Biochemistry of the Blood

Hemoglobin

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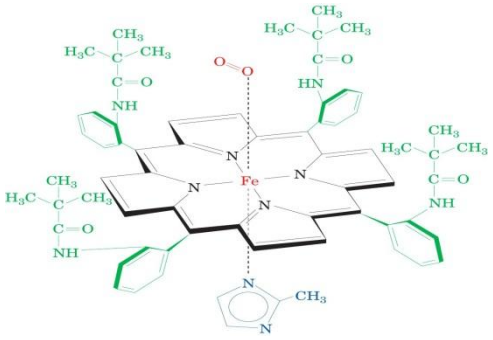
Hemoglobin (Hb) characteristics:

- A hemeprotein found only in red blood cells
- Oxygen transport function
- Contains heme as prosthetic group
- Heme reversibly binds to oxygen
- Hemoglobin is found only in RBC's while myoglobin is found in muscles.

The heme group

- A complex of protoporphyrin IX and ferrous iron (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:
    1. Histidine residue of globin chain
    2. Oxygen
- Contains heme as a prosthetic group: means that it is always attached to it even after finishing its job.

Note: Heme reversibly binds to oxygen; because it has to carry it from a place to another (lung to tissue).



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

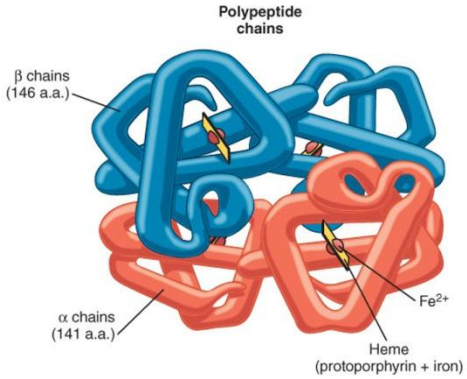
Types of Hb:

Normal:	HbA (97%)
	HbA_2 (2%)
	HbF (1%)
	HbA_{1c}
Abnormal:	Carboxy Hb
	Met Hb
	Sulf Hb

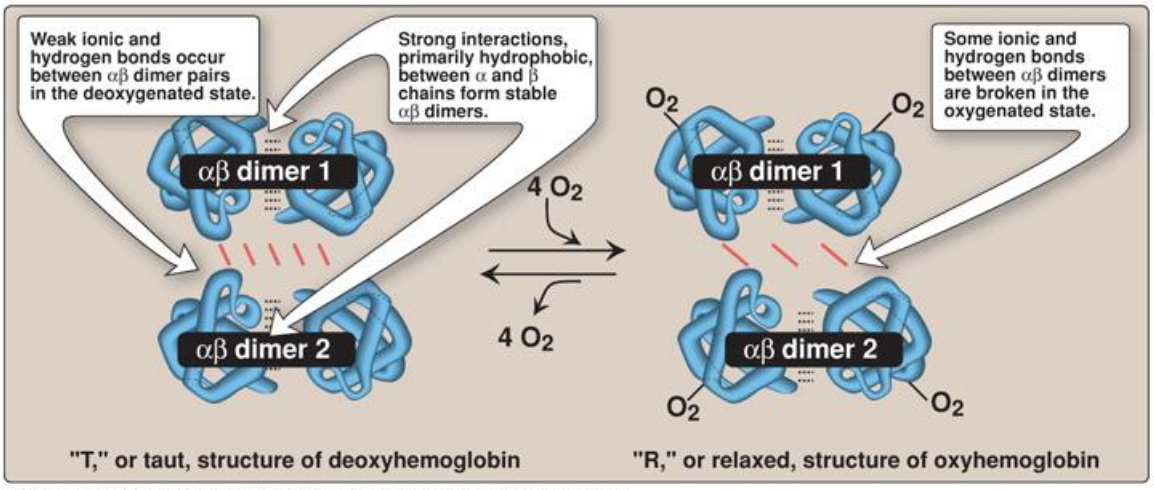
Hemoglobin A (HbA):

