Structure and function of hemoglobin

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Objectives

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

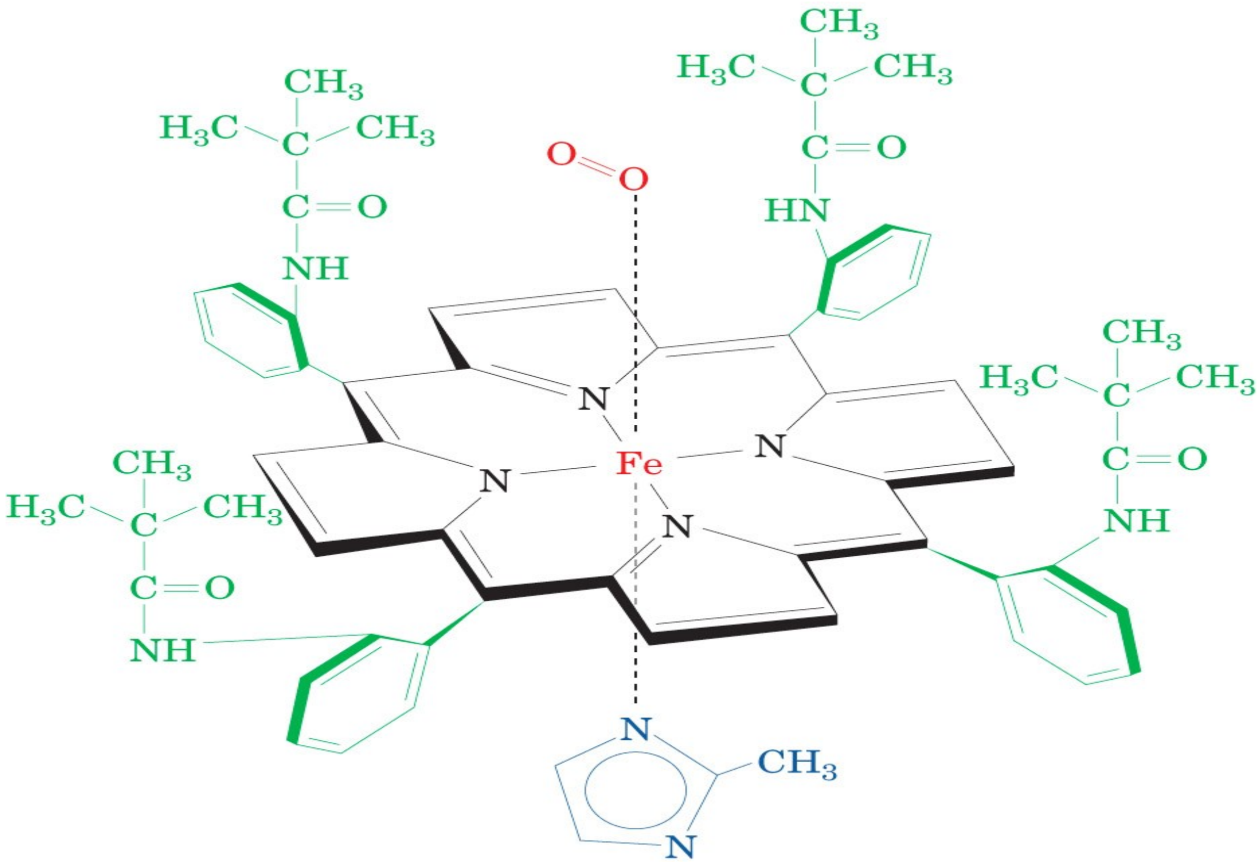
- the structure and function of hemoglobin.
- the factors affecting oxygen binding to hemoglobin.
- examples of normal and abnormal hemoglobin structures.

