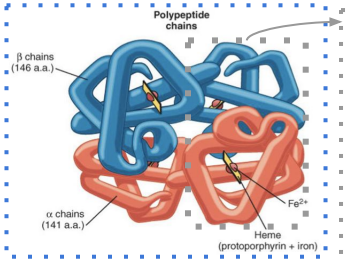
Contains two dimers of aβ subunits[1]

Held together by non-covalent interactions[2]

Each chain is a subunit with a heme group in the center that carries oxygen

A Hb molecule contains 4 heme groups and carries 4 molecules of O_2





1- A dimer is made of one a and one β chains.

2- The bond between the two subunits in one dimer is called an intradimer bond

-The bond between the 2 dimers are called interdimer bonds

-The intradimer bonds are much stronger than the interdimer bonds, which allows the movement of the 2 dimers

T-form of Hb

→ The deoxy form of Hb

→ Taut form

→ The movement of dimers is constrained

→ Low-oxygen-affinity form

VS

R-form of Hb

→ The oxygenated form of Hb

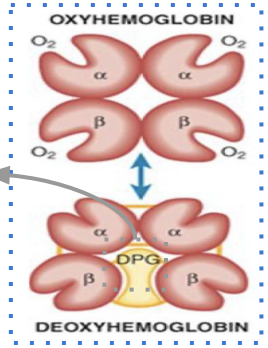
→ Relaxed form

→ The dimers have more freedom of movement

→ High-oxygen-affinity form

- a molecule made by the shunt in the pathway of glycolysis in the RBCs. This molecule binds to the deoxy form of Hb and stabilizes it, allows the release of O_2.

- In case of deficiency of DPG, the Hb can bind to oxygen but can't release it, resulting in the trapping of O_2 in the Hb



Hemoglobin function

Carries O_2 from the lungs to tissues

Carries CO_2 from tissues back to the lungs

Normal level (g/dL):

: 14-16 (g/dL)[1]

:13-15 (g/dL)[2]

Factors affecting oxygen binding

1. pO_2 (partial oxygen pressure)
2. pH of the environment
3. pCO_2 (partial carbon dioxide pressure)
4. Availability of 2,3-bisphosphoglycerate

1- in smokers the Hemoglobin level could be physiologically higher due to adaptation mechanisms.
2- the decreased level in female due to the menstrual period

Oxygen Dissociation Curve (ODC)

- The curve is sigmoidal[1]
- Indicates cooperation of subunits in O_2 binding
- Binding of O_2 to one heme group increases O_2 affinity of others
- Heme-heme interaction[2]

P_{50}:

- Indicates affinity of Hb to O_2.
- P_{50} (mmHg): the pressure at which Hb is 50% saturated with O_2
- The affinity:

slow unloading of O_2 ◀ High — Low ▶ fast unloading of O_2

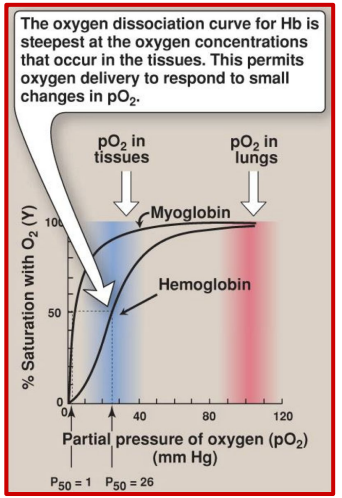
Lung pO_2	100 mmHb saturation 100%
Tissue pO_2	40 mmHb saturation reduces

- Hence O_2 is delivered to tissues

Percent Saturation depends on how many O_2 molecules are bound to Hb, for example Hb bound to one O_2 molecule is 25% saturated, if 2 molecules it is 50% saturated and so on.

we have different degrees of saturation.

As we shift to the right the affinity to O_2 decreases.



