

Structure and function of hemoglobin

Objectives

By the end of this lecture, the students should be able to know:

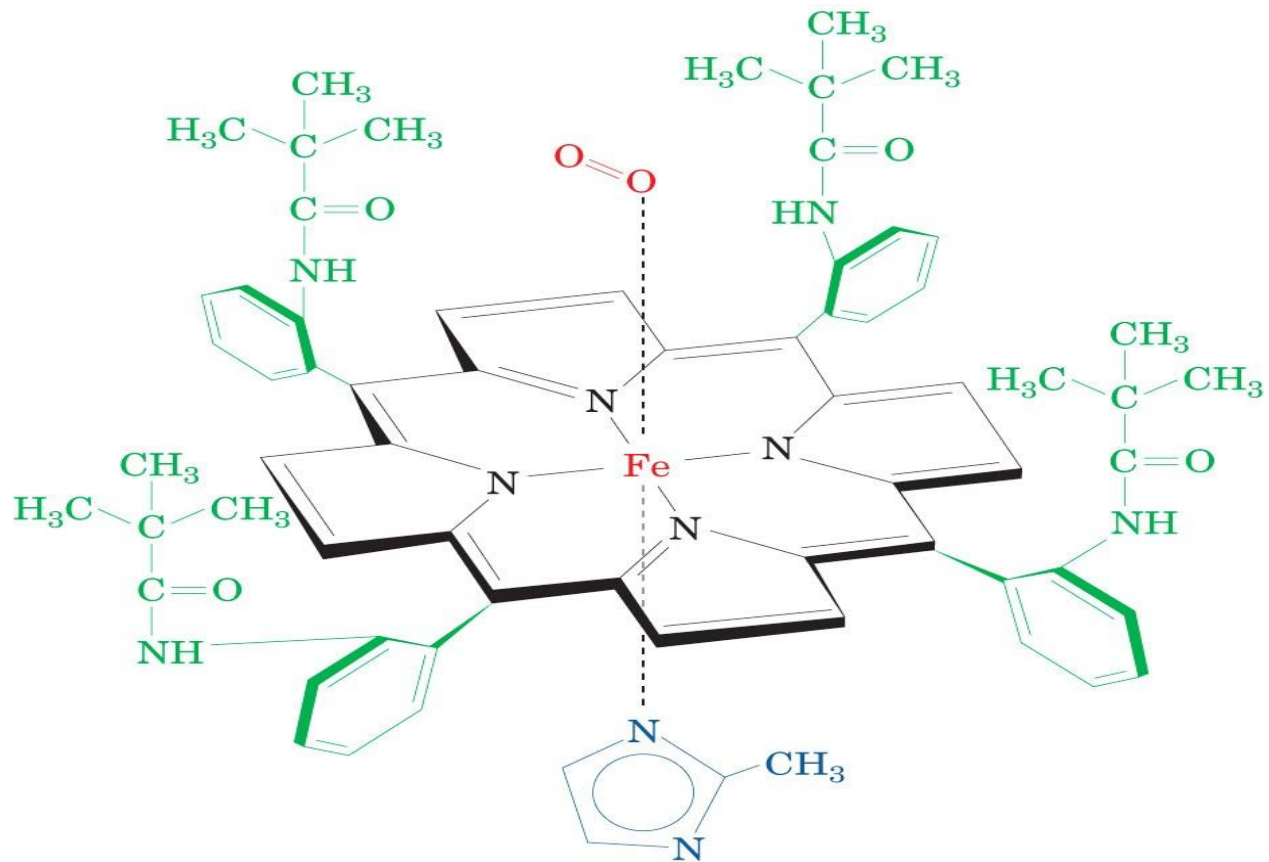
- the structure and function of hemoglobin.**
- the factors affecting oxygen binding to hemoglobin.**
- examples of normal and abnormal hemoglobin structures.**

Hemoglobin (Hb)

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

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:
 - Histidine residue of globin chain
 - Oxygen



