Structure and function of hemoglobin

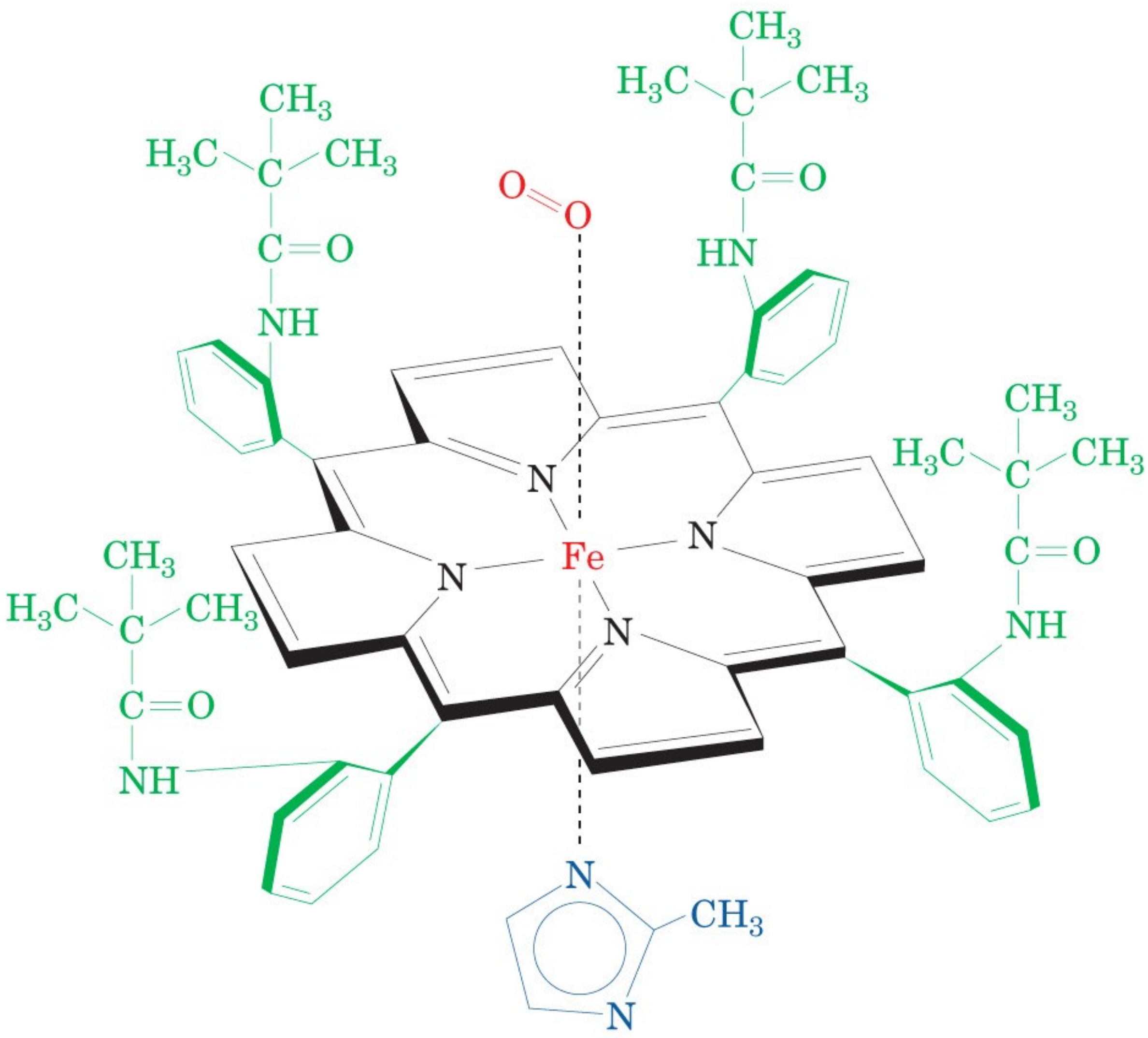
Dr. Sumbul Fatma

Hemoglobin (Hb)

- A hemeprotein found only in red blood cells
- Oxygen transport function
- Contains heme as a 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 heme
- Binds to four nitrogens of the porphyrin ring
- Plus two additional bonds with:
  - Histidine residue of globin chain
  - Oxygen