May come as SAQ alhuwaykan way (;

Dr.kurdy said "For you in the future If you asked to read a graph:
1- you have to define what you see in the X and Y axis and the scale
2- explain the normal then explain the abnormal"

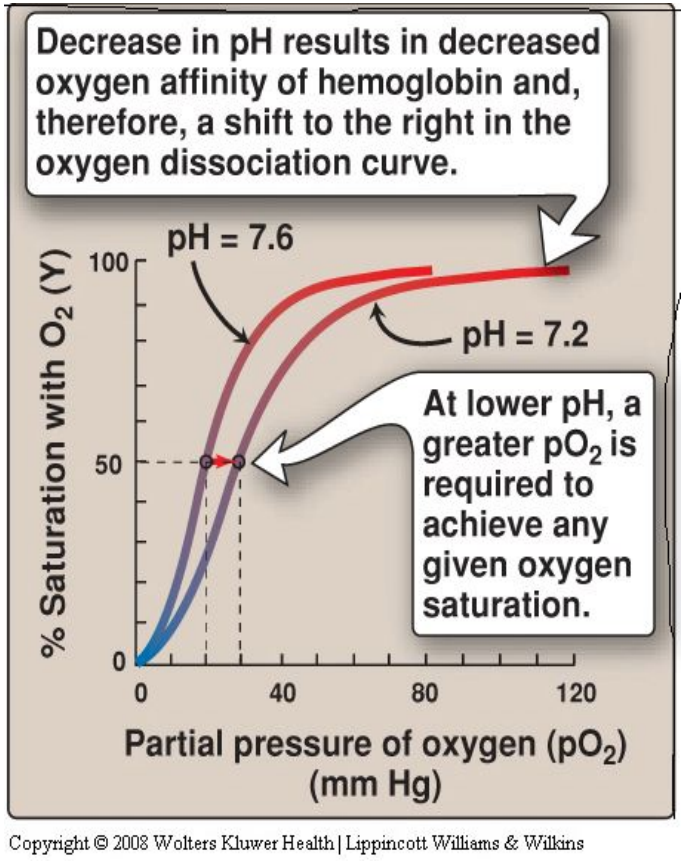
1- The shape of the curve has a lag phase and a steep phase which indicates the presence of cooperative binding.

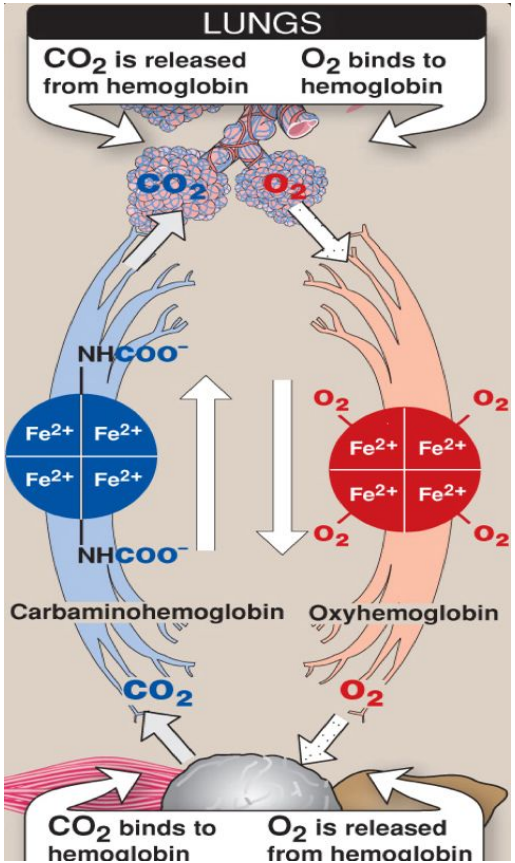
2- Happens when the binding of the first O_2 molecule facilitates the binding of the second molecule "makes it faster". And the binding of the first and second facilitates the third and so on.

The Bohr effect

- It is the shift of the ODC "oxygen dissociation curve" to <u>the right</u> in response to an increase in pCO_2 or a decrease in pH.
- It describes the Effect of ph and pCO_2 on:
  1. Oxygenation of Hb in the lungs.
  2. Deoxygenation in tissues.