-**HbA**: is the most abundant one it is found in 97% of people

- Major Hb in adults
- Composed of four polypetide chains:
  -Two α and two β chains
- Contains two dimers of αβ subunits
- Held together by non-covalent interactions
- 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 moelcules of O_2



HbA structure



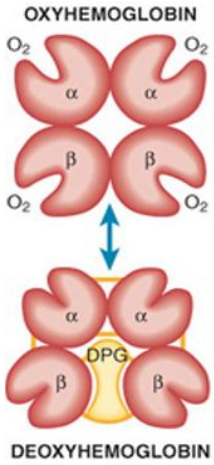
Note: the interaction between the diamer itself is stronger than the interaction between two diamers.

❖ **T-form of Hb**

- The deoxy form of Hb
- Taut form
- The movement of dimers is constrained
- Low-oxygen-affinity form

❖ **R-form of Hb:**

- The oxygenated form of Hb
- Relaxed form
- The dimers have more freedom of movement
- High-oxygen-affinity form



-When there is no O_2 (deoxygenated) = stronger bonding = tight or tens form -O_2 + hemoglobin = break down of some ionic bonds between two diameters → relaxed form of hemoglobin so they move more freely

Hemoglobin function

- Carries oxygen from the lungs to tissues
- Carries carbon dioxide from tissues back to the lungs
- Normal level (g/dL):
  - Males: 14-16
  - Females: 13-15

It carries carbon dioxide from tissues back to the lungs: carbon dioxide goes back to lung as bicarbonate with the help of hemoglobin.

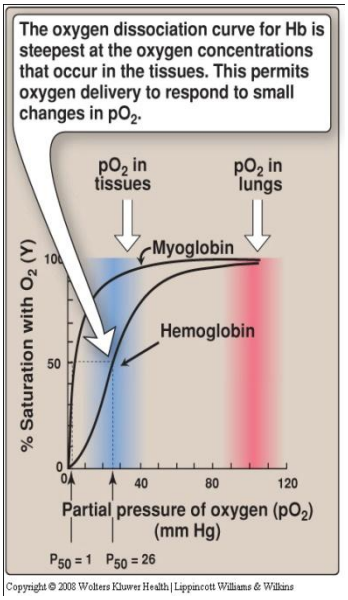
Factors affecting oxygen binding

Three allosteric effectors:

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

2,3bisphosphoglycerate is an organic phosphate that is produced by glycolysis and it is the most abundant phosphate in RBC's, its concentration is almost the same as the hemoglobin.

Oxygen Dissociation Curve

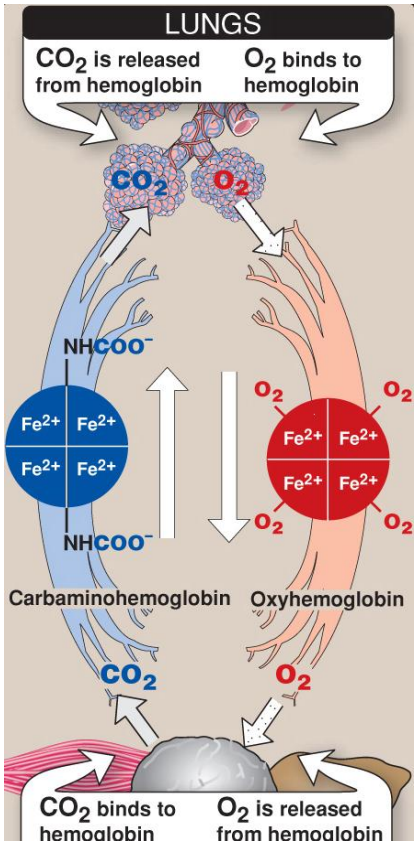


- The curve is sigmoidal
- Indicates cooperation of subunits in O_2 binding
- Binding of O_2 to one heme group increases O_2 affinity of others
- Heme-heme interaction

pO_2 (Partial oxygen pressure)