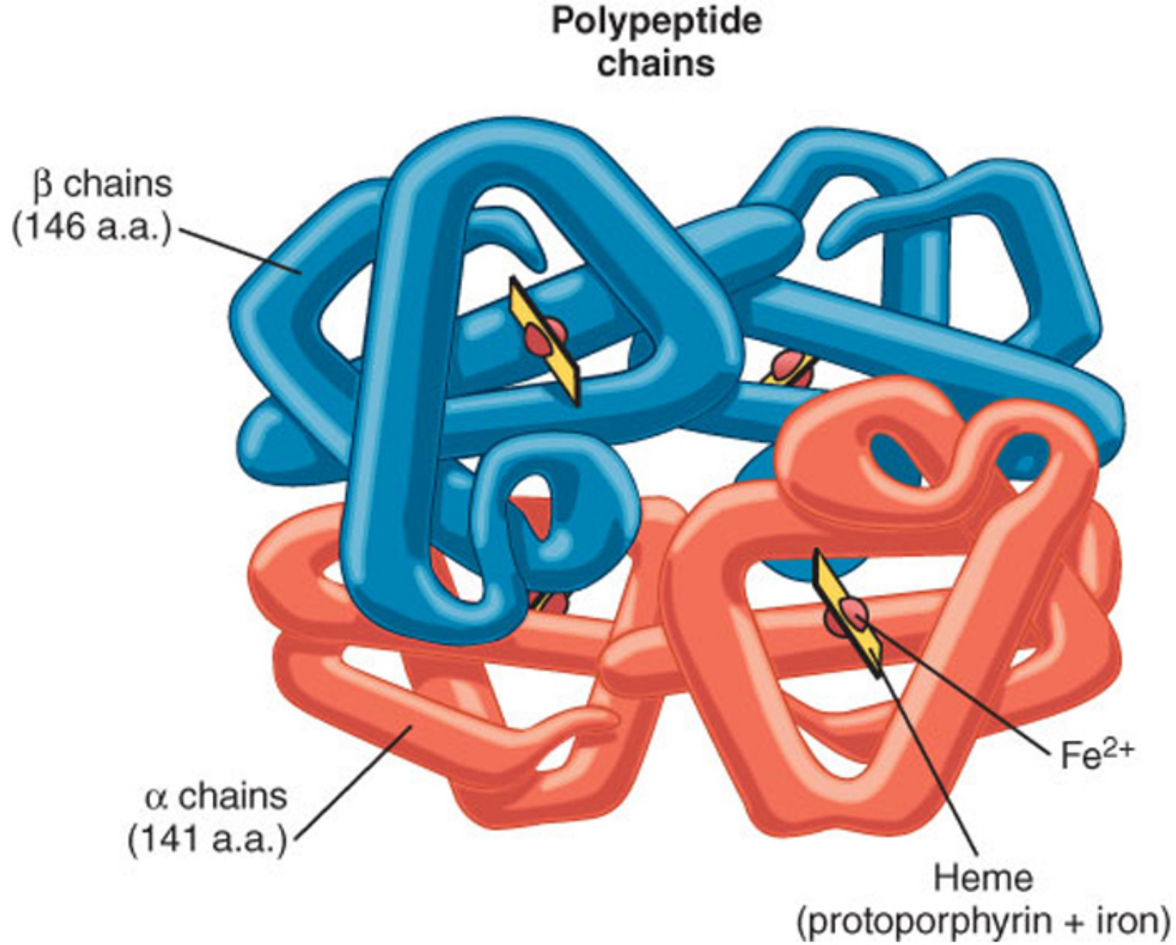
The heme group: Fe^{2+}– porphyrin complex with bound O_2