The heme group: Fe²⁺– porphyrin complex with bound O₂

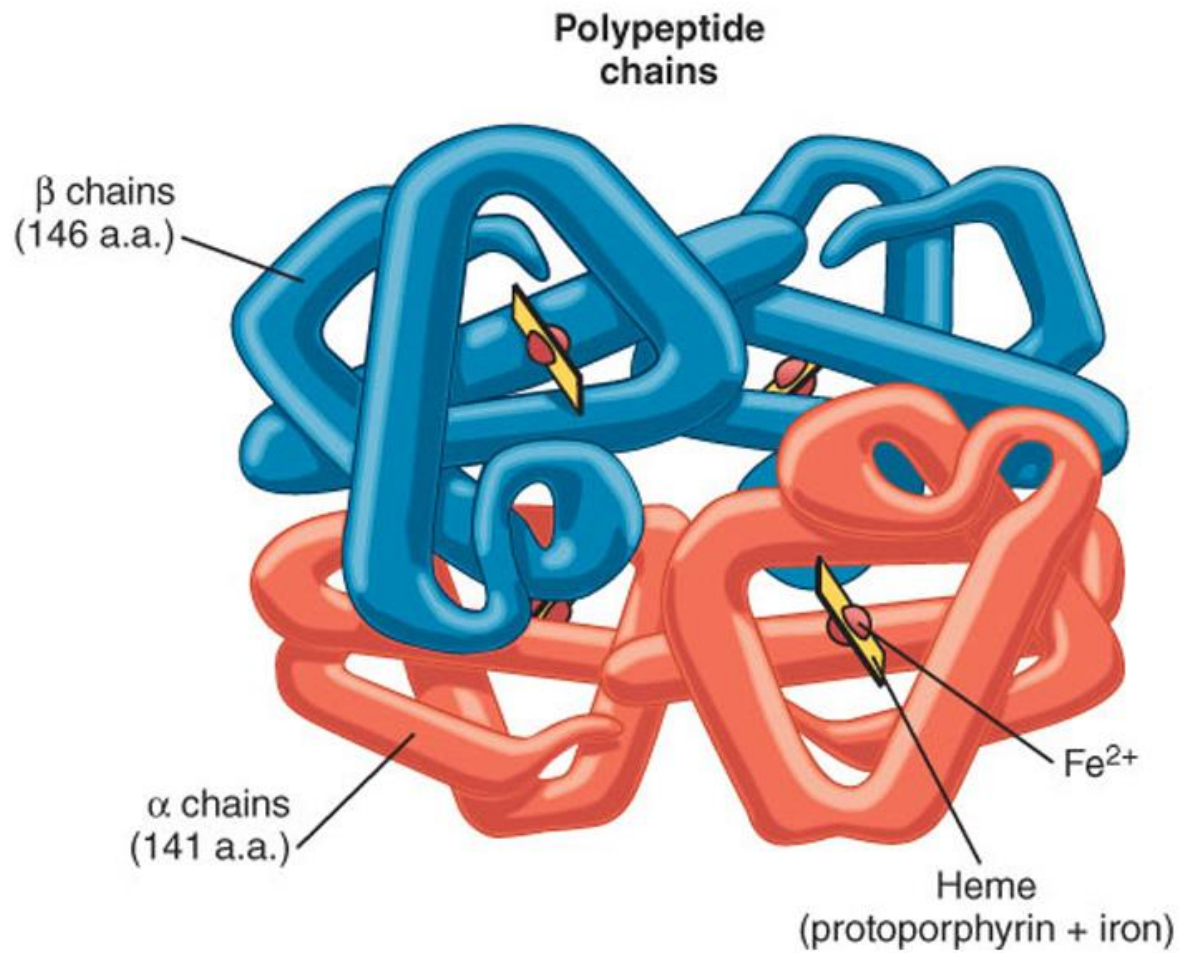
Types of Hb

Form	Chain composition	Fraction of total hemoglobin
HbA	$\alpha_2\beta_2$	90%
HbF	$\alpha_2\gamma_2$	<2%
HbA ₂	$\alpha_2\delta_2$	2%–5%
HbA _{1c}	$\alpha_2\beta_2$ -glucose	3%–9%

