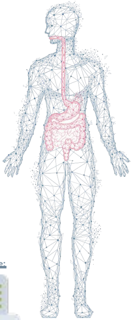
L1:

Structure and function of haemoglobin

GNT Block



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Objectives:

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

Lecture presented by :

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Hemoglobin

A hemeprotein found only in red blood cells
protein part (Globin chain)and
non protein part (heme group - attach)

Female Dr: Actually hemeproteins are aslo found in Cytochromes & Catalase

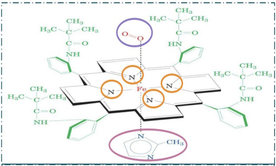
Oxygen transport function

Contains heme as prosthetic group

Heme reversibly binds to oxygen
(It's important for binding to oxygen -Load- then release it -unload- in the tissue)

The heme group

- A-complex of protoporphyrin IX and ferrous iron(Fe2+)
- Fe2+ is present in the center of the heme
- Fe2+ binds to four nitrogen atoms of the porphyrin ring
- Forms two additional bonds with:
  1-Histidine residue of globin chain
  2-Oxygen
- Thus making 6 bond in total



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

Fe2+ binds to six molecules because it's in
binds to 6 different molecules.
ferrous state:
Four nitrogen atoms of the porphyrin ring.
Histidine residue of globin chain
Oxygen

Hemoglobin types

Normal Hemoglobin We call them normal because they can bind to oxygen		
Form	Chain composition	Fraction of total hemoglobin
HbA	**α2β2**	**90%**
HbA1c	**α2β2-Glucose**	**3% - 9%**
HbF	**α2γ2**	**<2%**
HbA2	**α2δ2**	**2%-5%**

Abnormal Hemoglobin unable to transport oxygen due to abnormal structure They can't bind to oxygen (For example Met-Hb and Sulf-Hb), or they can't release oxygen (For example Carboxy-Hb)	
Carboxy-Hb	**CO replaces O2 and binds 220X tighter than O2 (in smokers)** (reversible) (that's why they have difficulty in breathing sometimes)
Met-Hb	**Contains oxidized Fe+3** (~2%) that cannot carry O2 (reversible) Can only form 5 bonds
Sulf-HB	Forms due to **high sulfur level in blood(irreversible** reaction) (Maybe caused by drugs that increasing the in sulfur)

HbA

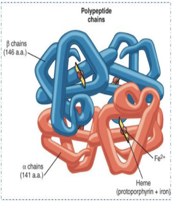
It is the major Hb in adults

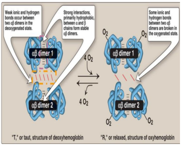
Composed of 4 polypeptide chains:
○ 2 α chains and 2 β chains

Contains 2 dimers of αβ subunits, held together by noncovalent interactions

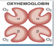
A hemoglobin molecule contains 4 heme groups and carries 4 molecules of O2 or 8 atoms of O

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





There are two types of bonding in the HbA structure:
- Intra-dimer bonding: strong bonds between 2 subunits (between α and β) (hydrophobic bond)
- Inter-dimer bonding: weak bonds between 2 dimers (between αβ and αβ)

 T-Form (Found in tissues)	R-Form (Found in lung) 
Deoxy form of Hb	Oxygenated form of Hb
“Taut” or “Tense” form	Relaxed form
The movement of dimers is constrained	Dimers have more freedom of movement
Low oxygen affinity form	High oxygen affinity form

Hemoglobin function

- Hemoglobin carries **oxygen** from the lungs to tissues
- Hemoglobin carries some **carbon dioxide** (In form of carbaminohemoglobin) **and protons** from tissues back to the lung
- Normal level of hemoglobin (g/dL)

Male: **14-16** (g/dL)
Female: **13-15** (g/dL) (Menstrual cycle is the reason that female has less Hb)

factors affect O2 binding

four allosteric effectors: (bind to Hb and modify O2 binding capacity)

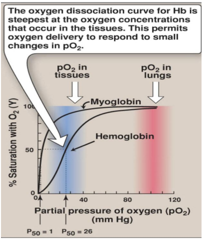
1. **PO2** (partial O2 pressure)
2. **PH** of the environment
3. **PCO2** (partial CO2 pressure)
4. Availability of **2,3-bisphosphoglycerate** (2,3BPG)