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



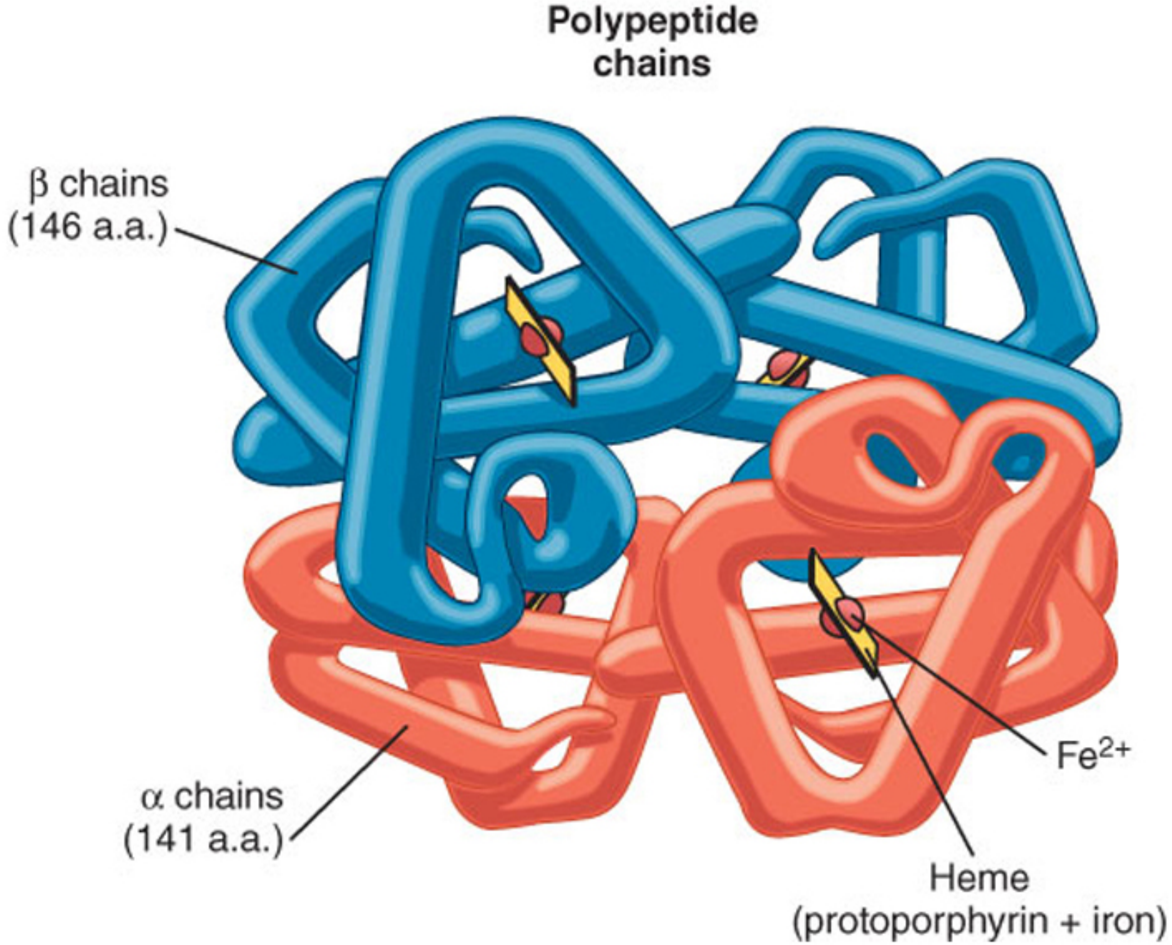
The heme group: Fe^{2+}– porphyrin complex with bound O_2

Types of Hb

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

Hemoglobin A (HbA)