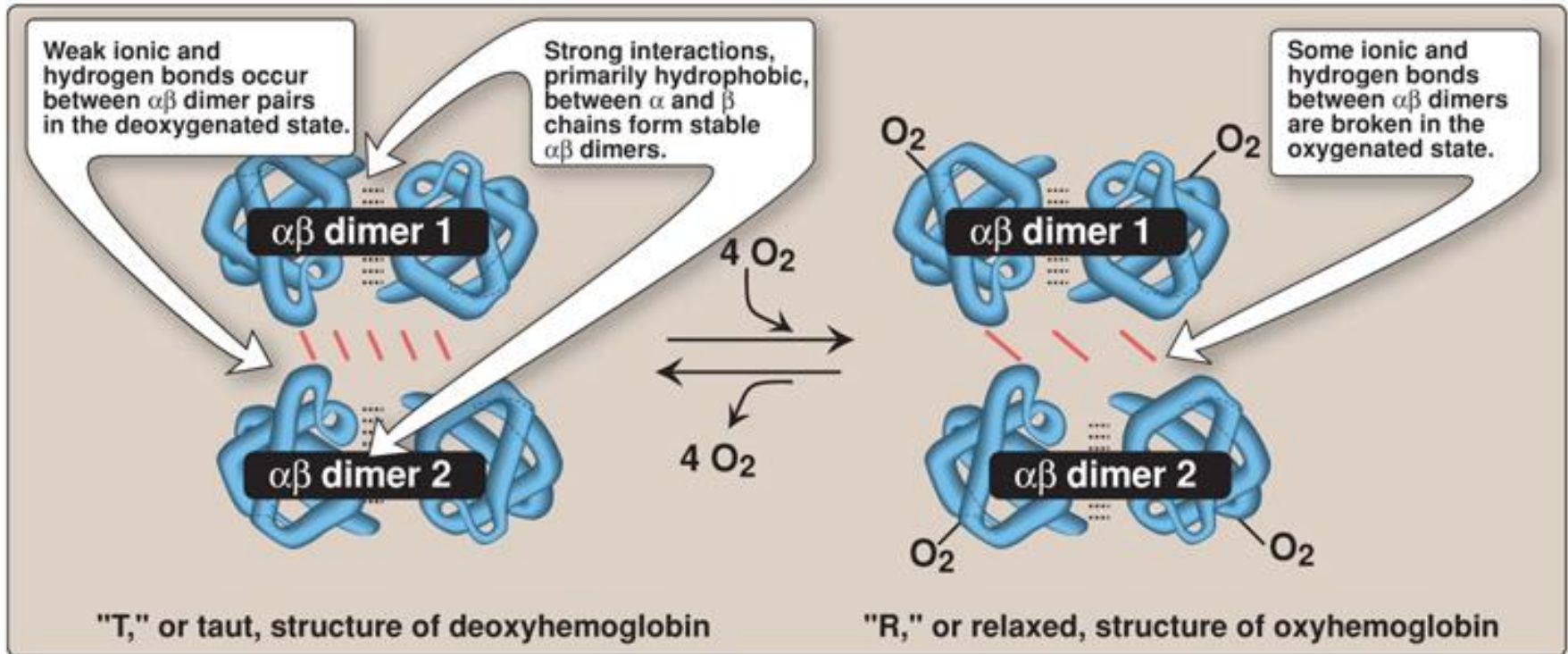
Abnormal:	Carboxy Hb
	Met Hb
	Sulf Hb

Hemoglobin A (HbA)

- Major Hb in adults
- Composed of four polypeptide chains:
 - Two α and two β chains
- Contains two dimers of $\alpha\beta$ 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 molecules of O_2