Types of Hb

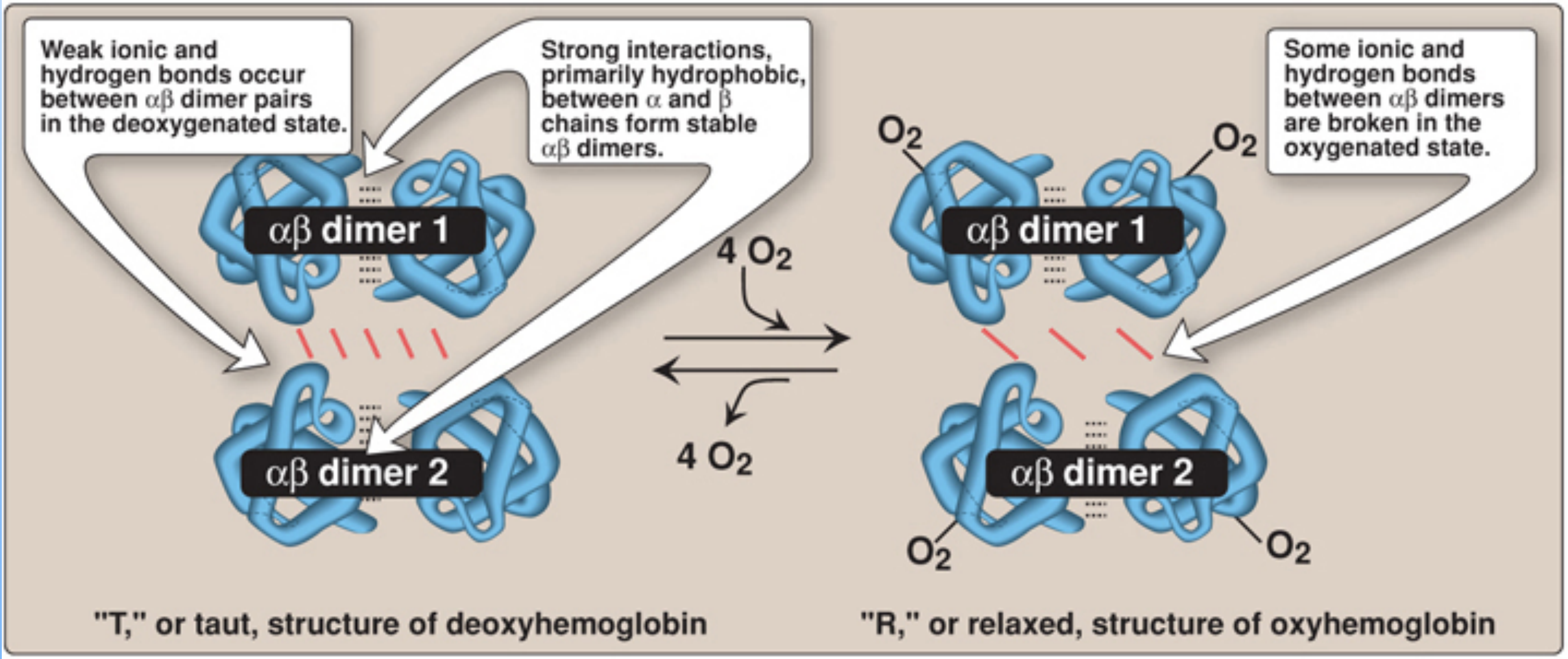
Normal:	HbA (97%)
	HbA_2 (2%)
	HbF (1%)
	HbA_{1c}
Abnormal:	Carboxy Hb
	Met Hb
	Sulf Hb

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 noncovalent 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

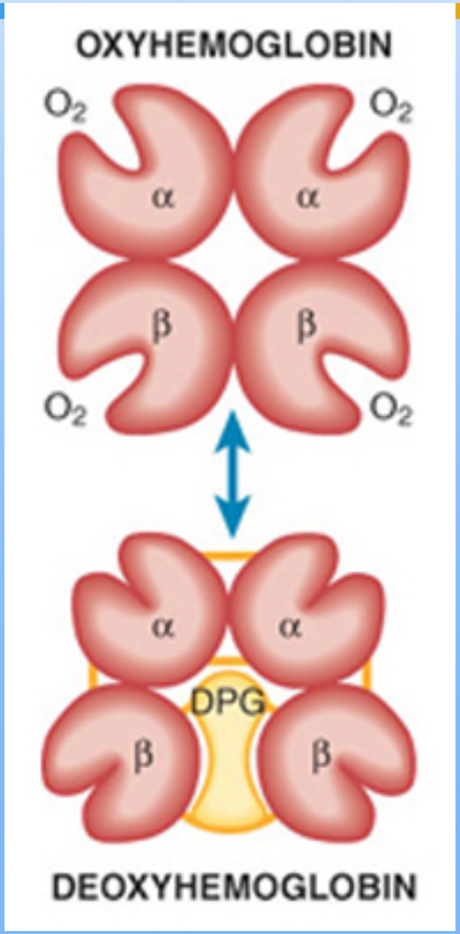

Polypeptide chains
β chains (146 a.a.)
α chains (141 a.a.)
Fe2+
Heme (protoporphyrin + iron)

