Heme Metabolism

Hemoglobin & Heme:

Normal level - Males = 14-16 g/dL

Females = 13-15 g/dl

Structure: Hb is a conjugate protein

Hb = Heme (non-protein conjugate part) + globin (protein part)

Heme = Iron (Fe^{2+}) + Protoporphyrin IX

Protoporphyrin IX = 4 tetrapyrrole rings linked by methene bridges

Globin = 4 subunits.

Normal Hb: HbA_1, HbA_2, HbF

HbA_1: 2α + 2β
($141\ \bar{a}\cdot\bar{a}$) ($146\ \bar{a}\cdot\bar{a}$)

HbA_2: $2\alpha + 2\delta$

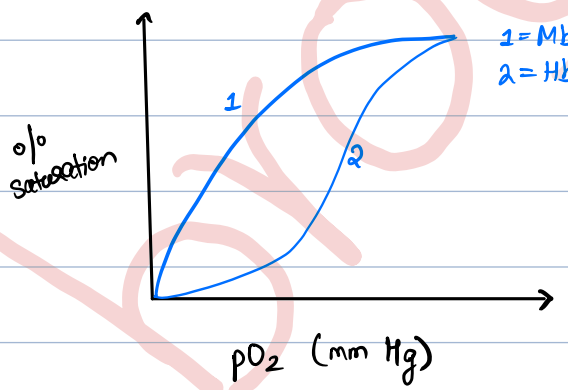
HbF: $2\alpha + 2\gamma$ (lifespan = 60-90 days)

Functions:

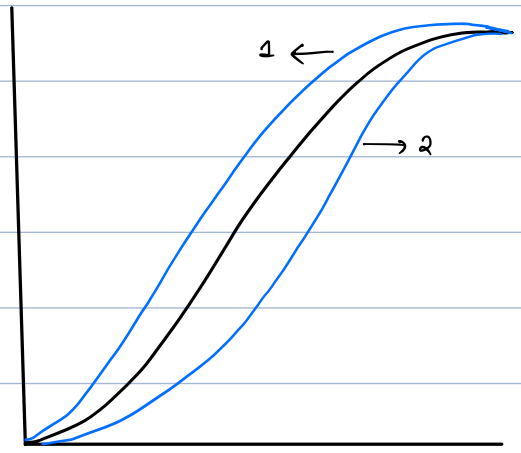
→ transport respiratory gases — O_2 & CO_2

→ buffering capacity (due to presence of histidine residues)

Binding of O_2 to Hb: Each Hb binds to 4 molecules of oxygen



Taut/Tense (T) Hb (deoxy) ⇌ Relaxed (R) Hb (oxy)



1 ⇒ high pO_2
⇒ decreased pCO_2
⇒ decreased H^+
⇒ decreased temp.
⇒ decreased 2,3-BPG
} favours O_2 loading

2 = increased pCO_2
= decreased pO_2
= increased H^+
= increased 2,3-BPG
} favours O_2 release

Hb Derivatives:

Carbaminohemoglobin → Hb + CO_2
↳ transports 2-10% of total CO_2 in blood.

Carboxyhemoglobin → Hb-CO
↳ affinity of Hb to CO is 200 times more than O_2
→ Normal CO-Hb = 0.16%
→ in smokers = 4-5%

Methemoglobin → Heme iron in Fe^{3+} form

Sulfhemoglobin → H_2S + oxy-Hb
↳ mainly seen in people taking sulfa drugs

Abnormal Hb:

Abnormal Hb due to altered primary structure:

Sickle Cell Hb (HbS): → glutamic acid at 6th position of β chain is replaced by valine

↳ formation of sticky patch on surface of β chain of oxy HbS & deoxy HbS

→ deoxy HbS has the receptor site complimentary to stick patch.

∴ HbS undergoes polymerization to form sickle shaped RBCs

→ sickle cell RBCs are fragile & cause hemolysis (sickle cell anemia)

HbC: → glutamic acid at 6th position of β chain is replaced by lysine

HbM: → α 58 histidine is replaced by tyrosine (HbM Boston) or β 92 histidine is replaced by tyrosine (HbM Hydepark)

→ HbM leads to formation of methemoglobin.

HbD: → glutamic acid at 121st position of β chain is replaced by glutamine.

Abnormal Hb due to altered subunit makeup: – Thalassemia

→ absence of one or more α or β chains of Hb (due to defect in production of globin chain)

→ α globin gene = chromosome 16 ; β globin gene = chromosome 11. [4 copies ⇒ 2 in each chromosome]
[4 copies of α]
[2 copies of β]

→ all thalassemias are characterized by hypochromic microcytic anemia.