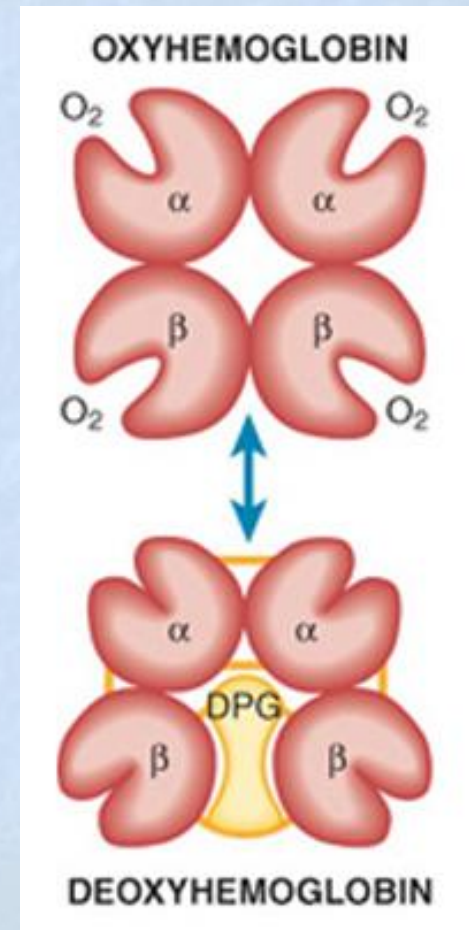


HbA structure



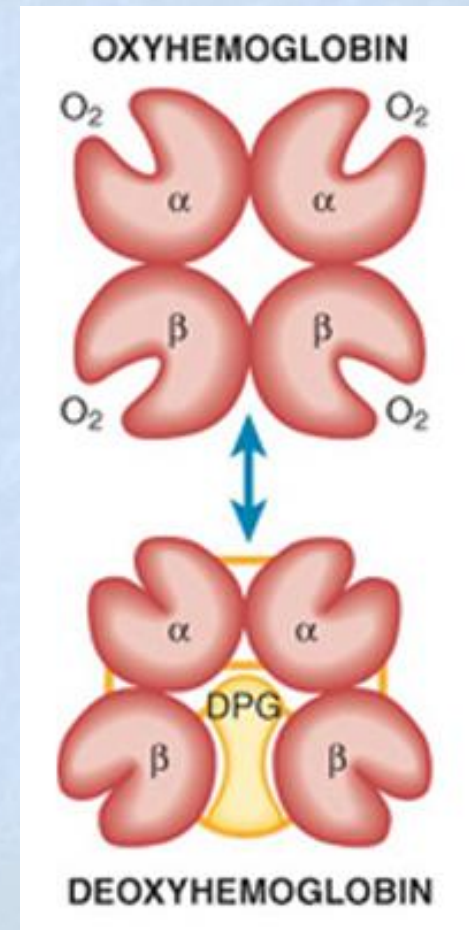
T-form of Hb

- 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



Hemoglobin function

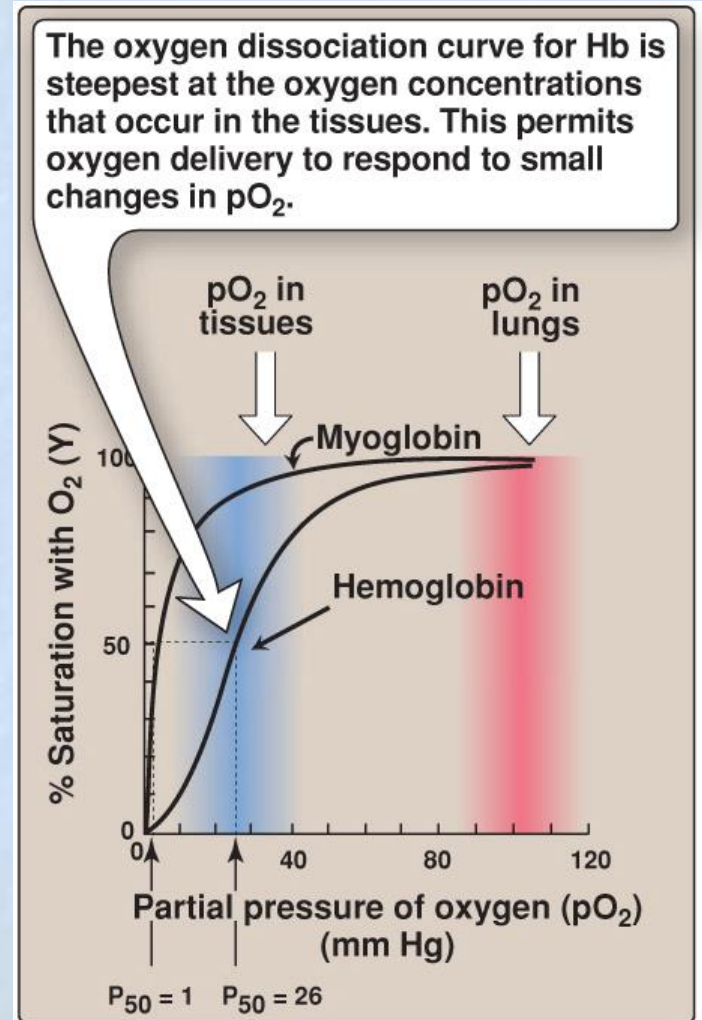
- Carries oxygen from the lungs to tissues
- Carries carbon dioxide from tissues back to the lungs
- Normal level (g/dL):
 - Males: 14-16
 - Females: 13-15

Factors affecting oxygen binding

- Four allosteric effectors:
 - pO_2 (partial oxygen pressure)
 - pH of the environment
 - pCO_2 (partial carbon dioxide pressure)
 - Availability of 2,3-bisphosphoglycerate