- 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



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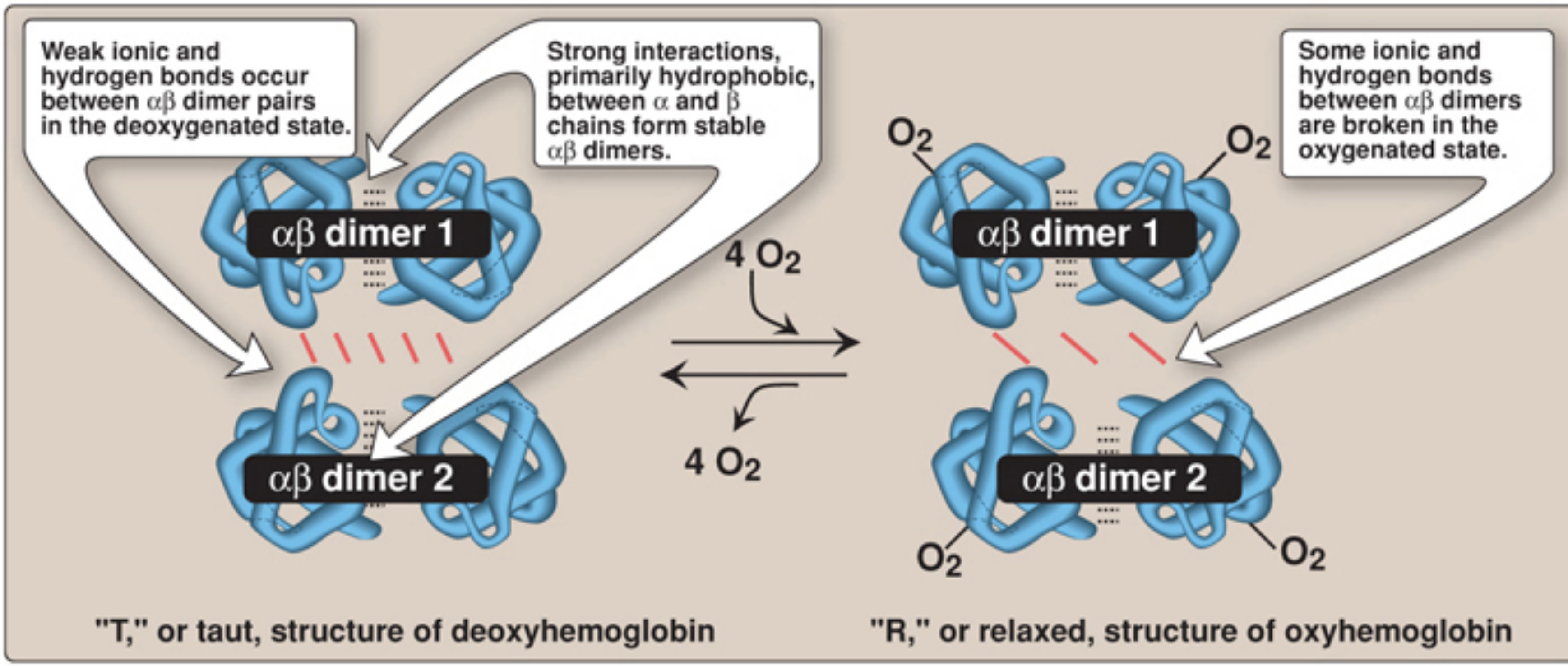
HbA structure