HbA structure



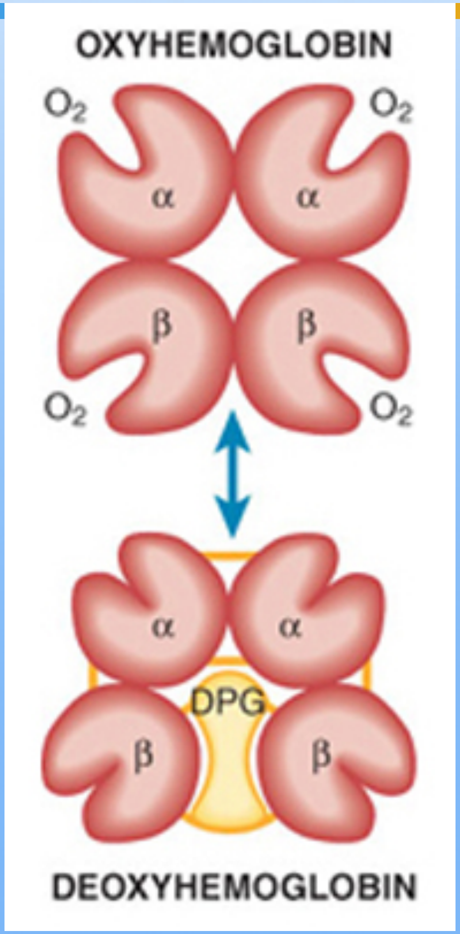
T-form of Hb

- 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

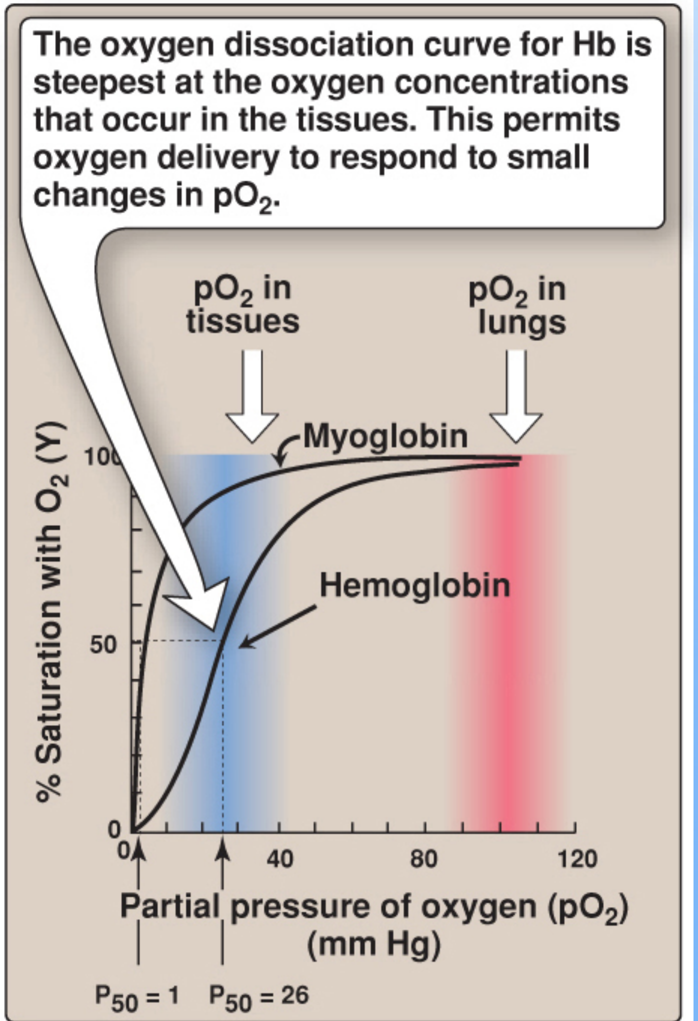
- Carries oxygen from the lungs to tissues
- Carries carbon dioxide from tissues back to the lungs
- Normal level:
  - Males: 14-16 g/dL
  - Females: 13-15 g/dL

