Hemoglobin

Dr.Abrar Al-Badr

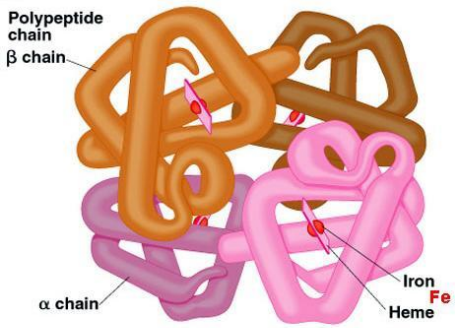
M.B.Ch.B FIBMS (Chem.Path.)

Hemoglobin

It's a hemoprotein whose primary function is to transport oxygen from the lungs to the body tissue.

Structure of hemoglobin

Hemoglobin consists of four heme molecules , covalently linked to four (two pairs) of polypeptide chains ,and may carry up to four molecules of oxygen.



Hemoglobin

Normal Hb types in adults:

The main type of Hb is **HbA1** (97%) consisting of 2 pairs of globin chains α and β (α2β2).

The other type of Hb which is also found in adult but in small amount is **HbA2** (α2δ2) (2%).

Other normal Hbs:

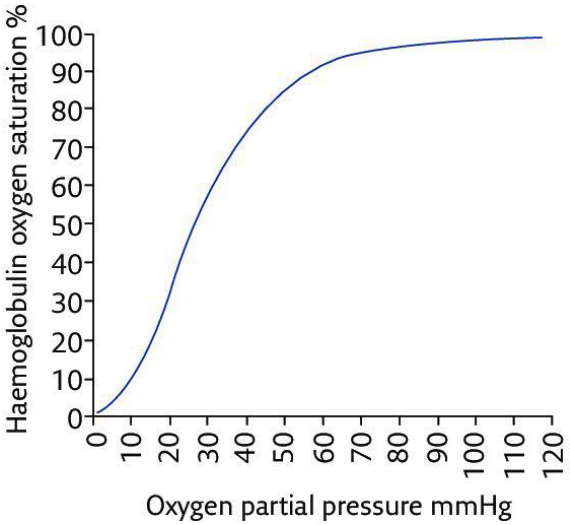
HbF: (α2γ2) This type of Hb is present primarily in embryonic life, and usually disappears from the circulation by the age of 6 months, HbF represents less than 1% of the Hb in adults.

Physiological Role

- The iron in heme is normally in the ferrous state (Fe^{2+}) and is able to act as the major oxygen-carrying entity by combining reversibly with oxygen.

- Cooperativity is the term used to describe the interaction of globin chains in such a way that oxygenation of one heme group enhances the probability of oxygenation of another or all heme groups.

- The cooperative binding process of Hb is highlighted in the **oxygen dissociation curve**
- Joining of the first oxygen molecule is slow
- Joining of the 2nd and 3rd oxygen molecules is faster
- Joining of the 4th oxygen molecule is more difficult



Biosynthesis

The biosynthesis of Hb requires the biosynthesis of both heme and the globin polypeptide chains.

Globin Synthesis

The genes coding for the α globin are found as 2 genes on chromosome 16, while the genes coding for non-α globin are found on chromosome 11, One gene for β-globin, one gene for δ-globin and 2 genes for γ-globin.

Biosynthesis of heme

Bone marrow

70-80%

Hemoglobin

Liver

15%

cytochrome P450

Biosynthesis of heme

Succinyl – CoA + glycine $\xrightarrow{\textbf{ALA synthase}}$ aminolevulinic acid

- The enzyme requires pyridoxal phosphate as a cofactor.
- This is the rate –limiting step in the synthetic pathway and is regulated by feed back inhibition by heme.

Condensation of two aminolevulinic acids yields porphobilinogen.