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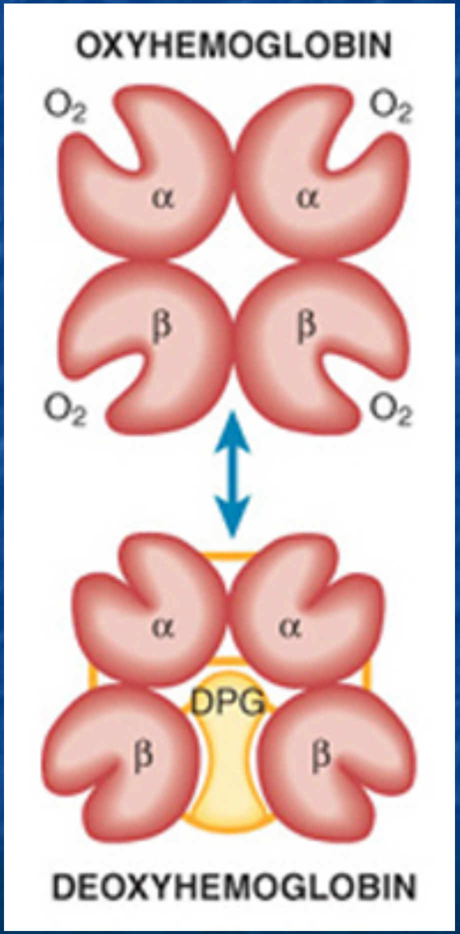
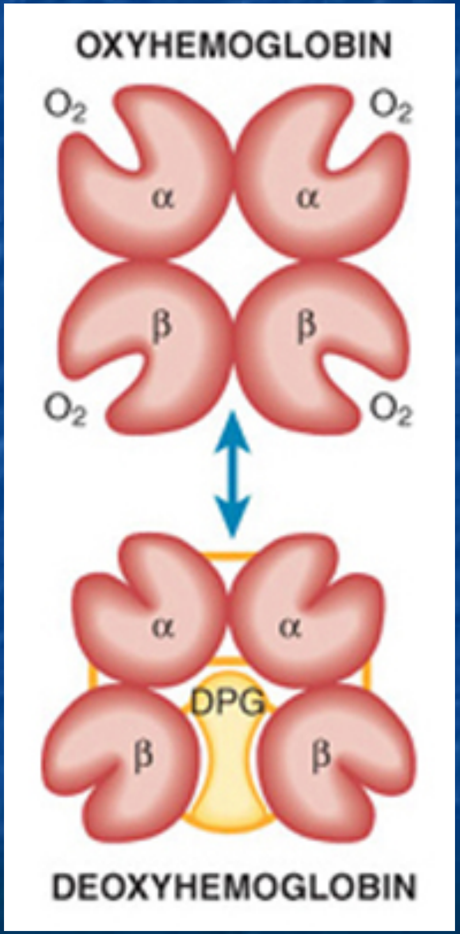
T-form of Hb

- 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

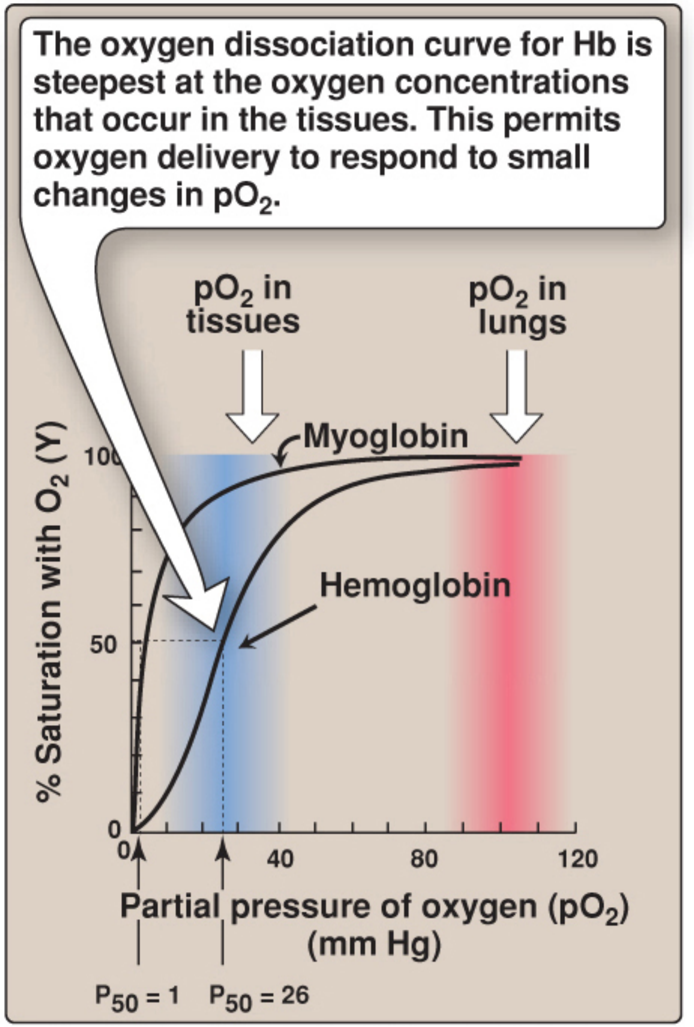
- Carries oxygen from the lungs to tissues
- Carries carbon dioxide from tissues back to the lungs
- Normal level (g/dL):
  - Males: 14-16
  - Females: 13-15