Factors affecting oxygen binding

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

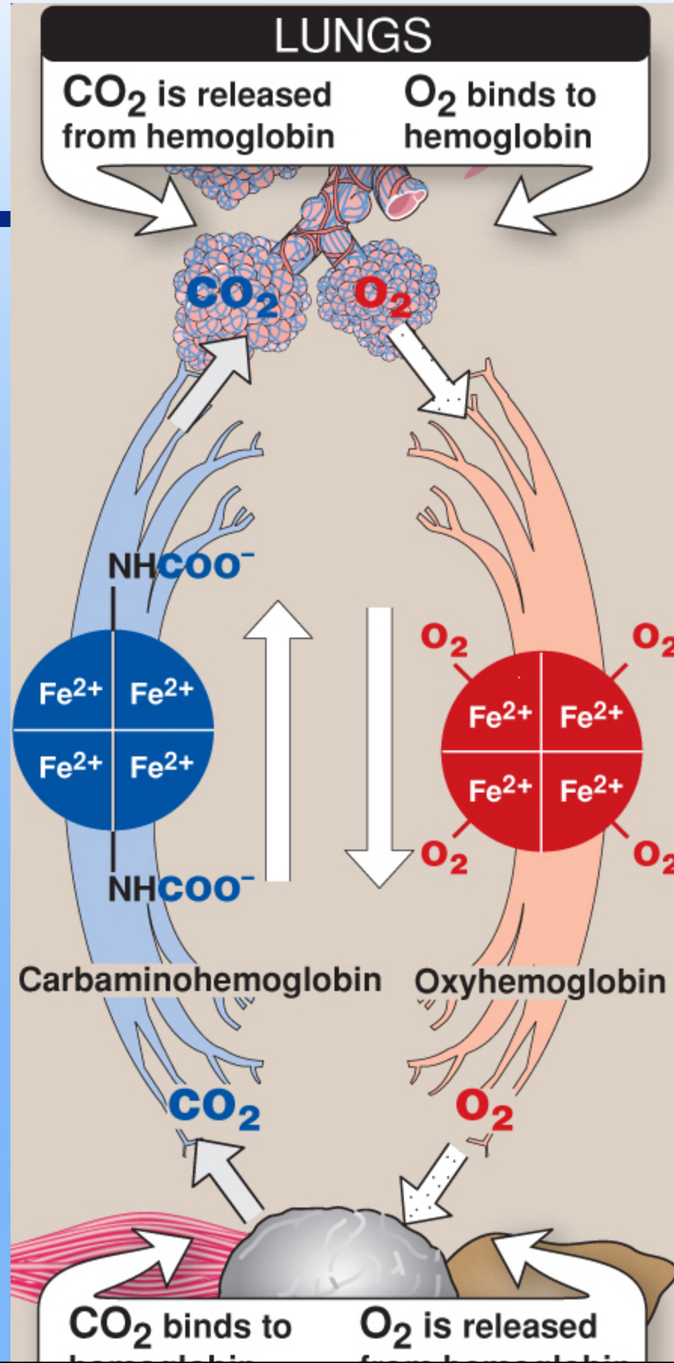
Oxygen Dissociation Curve (ODC)

- 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



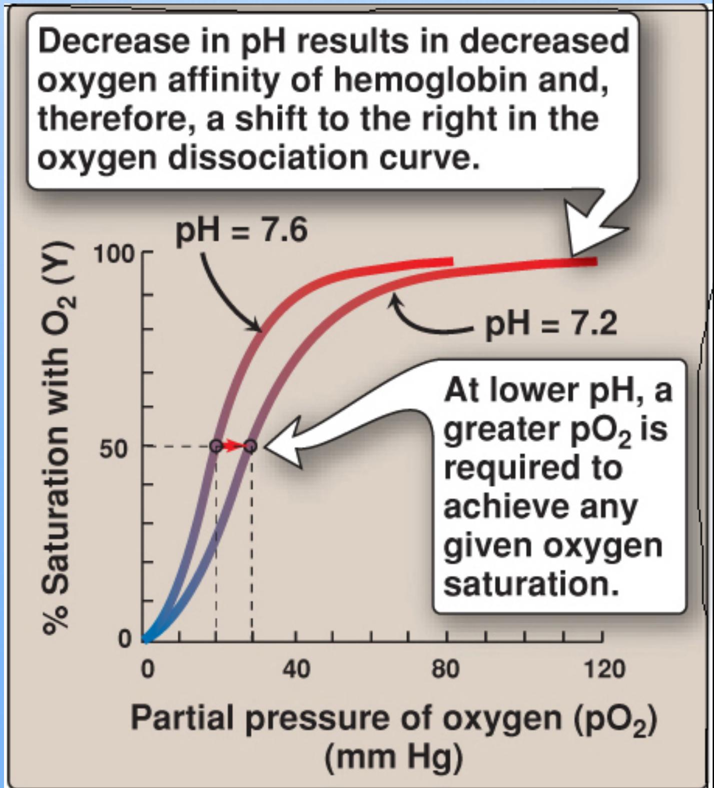
pO_2 (Partial oxygen pressure)