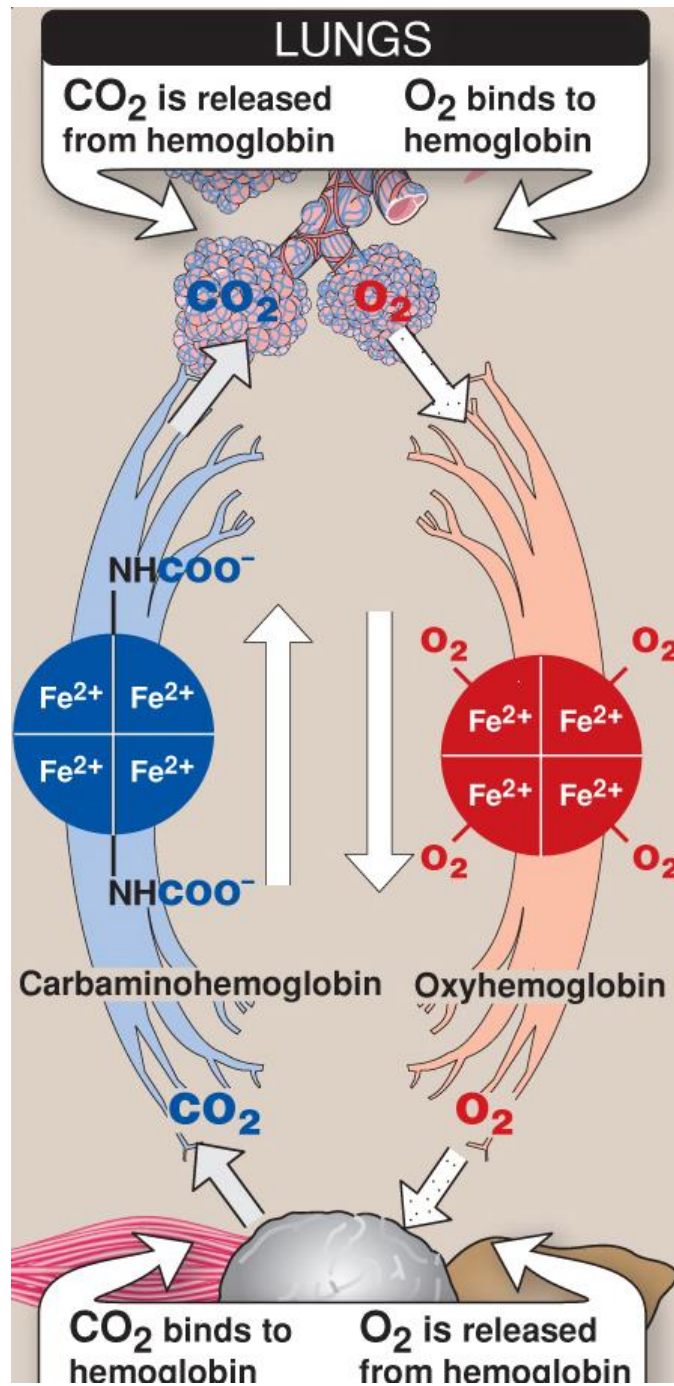
Oxygen Dissociation Curve

- 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



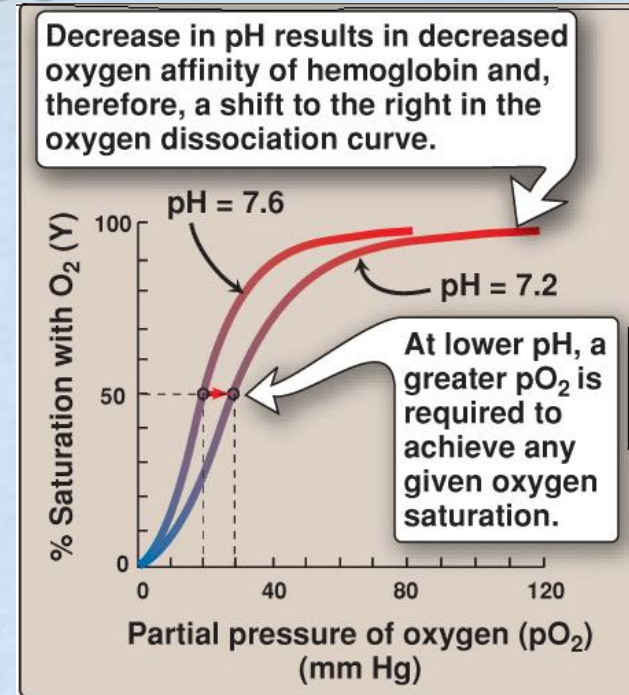
P_{50}

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



The Bohr effect

- It is the shift of the ODC to the right in response to an increase in pCO₂ or a decrease in pH
- Effect of pH and pCO₂ on:
 - Oxygenation of Hb in the lungs
 - Deoxygenation in tissues
- Tissues have lower pH (acidic) than lungs
- Due to proton generation (two reactions):
 - $\text{CO}_2 + \text{H}_2\text{O} \rightleftharpoons \text{H}_2\text{CO}_3$
 - $\text{H}_2\text{CO}_3 \rightleftharpoons \text{HCO}_3^- + \text{H}^+$
- Protons reduce O₂ affinity of Hb