α Thalassemia:

- Silent Carrier ⇒ Absence of one α globin gene
- Trait ⇒ Absence of two α globin genes ⇒ Minor anemia
- Minor (HbH) ⇒ Absence " 3 " " " ⇒ mild anemia
- Major (Hb Barts, Hydrops fetalis) ⇒ absence of all 4 α globin genes ⇒ fetus usually survives only until birth.

β-Thalassemia:

- Minor ⇒ absence of one β globin gene
- Major ⇒ absence of both globin genes

Chipmunk facies ⇒ thalassemia can result in maxillary enlargement leading to an appearance called chipmunk face

⇒ Hair on end (Crew Cut) appearance in skull X-ray due to new bone formation is a common feature.

Heme Synthesis:

Tissue Site: liver & reticuloendothelial cells

Intracellular site: Steps 1, 6, 7, 8 ⟶ mitochondria
Steps 2, 3, 4, 5 ⟶ cytosol

Succinyl coA + Glycine
↓ ALA synthase
δ-ALA
↓ ALA dehydratase
Porphobilinogen
↓ Uroporphyrinogen I synthase
Hydroxymethylbilane
↓ Uroporphyrinogen III synthase
Uroporphyrinogen III
↓ Uroporphyrinogen carboxylase
Coproporphyrinogen III
↓ Coproporphyrinogen oxidase
Protoporphyrinogen III
↓ Protoporphyrinogen oxidase
Protoporphyrin III
Fe^{2+} → Ferrochelatase (Heme synthase)
Heme

Block

Uroporphyrinogen I synthase	→ Acute Intermittent Porphyria (AIP)
Uroporphyrinogen III Synthase	→ Congenital erythropoietic Porphyria (CEP)
Uroporphyrinogen carboxylase	→ Porphyria cutanea tarda (PCT)
Coproporphyrinogen oxidase	→ Hereditary coproporphyria (HC)
Protoporphyrinogen oxidase	→ Variegate porphyria (VP)
Ferrochelatase (Heme synthase)	→ Protoporphyria (PP)

Regulation:

Feed back Inhibition: when heme concentration is high, it blocks its own synthesis by allosterically inhibiting ALA synthase

Feedback Repression: when heme level is high → heme (co-repressor) binds with aporepressor to form holorepressor which binds to DNA of ALA synthase & prevents its transcription (ALA production decreased).

Type	Findings	Manifestations
AIP	Increased PBG & ALA in blood & urine (Urine darkens on exposure to air & light due to conversion of porphobilinogen to porphobilin)	• Abdominal pain, vomiting, constipation • Neuropsychiatric symptoms (seizures, insomnia, confusion, agitation) — no photosensitivity
CEP	Urinary uroporphyrin I & coproporphyrin I. (Presence of porphyrins in urine turns urine to port wine colour)	• Photosensitivity (due to presence of porphyrins)
PCT	Urinary uroporphyrin I & uroporphyrin III	• cutaneous photosensitivity • Blisters on skin that's exposed to sunlight (Vampire's disease)
HC	•Urinary ALA, PBG, coproporphyrin III • fecal coproporphyrin III	• Photosensitivity • neuropsychiatric symptoms • Abdominal pain, vomiting, constipation
VP	•Urinary ALA, PBG, coproporphyrin III • fecal protoporphyrin IX	• Photosensitivity • neuropsychiatric symptoms • Abdominal pain, vomiting, constipation
PP	• Increased fecal & RBC protoporphyrin IX (not found in urine)	• Photosensensitivity • Blisters on exposure to sunlight

Management (Possible Treatment) of Porphyria:

- Infusion of glucose & hematin

Acquired (Toxic) Porphyria: results from exposure to toxic compounds such as hexachlorobenzene, lead, griseofulvin