Factors affecting oxygen binding

- Three 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



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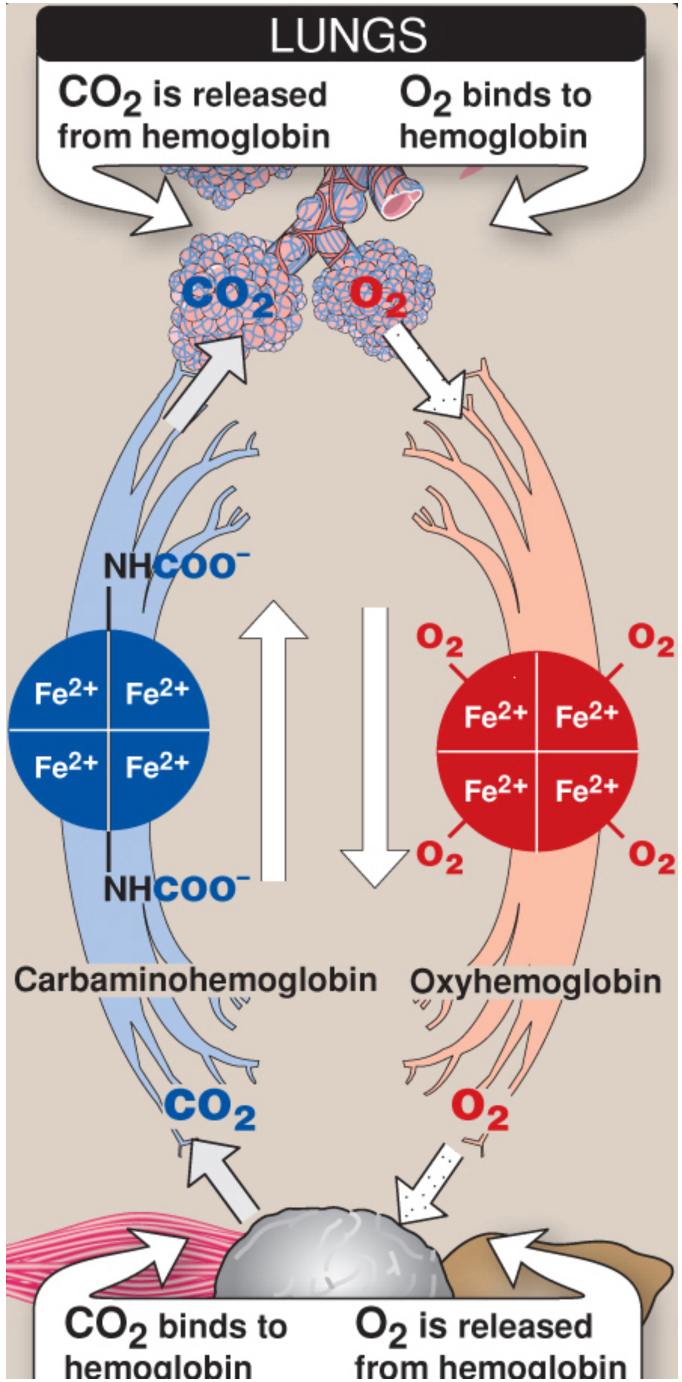
P_{50}