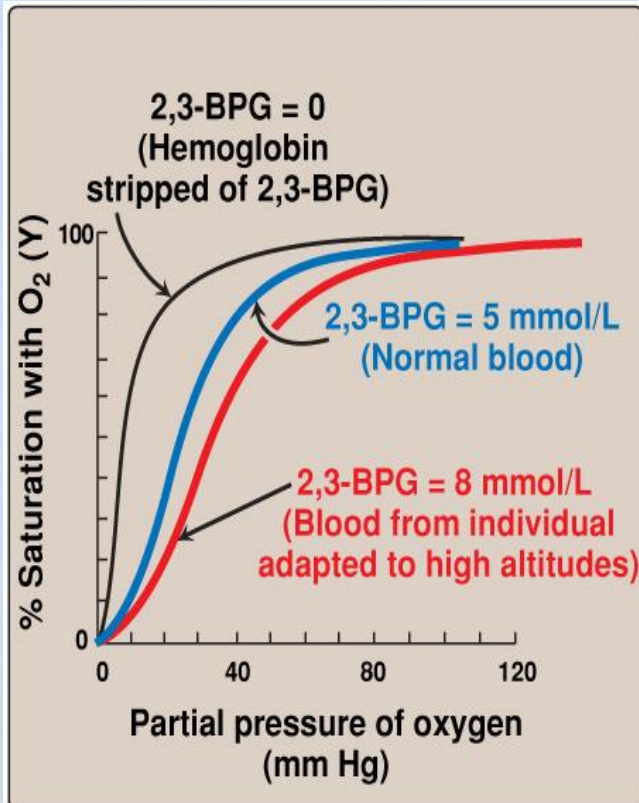


The Bohr Effect

- Causing easier O₂ release into the tissues
- The free Hb binds to two protons
- Protons are released and react with HCO₃⁻ to form CO₂ gas (HCO₃⁻ + H⁺ → CO₂ + H₂O)
- The proton-poor Hb now has greater affinity for O₂ (in lungs)
- The Bohr effect removes insoluble CO₂ from blood stream
- Produces soluble bicarbonate

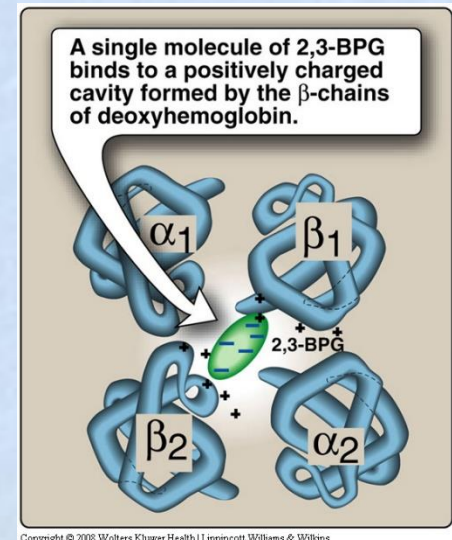
Availability of 2,3 bisphosphoglycerate

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



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At high altitudes:
-RBC number increases
-Hb conc. increases
-BPG increases