- The result of Bohr effect is unloading O_2 inside the tissues and taking CO_2 outside.
- Also BPG has the same result to unload O_2 inside the tissues.





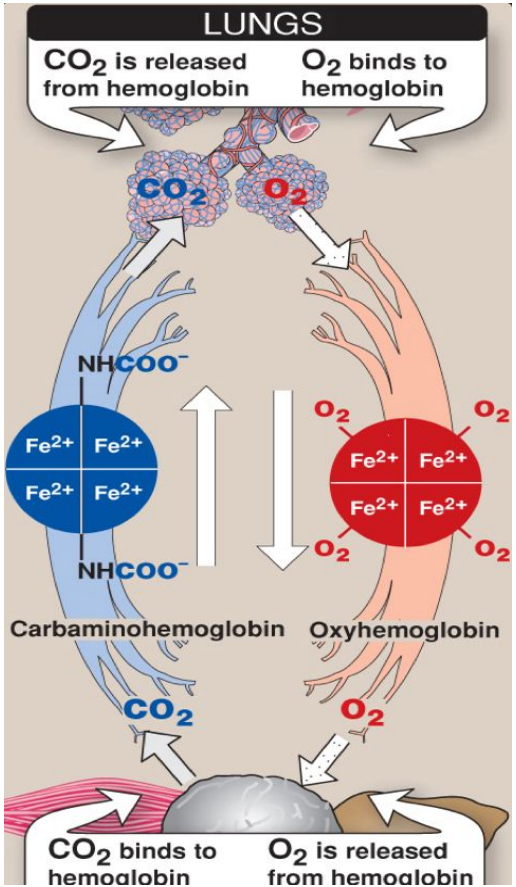
The Bohr effect

- Tissues have lower pH (acidic) than lungs Due to proton generation (two reactions):

$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow HCO_{3-} + H^+$ →

- Protons reduce O_2 affinity of Hb Causing easier O_2 release into the tissues.
- The free Hb binds to two protons.

In the tissues



In the lungs

- Protons are released and react with HCO3- to form CO_2 gas

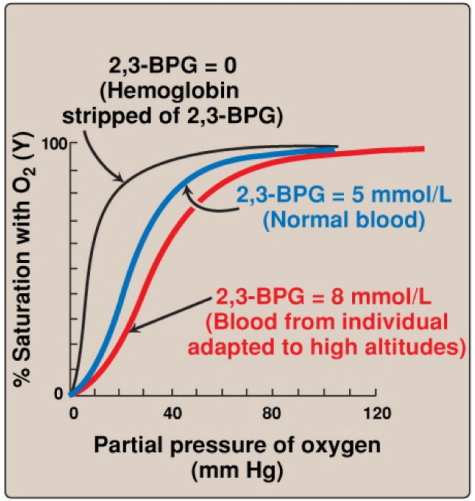
$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow HCO_{3-} + H^+$ ←

- The proton-poor Hb now (in the lungs) has greater affinity for O_2.
- The Bohr effect removes insoluble CO_2 from bloodstream and Produces soluble bicarbonate.

Availability of 2,3 bisphosphoglycerate (BPG/DPG)

In the tissues — BPG Binds to deoxy-hb and stabilizes the T-form.

In the lungs — When oxygen binds to Hb, BPG is released.



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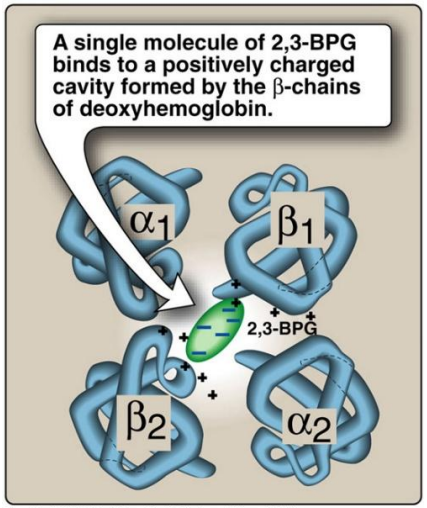