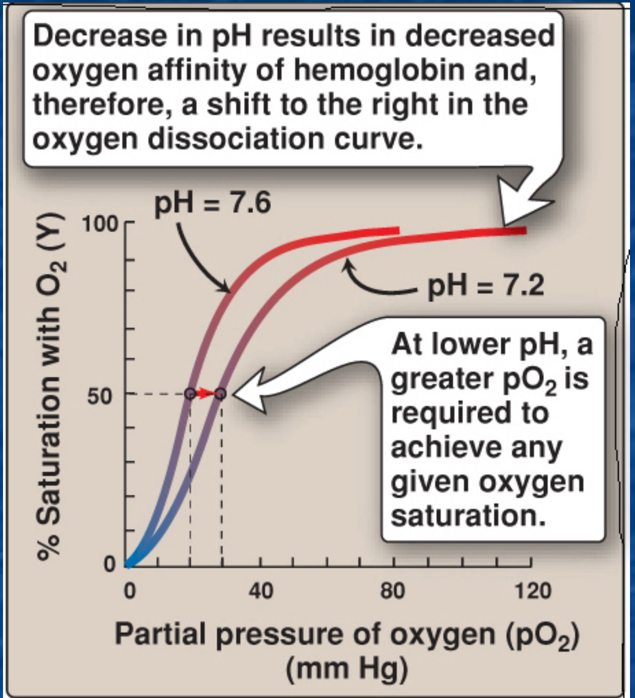
- Indicates affinity of Hb to O_2
- P_{50}(mm Hg): the pressure at which Hb is 50% saturated with O_2
- High affinity → slow unloading of O_2
- Low affinity → fast unloading of O_2
- Lung pO_2 is 100 mm → Hb saturation 100%
- Tissue pO_2 is 40 mm → Hb saturation reduces
- Hence O_2 is delivered to tissues



LUNGS
CO2 is released from hemoglobin
O2 binds to hemoglobin
CO2
O2
NHCOO−
Fe2+ Fe2+ Fe2+ Fe2+
NHCOO−
O2 O2 O2 O2
Fe2+ Fe2+ Fe2+ Fe2+
Carbaminohemoglobin
Oxyhemoglobin
CO2
O2
CO2 binds to hemoglobin
O2 is released from hemoglobin

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 (two reactions):
  - $CO_2 + H_20 \rightarrow HCO_3^- + H^+$
- Protons reduce O_2 affinity of Hb



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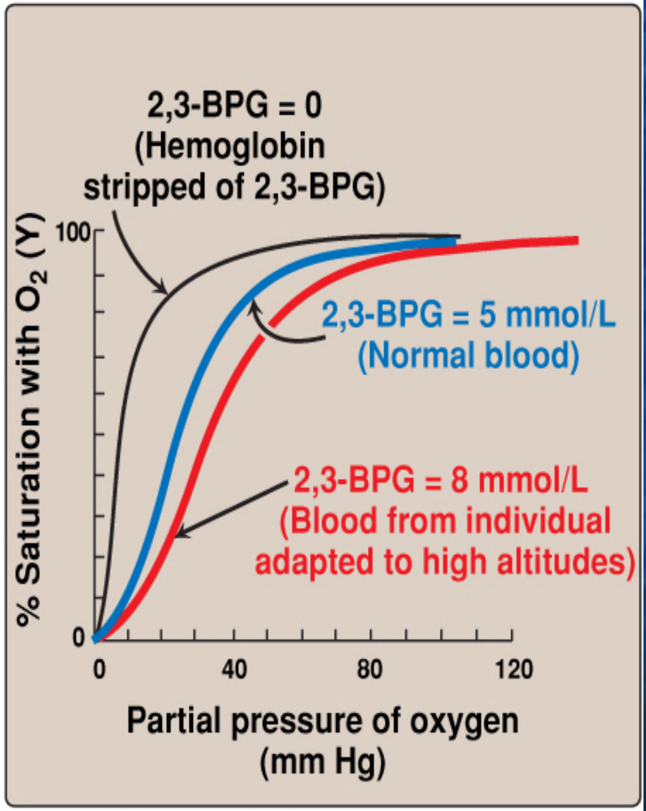
The Bohr Effect