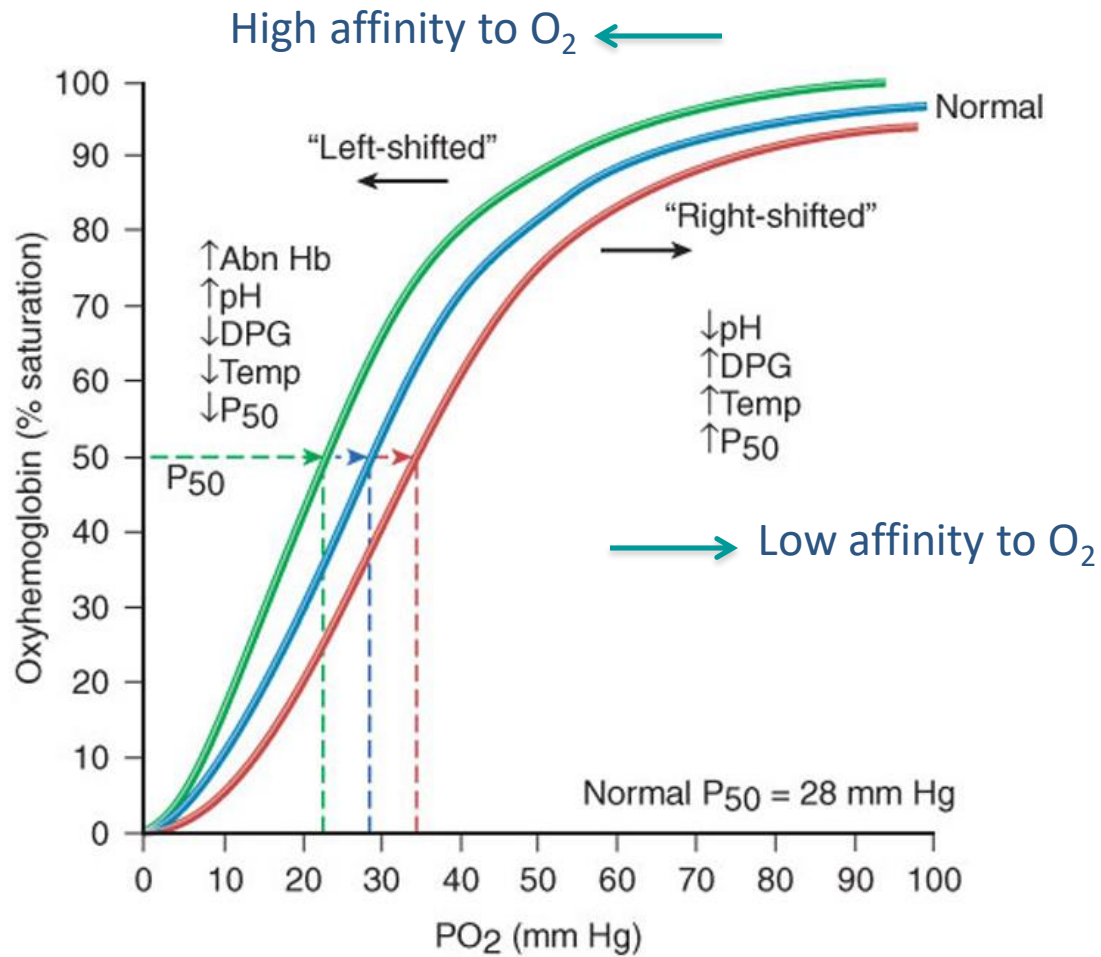
High altitude and O₂ affinity

- In hypoxia and high altitude
 - 2,3 BPG levels rise
 - This decreases O₂ affinity of Hb
 - Thus increases O₂ delivery to tissues

High O₂ affinity

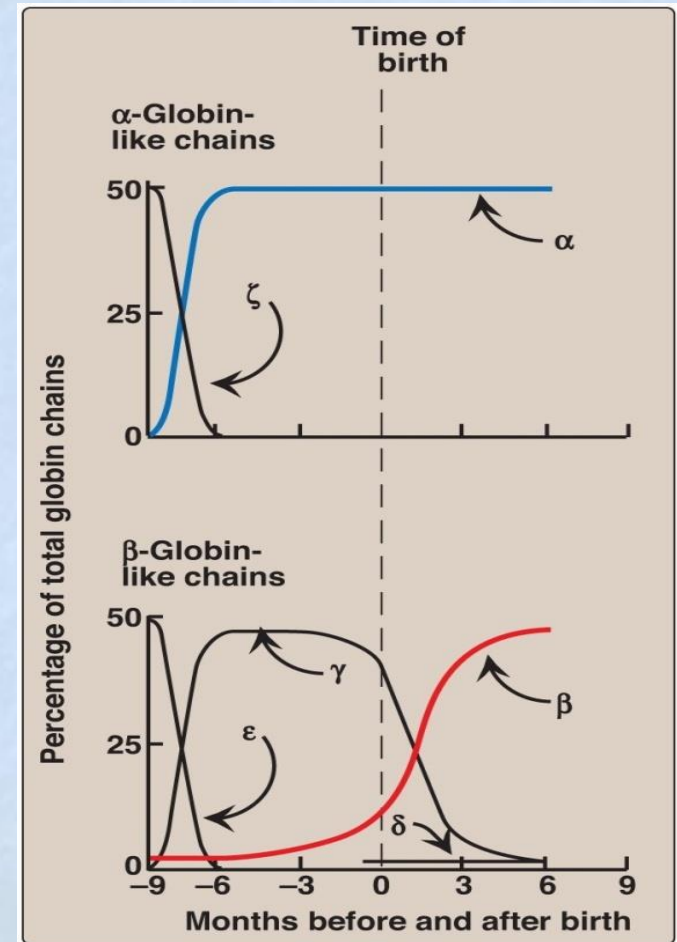
High O₂ affinity is due to:

- Alkalosis
- High levels of Hb F
- Multiple transfusion of 2,3 DPG-depleted blood