- p50 (mm Hg): the pressure at which Hb is 50% saturated with O_2
- Indicates affinity of Hb to 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, oxygen is delivered to tissues


LUNGS
CO_2 is released from hemoglobin
O_2 binds to hemoglobin
CO_2
O_2
$NHCOO^-$
Fe^{2+} Fe^{2+}
Fe^{2+} Fe^{2+}
$NHCOO^-$
O_2 O_2
Fe^{2+} Fe^{2+}
Fe^{2+} Fe^{2+}
O_2 O_2
Carbaminohemoglobin
Oxyhemoglobin
CO_2
O_2
CO_2 binds to
O_2 is released

The Bohr effect

- Effect of pH and pCO_2 on:
  - Oxygenation of Hb in the lungs
  - Deoxygenation at the tissues
- Tissues have lower pH (acidic) than lungs
- Due to proton generatation:
  $CO_2 + H_20$ ------> $HCO_3^- + H^+$
- Protons reduce O_2 affinity of Hb
- Causing easier O_2 release into the tissues
- The free Hb binds to two protons

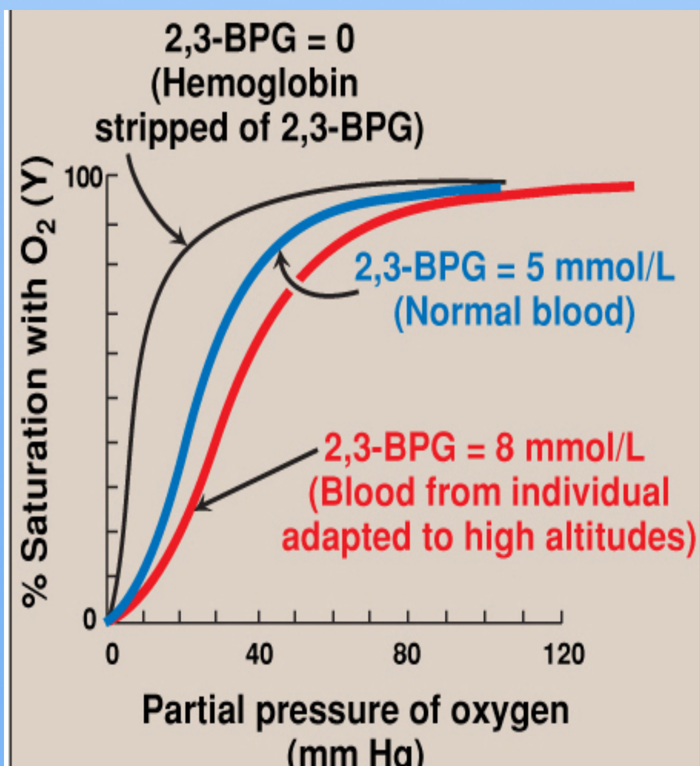


The Bohr Effect

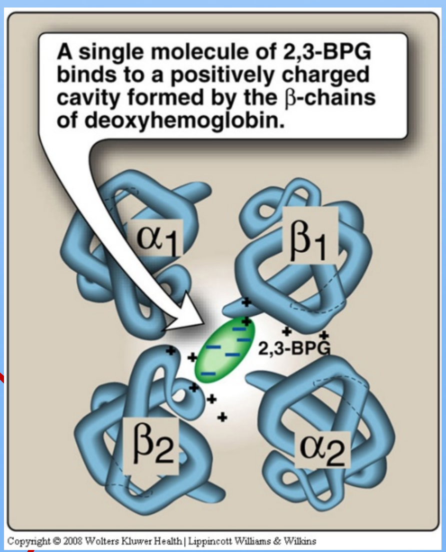
- Protons are released and react with HCO^{3-} to form CO_2 gas
- The proton-poor Hb now has greater affinity for O_2
- The Bohr effect removes insoluble CO2 from blood stream
- Produces soluble bicarbonate