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At high altitude: ↑RBC number → ↑Hb conc. → ↑2,3 BPG

High altitude and O_2 affinity

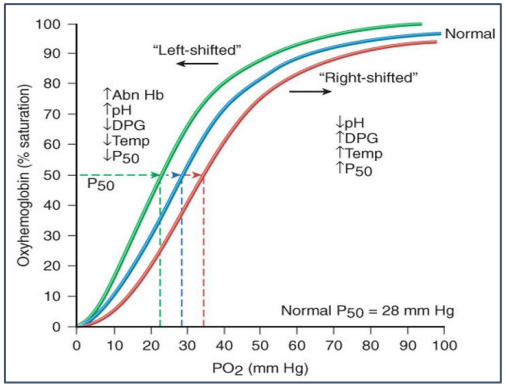
In hypoxia and high altitude:

2,3 BPG levels↑ → ↓O_2 affinity of Hb → ↑O_2 delivery to tissues

High O2 affinity

High O2 affinity is due to:

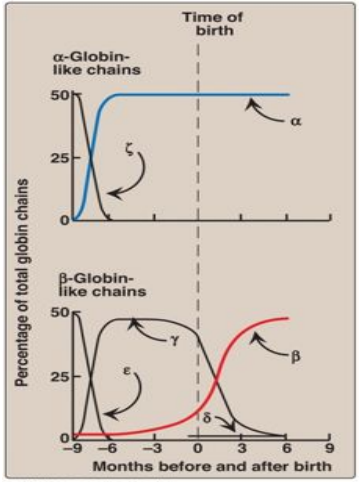
- Alkalosis
- High levels of HbF
- Multiple transfusion of 2,3 DPG-depleted blood[1]

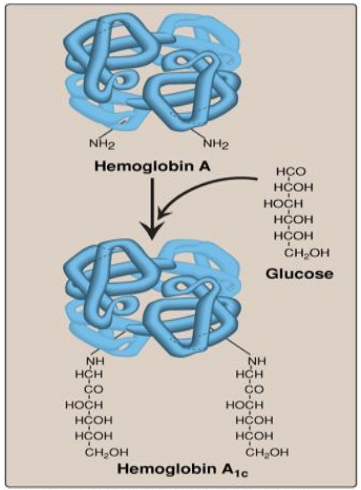


1- Dr.kurdy: A blood unit can withstand for about 90 days, because it has anticoagulants, but these anticoagulants can cause depletion of the normal amount of DPG, which means this blood unit may has a partially depleted amount of DPG, thus deficiency of DPG, so it can't do its job and it needs time to compensate that loss.

Other hemoglobin forms

Types	HbF	HbA_2	HbA_{1c}
Structure (All Tetramer)	two **α** and two (gamma) **γ** chains	two **α** and two (delta) **δ** globin chains	Two **α** and two **β** -Glucose
Found	Major hemoglobin found in the fetus and newborn.	Appears shortly before birth.	high in patients with diabetes mellitus.
Deference	• Higher affinity for O_2 than HbA • Transfers O_2 from maternal to fetal circulation across placenta	Constitutes ~2% of total Hb	• it's HbA undergoes non-enzymatic glycosylation • Glycosylation depends on plasma glucose levels