- 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 ($HCO_3^- + H^+ \rightarrow CO_2 + H_20$)
- 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

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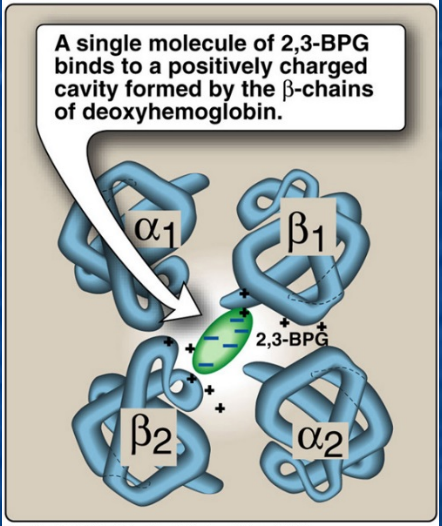
At high altitudes:
-RBC number increases
-Hb conc. increases
-BPG increases



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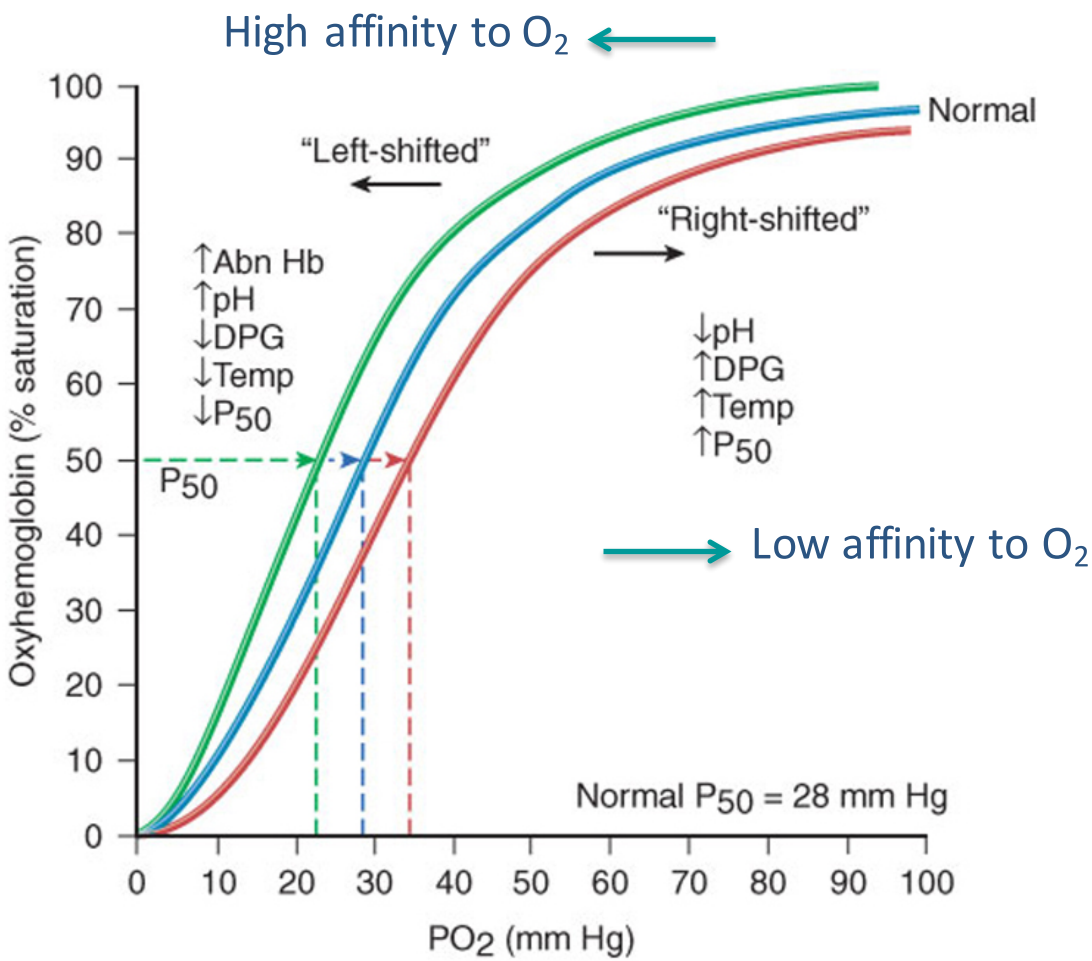
High altitude and O_2 affinity