Availability of 2,3-bisphosphoglycerate

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



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



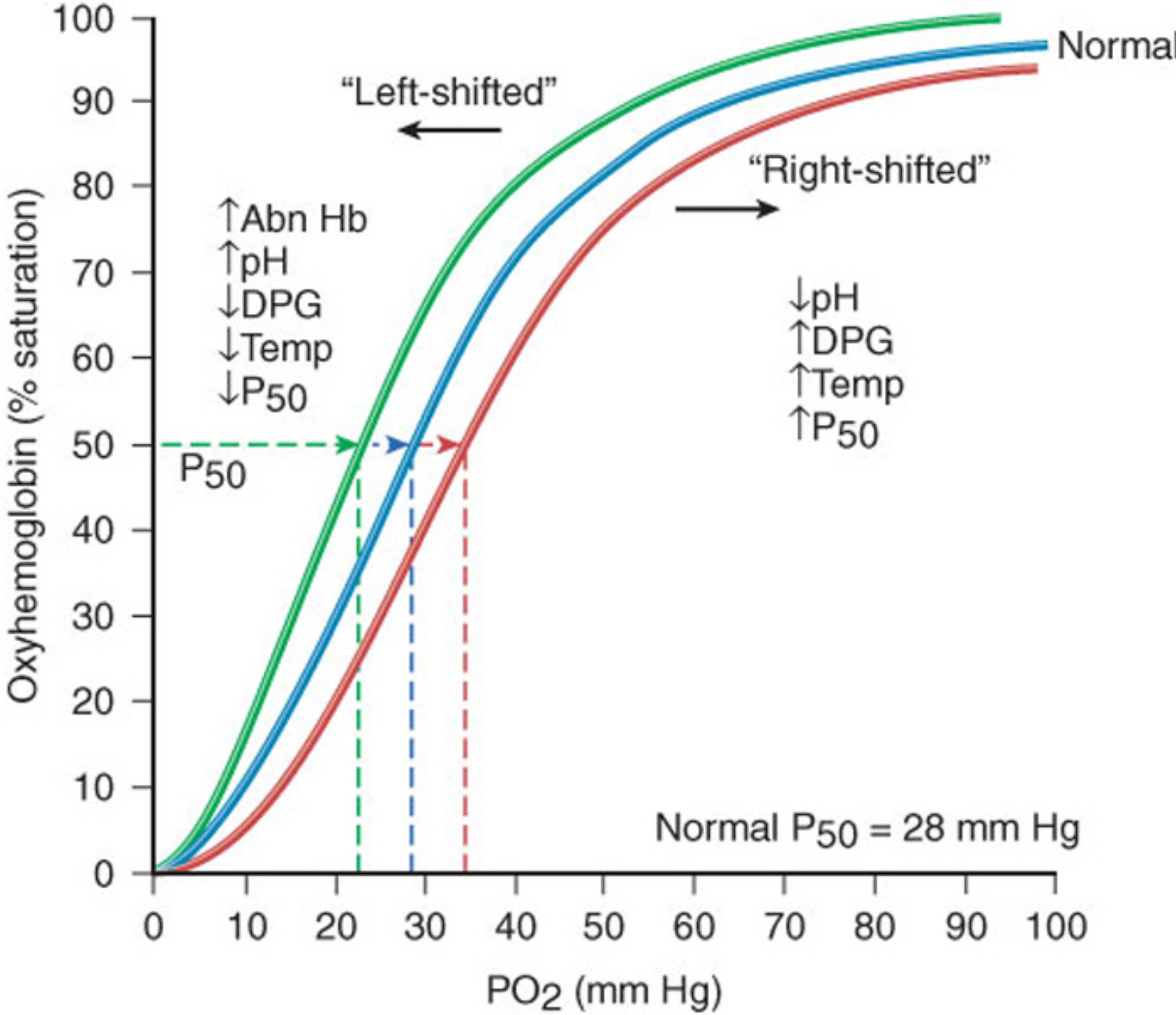
High altitude and O_2 affinity

- High altitude decreases Hb O2 affinity
- Hypoxia
  - Increases 2,3 DPG levels
  - Decreases O2 affinity
  - Increases O_2 delivery to tissues