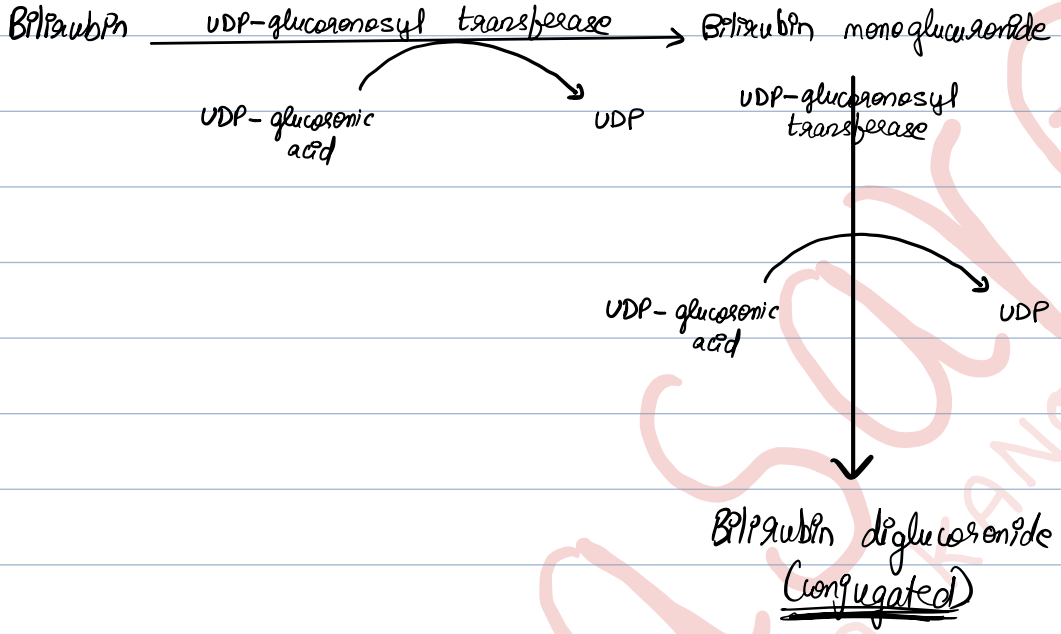
→ they inhibit several enzymes of heme synthesis.

Heme Catabolism: In reticuloendothelial tissues of liver, bone marrow, spleen

Heme $\xrightarrow[\text{microsomal heme oxygenase}]{Fe^{+2}}$ Biliverdin $\xrightarrow[(NADPH)]{\text{Biliverdin reductase}}$ Bilirubin

→ Bilirubin is not soluble in plasma ∴ transported after binding with albumin forming unconjugated bilirubin (bound form)

Fate of Bilirubin:



Conjugated bilirubin $\xrightarrow[\text{bacterial enzymes}]{\text{(in intestine)}}$ urobilinogen $\xrightarrow{\text{oxidation}}$ urobilins ⟶ excreted in feces

urobilinogen ⟶ small amount is excreted in urine (4mg/day)

Serum Levels:

- Total bilirubin = 0.2 to 1 mg/dL
- unconjugated bilirubin = 0.2 to 0.8 mg/dL
- conjugated bilirubin = 0 to 0.2 mg/dL

Hyperbilirubinemia ⇒ > 1 mg/dL (total bilirubine)

Beyond 2-2.5 ⇒ Jaundice / Icterus

Tests:

- Serum bilirubin — van den Bergh reaction
- Urinary UBG — Ehrlich's test
- Urinary Bilirubin — Fouchet's test
- Urinary Bile salts — Hay's test
- Urinary Ketone bodies — Rothera's test

Types of Jaundice:

(i) Prehepatic (generally hemolytic)

(ii) Hepatic (Liver dysfunction)

(iii) Posthepatic (generally obstructive — obstruction of bile duct due to cholelithiasis or tumour)

(iv) Neonatal Physiological Jaundice: temporary condition seen in newborns

→ due to increased hemolysis caused due to immature hepatic system for uptake & conjugation of bilirubin & low activity of UDP-glucuronyl transferase.

Kernicterus: > 20 mg/dL ⇒ bilirubin (most of it is unconjugated) crosses the blood brain barrier ⇒ mental retardation.

Treatment: • phototherapy ⇒ exposure of neonates to blue light that converts unconjugated bilirubin to easily excretable forms

• phenobarbital (induces bilirubin metabolizing system in liver)

Diagnosis of Jaundice:

- Prehepatic — serum unconjugated bilirubin ↑ ; urine UBG ↑
- Hepatic — serum conjugated & unconjugated bilirubin ↑; bilirubin & bile salt in urine ↑
- Posthepatic — serum conjugated bilirubin ↑ ; bilirubin & bile salt in urine ↑

Congenital Hyperbilirubinemia :

Gilbert disease: autosomal dominant

↳ defect in uptake of bilirubin or in conjugation

→ Bilirubin up to 3 mg/dL ⇒ mild jaundice

Crigler - Najjar Syndrome: due to conjugation defects

- Type 1 ⇒ deficiency of UDP glucuronyl transferase
  ⇒ bilirubin > 20 mg/dL ; children die before 2 years of age
- Type 2: partial deficiency of UDP glucuronyl transferase ; milder form

Dubin - Johnson Syndrome: autosomal recessive trait

↳ defective secretion of bilirubin into bile & increased conjugated bilirubin in blood

→ conjugated bilirubin gets deposited in liver ⇒ black liver jaundice (blackish discolouration of liver).