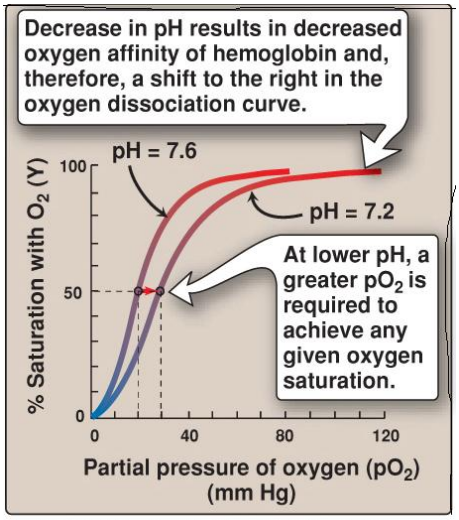
- Indicates affinity of Hb to O_2
- P_{50}(mm Hg): the pressure at which Hb is 50% saturated with O_2
- High affinity → slow unloading of O_2
- Low affinity → fast unloading of O_2
- Lung pO_2 is 100 mm → Hb saturation 100%
- Tissue pO_2 is 40 mm → Hb saturation reduces
- Hence O_2 is delivered to tissues

*Partial pressure in lung =100 and the saturation with the O_2=100% ,when it goes to the tissue the partial pressure changes to 26 and even a small changes can deliver O_2.
*The time for the first O_2 to bind to the heme group is 300 times the last O_2.
*Unloading of O_2 = releasing it in the tissue
-in lungs = high affinity
-in tissue = low affinity



The Bohr effect

- Effect of pH and pCO_2 on:
  - Oxygenation of Hb in the lungs
  - Deoxygenation in tissues
- Tissues have lower pH (acidic) than lungs
- Due to proton generation:
  - $CO_2 + H_20 \rightarrow HCO_3^- + H^+$
- Protons reduce O_2 affinity of Hb



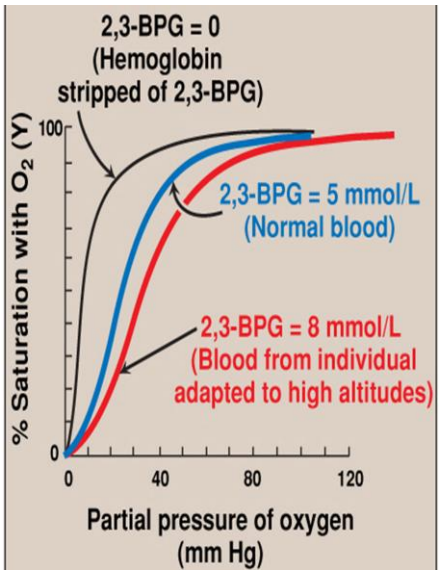
The Bohr Effect

- Causing easier O_2 release into the tissues
- The free Hb binds to two protons
- Protons are released and react with HCO^{3-} to form CO_2 gas
- The proton-poor Hb now has greater affinity for O_2 (in lungs)
- The Bohr effect removes insoluble CO_2 from blood stream
- Produces soluble bicarbonate

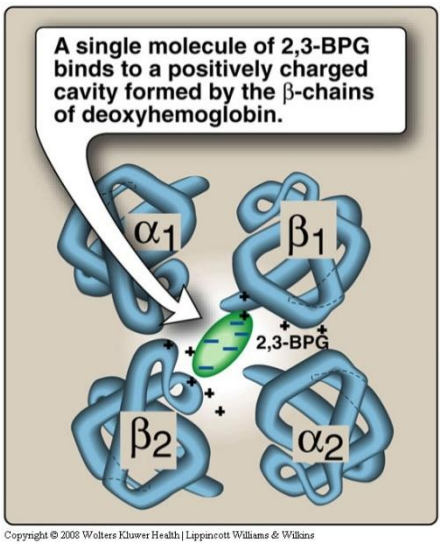
In tissue: high H ion concentration = more acidic comparing to lung =low Ph=decrease O_2 affinity to hemoglobin due to proton generation: $CO_2 + H_20 \rightarrow HCO_3^- + H^+$ = shift to right.