High O_2 affinity

High O2 affinity occurs due to:

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



Normal
"Left-shifted"
"Right-shifted"
↑Abn Hb
↑pH
↓DPG
↓Temp
↓P_{50}
↓pH
↑DPG
↑Temp
↑P_{50}
P_{50}
Normal P_{50} = 28 mm Hg
Oxyhemoglobin (% saturation)
0
10
20
30
40
50
60
70
80
90
100
PO_2 (mm Hg)

Fetal Hemoglobin (HbF)

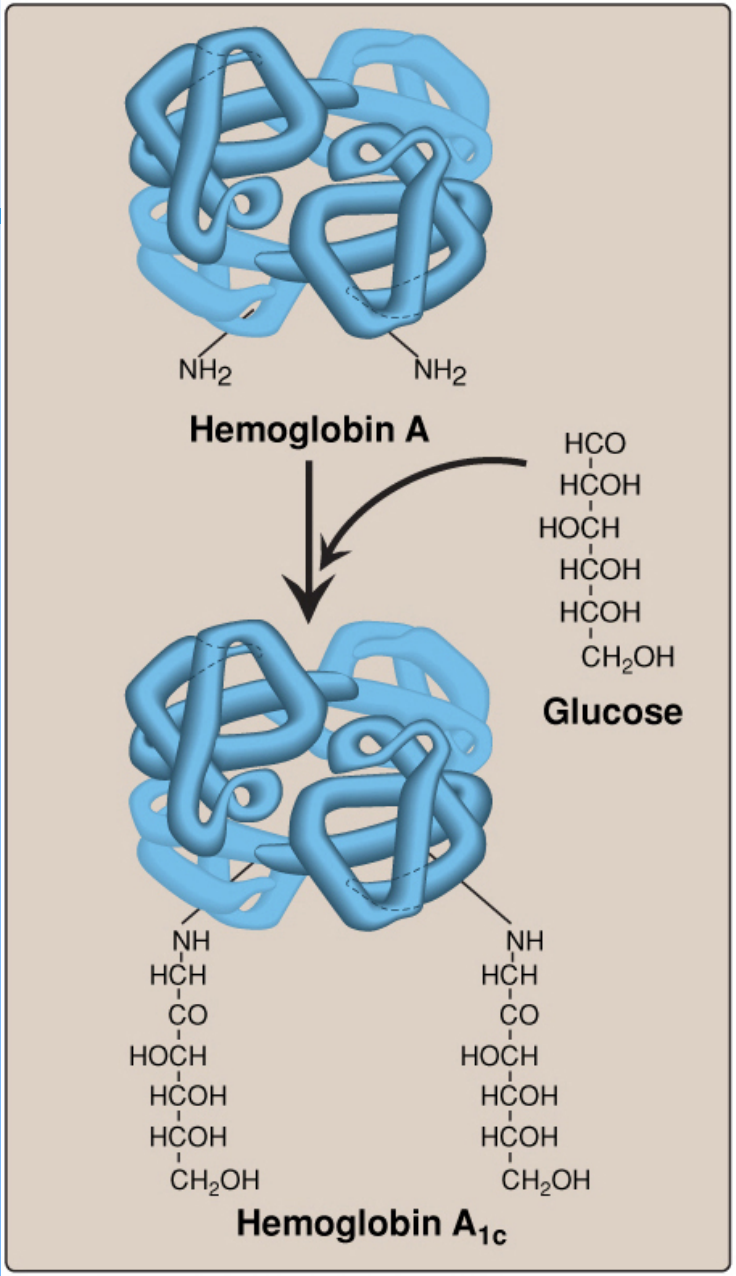
- Major hemoglobin found in the fetus and newborn
- Tetramer with two α and two γ chains
- Higher affinity for O_2 than HBA
- Transfers O_2 from maternal to fetal circulation across placenta

HbA_2

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

HbA_{1c}

- HbA is slowly and non-enzymatically glycosylated
- Glycosylation depends on plasma glucose levels
- HbA1c levels are high in patients with diabetes mellitus



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)
- Met-Hb: Contains oxidized Fe3+ (~2%) that cannot carry O_2
- Sulf-Hb: Forms due to high sulfur levels in blood (irreversible reaction)

References

- Lippincott’s Illustrated Reviews- Biochemistry
  (pp 25-34)