2 aminolevulinic acid $\xrightarrow{\textbf{Porphobilinogen synthase}}$ Porphobilinogen

- Lead inhibits PBG synthase enzyme so lead poisoning will lead to anemia

4 porphobilinogens $\xrightarrow{\textbf{Porphobilinogen deaminase}}$ Hydroxymethylebilane

Hydroxymethylbilane —(**Uroporphyrinogen** III **synthase**)→ Uroporphyrinogen III

Uroporphyrinogen III —(**Uroporphyrinogen** III **decarboxylase**)→ Coproporphyrinogen III

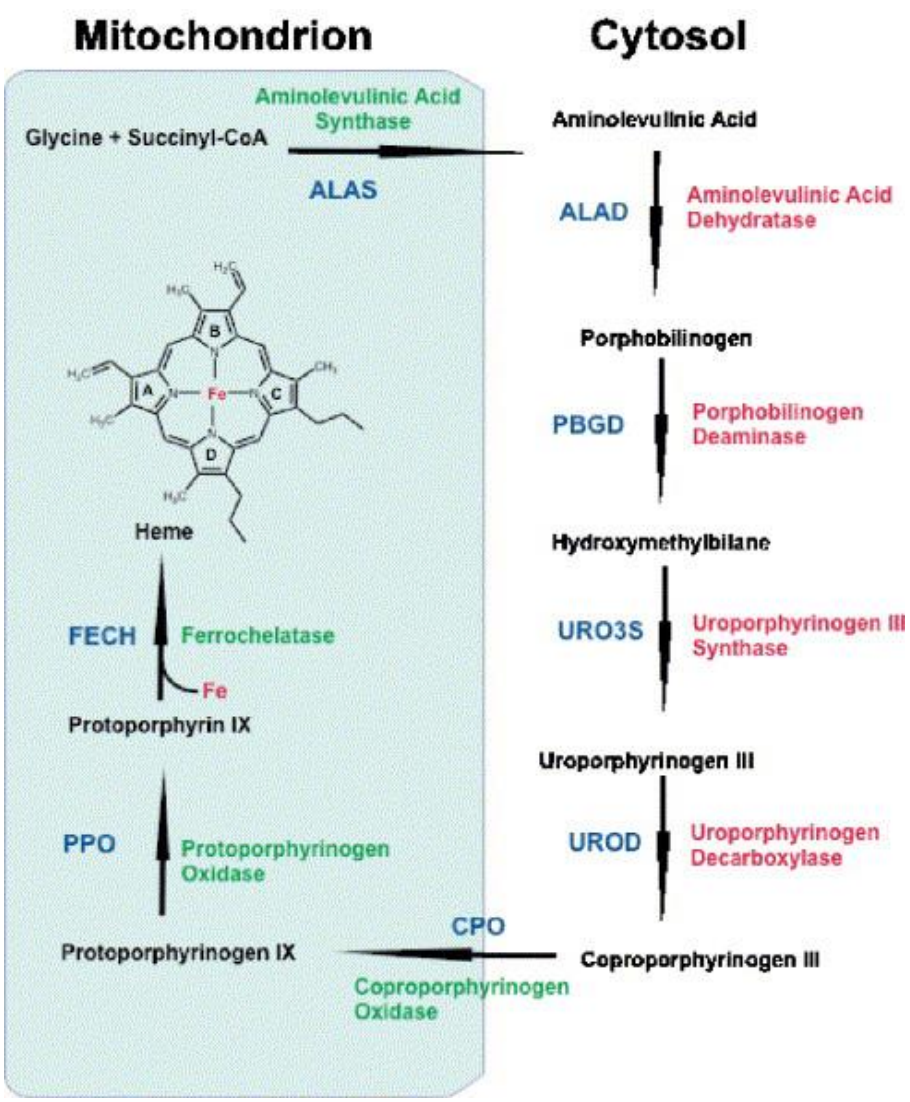
Coproporphyrinogen III —(**Coproporphyrinogen oxidase**)→ Protoporphyrinogen IX

Protoporphyrinogen IX —(**Protoporphyrinogen IX oxidase**)→ Protoporphyrin IX

Protoporphyrin IX —(**Ferrochelatase**)→ heme

Fe^{2+}

- Lead inhibits ferrochelatase enzyme and cause anemia .


Mitochondrion
Cytosol
Aminolevulinic Acid Synthase
Glycine + Succinyl-CoA
ALAS
Aminolevulinic Acid
ALAD
Aminolevulinic Acid Dehydratase
Porphobilinogen
PBGD
Porphobilinogen Deaminase
Hydroxymethylbilane
UROS
Uroporphyrinogen III Synthase
Uroporphyrinogen III
UROD
Uroporphyrinogen Decarboxylase
Heme
FECH
Ferrochelatase
Fe
Protoporphyrin IX
PPO
Protoporphyrinogen Oxidase
Protoporphyrinogen IX
CPO
Coproporphyrinogen III
Coproporphyrinogen Oxidase