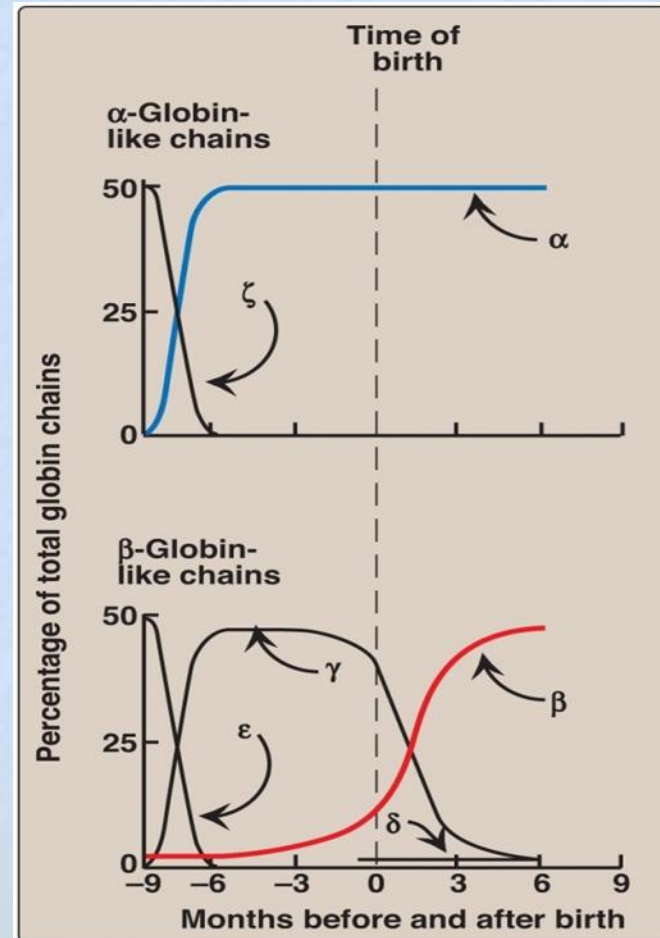
Fetal Hemoglobin (HbF)

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



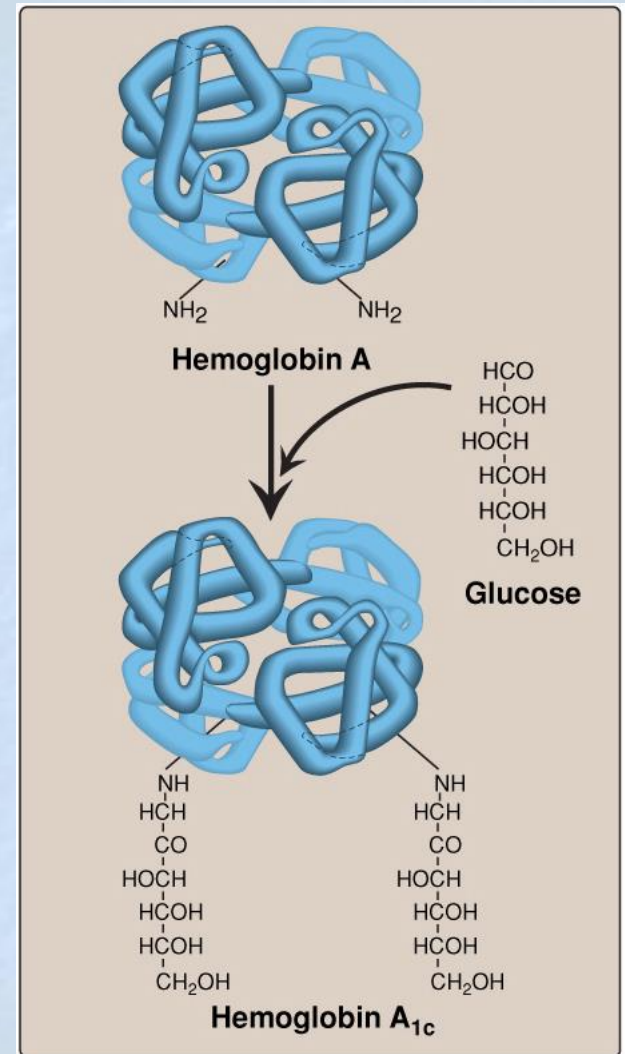
HbA₂

- Appears shortly before birth.
- Constitutes ~2% of total Hb
- Composed of two α and two δ globin chains



HbA_{1c}

- HbA undergoes non-enzymatic glycosylation
- Glycosylation depends on plasma glucose levels
- HbA_{1c} levels are high in patients with diabetes mellitus



Abnormal Hbs

Unable to transport O₂ due to abnormal structure

- Carboxy-Hb: CO replaces O₂ and binds 220X tighter than O₂ (in smokers)
- Met-Hb: Contains oxidized Fe³⁺ (~2%) that cannot carry O₂
- Sulf-HB: Forms due to high sulfur levels in blood (irreversible reaction)

Reference

**Lippincott's Illustrated Reviews Biochemistry:
Unit I, Chapter 3, Pages 25 -42.**