O2 dissociation curve

- The curve is sigmoidal in shape (S shaped curve),
- It indicates cooperation of subunits in O2 binding.
- Binding of O2 to one heme group **increases** O2 affinity of others (hence the term cooperation)
- Heme-heme interaction

Oxygen dissociation curve

Oxygen-dissociation curve for hemoglobin is sigmoidal in shape indicating that the subunits cooperate in binding oxygen. Cooperative binding of oxygen by the four subunits of hemoglobin means that the binding of an oxygen molecule at one heme group increases the oxygen affinity of the remaining heme groups in the same hemoglobin tetramer . This effect is referred to as heme-heme interaction . Although it is more difficult for the first oxygen molecule to bind to hemoglobin, the subsequent binding of oxygen occurs with high affinity, as shown by the steep upward curve in the region near 20-30 mmHg



P_{50}

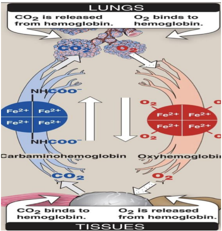
Video

Indicates affinity of Hb to O
P50(mm Hg): the pressure which Hb is 50% saturated with O

High affinity (left shift) → slow unloading of O
Low affinity (right shift)→ fast unloading of O

When lung partial pressure of O is 100 mmHg ,Hb saturation is 100%

When tissue partial pressure of O is 40 mmHg ,Hb saturation reduces, hence O is delivered to tissue



يعني باختصار اللي يحتاج تعرفونه من هالصورة أن الـ Hb ياخذ الأوكسجين من الـ Lungs ويصير اسمه (Oxyhemoglobin) بعدها يروح للـ Tissues وهناك يُفرز الـ Protons اللي راح يقلل الـ Affinity حقت الـ Hb للـ O_2 وراح يخليه يترك الأوكسجين وفي نفس الوقت راح تكون الـ Tissues أفرزت الـ CO_2 وحنا قلنا الـ Hb حاليًا ترك الأوكسجين فهو فاضي! يقوم وياخذ الـ CO_2 ويصير اسمه (Carbaminohemoglobin) ويروح يوديه للـ Lungs وبعدها يتركه ويأخذ أوكسجين وتستمر الدوامة

In lung: ↑ pO_2 → ↑ Hb binding → high affinity → slow unloading of O_2

In tissue: ↓ pO_2 → ↓ Hb binding → low affinity → fast unloading of O_2

The bohr effect

- It is the shift of the ODC Oxygen dissociation curve to the right in response to an increase in pCO_2 or a decrease in pH (acidity)
- It describe the effect of of pH and pCO_2 on:
  - Oxygenation of Hb in the lungs
  - Deoxygenation in tissues

Affinity is showing by saturations, if the curve shifts to the right that means the affinity is reduced and lead to unload (release) the oxygen In simple the Bohr effect shows how the production of CO2 leads to increase the production of protons (Hydrogens) that lowers the affinity between the Hb and O2 (so increase the release of O2 to the tissues)

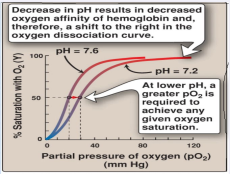
- Tissues have lower pH (more acidic) than lungs due to proton (H^+) generation (two reactions)
  - $CO_2 + H_20 \leftrightharpoons H_2CO_3$ (carbonic acid)
  - $H_2CO_3 \leftrightharpoons HCO_3^- + H^+$ HCO_3^- is bicarbonate (Base)

- Protons (H^+) reduce O_2 affinity of Hb causing easier O_2 release into the tissue.
- The free Hb bind to two protons (H^+)

- Protons are released at the lungs and react with HCO_3^- to form CO_2 gas (it will be exhaled) ($HCO_3^- + H^+ \rightarrow CO_2 + H_2O$)
- The proton-poor Hb now has greater affinity for O_2 (in lungs)

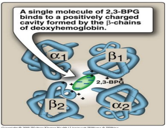
- The Bohr effect remove insoluble CO_2 from blood stream and produce soluble Bicarbonate

Results of a shift to the right: P50 is shifted to a higher value of oxygen pressure → affinity decreases (more oxygen is required to achieve 50% saturation) → facilitate delivery of oxygen



Availability of 2,3-Bisphosphoglycerate(BPG)