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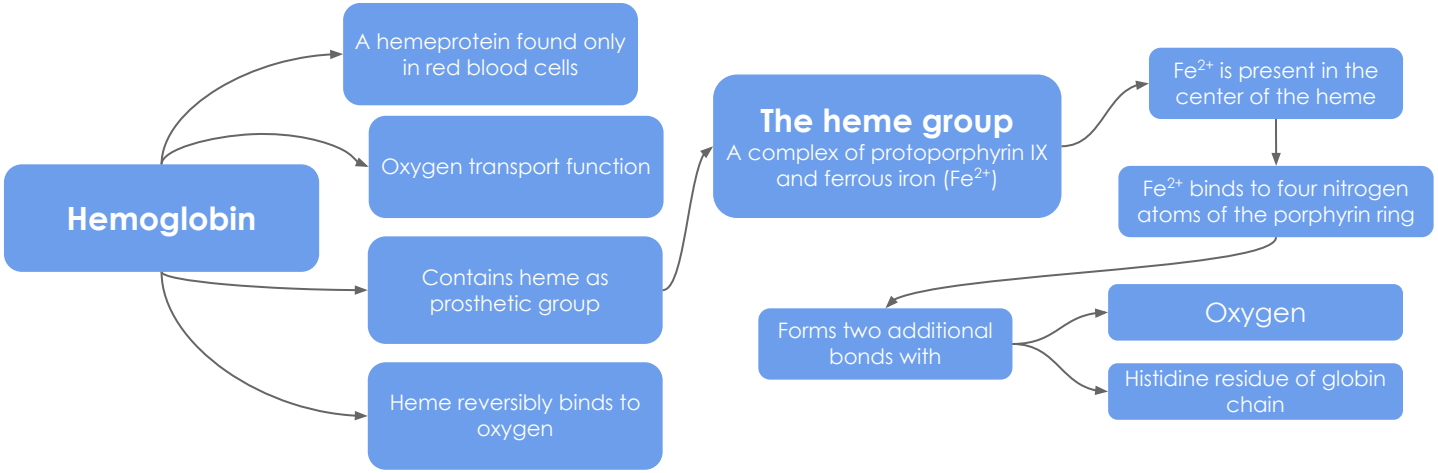
Summary



Affinity:		High O2 affinity:	Low O2affinity
Shift:		**Left** shift	**Right** shift
P50:		**Low**	**High**
Factors:	PH	**High** pH (alkalosis – low pCO2 – Low H+)	**Low** pH (acidity – high PCO2 – High H+)
	DPG	**Low** DPG: Multiple transfusion of 2,3 DPG-depleted blood.	**High** DPG
	Temp.	**Low** temperature	**High** temperature
		Abnormal Hb (e.g High levels of Hb F)	-

Quiz

MCQs :

Q1: The movement of dimers is constrained in which type of Hb:

a) Relaxed form **b)** High-oxygen-affinity form **c)** T form **d)** B&C

Q2: A type of Hb composed of $a_2\gamma_2$:

a) HbA_2 **b)** HbF **c)** HbA **d)** HbA_{1C}

Q3: The bond connect the two dimers is:

a) Ionic bond **b)** Covalent bond **c)** Non-covalent **d)** A&C

Q4: Shifting of the ODC "oxygen dissociation curve" to the right means?

a) pH ↓ **b)** DPG ↓ **c)** PCO_2 ↓ **d)** None of them

Q5: Ali patient with hypoxia went to visit his uncle in Abha, what do you expect to find?

a) BPG ↓ **b)** O_2 delivery to tissues ↓ **c)** O_2 affinity ↓ **d)** A&C

Q6: Which one of the following statements concerning the binding of oxygen by hemoglobin is correct?

a) The Bohr effect results in a lower affinity for oxygen at higher pH values.
b) Carbon dioxide increases the oxygen affinity of hemoglobin by binding to the C-terminal groups of the polypeptide chains.
c) The oxygen affinity of hemoglobin increases as the percentage saturation increases.
d) The hemoglobin tetramer binds four molecules of 2,3-bisphosphoglycerate.

SAQs :

Q1: In ODC what happen if the curve shift to the lift?

Q2: The bond between two dimers are broken in which state?

Q3: What happen to your blood at high altitude?

Q4: What are the factors affecting O_2 binding?

★ **MCQs Answer key:**

1) C 2) B 3) D 4) A 5) C 6) C

★ **SAQs Answer key:**

1) The affinity of Hemoglobin to the O_2 molecule increases
2) Oxygenated state.
3) ↑RBC number, ↑Hb conc., ↑2,3 BPG
4) pO_2, PH of the environment, pCO_2, availability of 2,3-bisphosphoglycerate

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Very secret lecture reviewer

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Mohannad Alqarni

★ **Don't study because you need to, study because knowledge is power and they can never take it away from you.**

438 BIOCHEMISTRY TEAM

We hear you