Availability of 2,3 bisphosphoglycerate

- Binds to deoxy-hb and stabilizes the T-form
- When oxygen binds to Hb, BPG is released



At high altitudes there is
-increase in no. of RBcs
-Increase in conc. Of Hb
-Increase in BPG



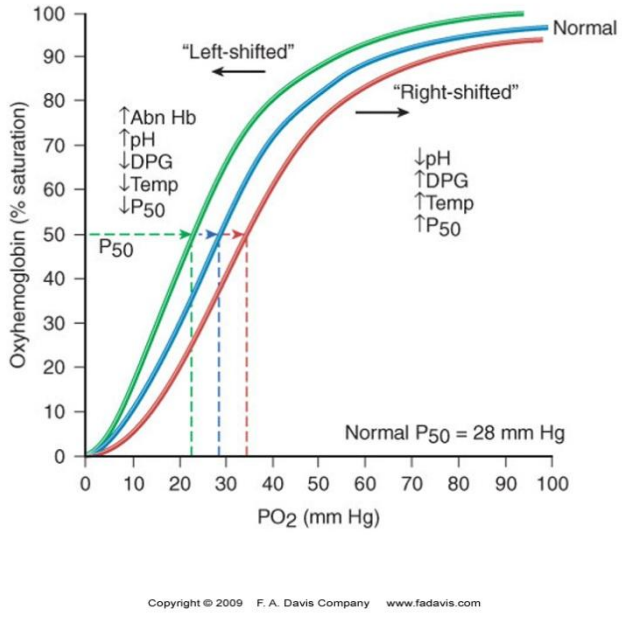
High altitude and O_2 affinity

- In hypoxia and high altitude
  - 2,3 BPG levels rise
  - This decreases O_2 affinity of Hb
  - Thus increases O_2 delivery to tissues

High O_2 affinity

- **High O_2 affinity is due to:**
- Alkalosis
- High levels of Hb F
- Multiple transfusion of 2,3 DPG-depleted blood

In acidic = low affinity = more delivery



- **2,3-bisphosphoglycerate (BPG):only bind to deoxy-hb and stabilizes the T-form causing low affinity to oxygen ,but if BPG is removed = the affinity will increase = unloading will be slow = left shifting will occur.**
- **We need the BPG to be high in tissue not in lungs in case of chronic hypoxia.**
- **2,3 DPG = 2,3BPG (could be named as 2,3 di or bis phosphoglycerate)**

Fetal Hemoglobin

(HbF)

After 8 month of pregnancy the hemoglobin start to goes down.

- Major hemoglobin found in the fetus and newborn
- Tetramer with two a and two g chains
- Higher affinity for O_2 than HBA
- Transfers O_2 from maternal to fetal circulation across placenta

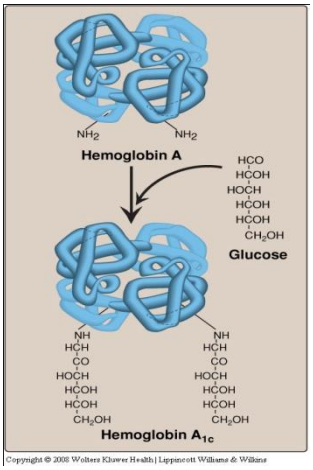
HbA_2

- Appears ~12 weeks after birth
- Constitutes ~2% of total Hb
- Composed of two a and two d globin chains

HbA_{1c}

- HbA undergoes non-enzymatic glycosylation
- Glycosylation depends on plasma glucose levels
- HbA1c levels are high in patients with diabetes mellitus

*HbA1c: it is a glycated form of hemoglobin, it is found in diabetic patients. It has become a gold stander for checking for diabetes.



Abnormal Hbs

- Unable to transport O_2 due to abnormal structure
- Carboxy-Hb: CO replaces O_2 and binds 200X tighter than O_2 (in smokers)

* Carboxy-Hb: CO replaces O_2 and binds 200X tighter than O_2 (in smokers and in carbon monoxide poisoning).

- Met-Hb: Contains oxidized Fe^{3+} (~2%) that cannot carry O_2
- Sulf-HB: Forms due to high sulfur levels in blood (irreversible reaction)