- 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



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Fetal Hemoglobin (HbF)

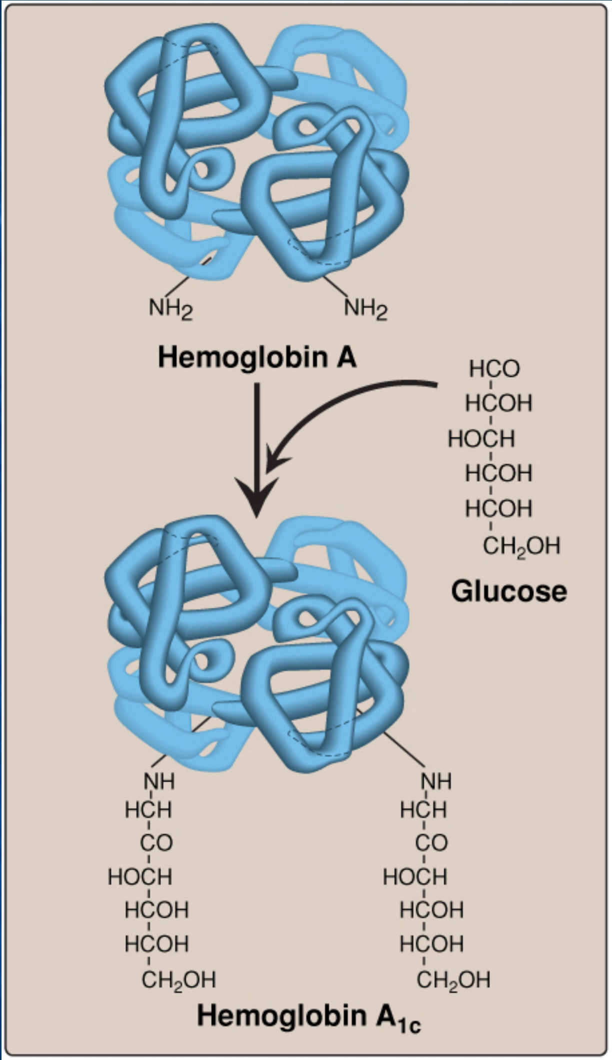
- Major hemoglobin found in the fetus and newborn
- Tetramer with two α and two γ chains
- Higher affinity for O_2 than HbA
- Transfers O_2 from maternal to fetal circulation across placenta

HbA_2

- Appears ~12 weeks after 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
- HbA1c levels are high in patients with diabetes mellitus



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Abnormal Hbs

Unable to transport O_2 due to abnormal structure

- Carboxy-Hb: CO replaces O_2 and binds 220X tighter than O_2 (in smokers)
- Met-Hb: Contains oxidized Fe^{3+} (~2%) that cannot carry O_2
- 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.