- Binds to deoxy-Hb and stabilizes the T form (in tissues), bind to the two β chains
- When oxygen bind to Hb BPG is released (in the lung)



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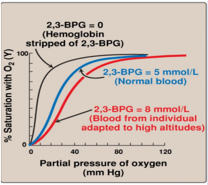
High altitude and O_2 affinity

Important

At high altitude :

- RBC number increases (compensatory mechanism)
- Hb Conc. increases
- BPG increases to decrease the affinity in the tissues (facilitate unloading), the saturation in the lungs didn't decrease by much due to high PO_2



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01 In hypoxia and high altitude

02 2,3 BPG levels rise

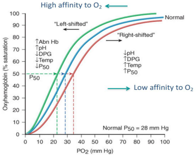
03 This decrease O_2 affinity of Hb

04 Thus increases O_2 delivery to tissues

High altitude and O_2 affinity

Important

High O2 affinity (left shift) is due to
- Alkalosis
- High levels of HbF (in thalassaemia)
- Multiple transfusion of 2,3-DPG depleted blood (2,3-DPG = 2,3-BPG) the anticoagulant found in blood transfusion bag deplete 2,3-DPG



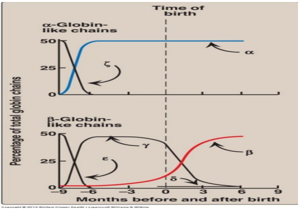
Know which factors shift the curve to the left and to the right

Extra (IMP)

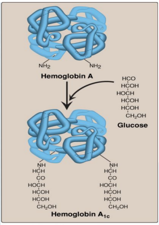
Shift to left	Shift to right
↑ pH	↓ pH
↓ DPG	↑ DPG
↓ Temperature	↑ Temperature
↓ P_{50}	↑ P_{50}
↑ Abnormal Hb	-

Other types of Hb

Fetal hemoglobin HbF	HbA_2	HbA_{1C}
Major hemoglobin found in **fetus and newborn**	Appears shortly **before birth**	High level in patients with **diabetes mellitus**
Tetramer with two **α** and two **γ** (gamma) chains	Composed of two **α** and two **δ** (delta) globin chains	Two α and two β , like in normal HbA
- Higher affinity for O_2 than HbA -Transfer O_2 from maternal to fetal circulation across placenta -Increased in individuals with thalassemia	Constitute ~ 2% of total Hb & remains constant throughout life.	- HbA undergoes **non-enzymatic** glycosylation - glycosylation **depends on plasma glucose level**



In the first curve you just need to know in the 1st trimester (the first 3 months of pregnancy) the major form of globins chains are zeta chains not the alpha chains, but in the 2nd trimester the alpha chains increase and becomes the major form. In the second curve the gamma chains start to appear in the second trimester and becomes the major form until the birth, after the birth the beta chains become the major form.



In other word the reaction will happen by Presence of HbA with glucose in blood.

Quiz

MCQs

Q1: Which of the following is NOT bound to the heme group of hemoglobin?
A- Histidine
B- Nitrogen
C- Oxygen
D- Sulfur

Q2: which of the following is irreversible?
A- carboxy Hb
B- sulf Hb
C- met Hb
D- none of them

Q3: HbA2 is composed of ?
A- two α and two δ globin chains
B- two α and two γ (gamma) chains
C- four α globin chains
D- Two α and two β globin chains

Q4: Which of the following is NOT a feature of T-form of hemoglobin?
A- movement of diner is constrained
B- low oxygen affinity
C- Abundant 2,3-BPG
D- Oxygenated form of Hb

Q5: Which of the following is NOT an allosteric effector?
A- Availability of 2,3- BPG
B- PCO
C- PO2
D- PH of environment

Q6: which of the following shift the curve to the right?
A- ↑PH
B- ↓DPG
C- ↓Temperature
D- ↑DPG

Answers:Q1-D, Q2- B, Q3- A, Q4- D, Q5- B, Q6-D

SAQ

Q: Enumerate the factors that cause Left shift of the Oxygen Dissociation Curve

A:
1- Inc. pH, Alkalosis, dec. Protons
2- Dec. Temperature
3- Dec. P_{50}
4- Dec. 2,3-BPG
5- Abnormal Hb
6- High levels of HbF

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