v. Heme synthesis and disorders

Overview of Heme Structure and Functions

1. **Molecular Architecture of Heme**
   - **Heme** consists of a **protoporphyrin IX** macrocycle (four pyrrole rings) coordinated to a central **ferrous iron (Fe^{2+})**.
   - The conjugated ring system gives the heme its characteristic deep red color and ability to reversibly bind gases (O_2, CO, NO).
2. **Biological Roles**
   - **Hemoglobin and Myoglobin**: Essential for oxygen transport and storage.
   - **Cytochromes (e.g., cytochrome c, P450 enzymes)**: Electron transport, oxidative metabolism, and detoxification.
   - **Catalase and Peroxidases**: Heme-based enzymes that decompose hydrogen peroxide, essential for cellular antioxidant defense.

Heme Synthesis: Steps and Regulation

Sites of Synthesis

- **Bone Marrow (Erythroid Cells)**: ~85% of total daily heme production for hemoglobin.
- **Liver**: ~10–15% for cytochrome P450 enzymes and other heme proteins.
- **Cellular Localization**: Some steps in the **mitochondrion**, others in the **cytosol**; the final step completes in mitochondria.

Key Steps in the Heme Biosynthetic Pathway

1. **Formation of δ-Aminolevulinic Acid (δ-ALA)**
   - **Rate-Limiting Step**: **ALA synthase (ALAS)** catalyzes the condensation of **glycine** and **succinyl-CoA** to form δ-ALA.
   - Occurs in the **mitochondrial matrix**.
   - Two isoforms: **ALAS1** (housekeeping, mainly in liver) and **ALAS2** (erythroid-specific).
2. **Cytosolic Steps**
   - **ALA dehydratase** (also called porphobilinogen synthase) condenses two δ-ALA to form **porphobilinogen (PBG)**.
   - **Porphobilinogen deaminase** links four PBG units → linear **hydroxymethylbilane**.
   - **Uroporphyrinogen III synthase** folds and cyclizes the linear tetrapyrrole → **uroporphyrinogen III**.
   - **Uroporphyrinogen decarboxylase** sequentially removes carboxyl groups, converting uroporphyrinogen → **coproporphyrinogen III**.
3. **Return to Mitochondria**
   - **Coproporphyrinogen oxidase** transforms coproporphyrinogen III → **protoporphyrinogen IX**.
   - **Protoporphyrinogen oxidase** oxidizes it to **protoporphyrin IX**.
   - **Ferrochelatase** inserts **Fe^{2+}** into protoporphyrin IX → **heme** (final step).

Regulation of Heme Synthesis

1. **Rate-Limiting Enzyme**: **ALA synthase** activity is tightly regulated by **heme** feedback (represses ALAS1 gene transcription in hepatocytes, modulates enzyme stability, etc.).
2. **Erythroid-Specific Control**: **ALAS2** regulated by iron availability (via iron-responsive elements) and erythroid differentiation signals (e.g., erythropoietin).
3. **Drug and Hormonal Influences**: Certain drugs (barbiturates, some steroids) induce cytochrome P450 → increased hepatic ALAS1 expression. This can precipitate porphyric attacks in susceptible individuals.

Disorders of Heme Synthesis: Porphyrias and Related Conditions

Porphyrias: An Overview

- **Definition**: Rare, mostly inherited disorders caused by defects in enzymes of the heme biosynthetic pathway.
- **Accumulation of Precursors**: Specific enzyme blocks lead to buildup of distinct intermediates, with associated clinical manifestations (neurovisceral or photosensitivity).

Major Porphyrias

1. **Acute Intermittent Porphyria (AIP)**
   - **Enzyme**: Deficiency in **porphobilinogen deaminase** (also called hydroxymethylbilane synthase).
   - **Accumulates**: ALA and PBG (δ-ALA, porphobilinogen).
   - **Clinical**: Neurovisceral attacks (abdominal pain, neuropathy, psychiatric symptoms), typically no cutaneous manifestations.
   - **Precipitated** by drugs inducing cytochrome P450, fasting, stress.
2. **Porphyria Cutanea Tarda (PCT)**
   - **Enzyme**: Deficiency in **uroporphyrinogen decarboxylase**.
   - **Accumulates**: Uroporphyrinogen (leading to photosensitive porphyrins in the skin).
   - **Clinical**: Photosensitivity, blistering on sun-exposed areas, hyperpigmentation, hypertrichosis.
   - Often **acquired**: Associated with liver disease (alcohol, hepatitis C), hemochromatosis.
3. **Hereditary Coproporphyria (HCP)** and **Variegate Porphyria (VP)**
   - Defects in **coproporphyrinogen oxidase** (HCP) or **protoporphyrinogen oxidase** (VP).
   - Mixed features (neurovisceral attacks + cutaneous photosensitivity) due to accumulation of porphyrin precursors.
4. **Erythropoietic Protoporphyria (EPP)**
   - **Enzyme**: Ferrochelatase deficiency or reduced activity.
   - **Accumulates**: Protoporphyrin IX in erythrocytes, causing photosensitivity (painful but minimal blistering).

Lead Poisoning (Plumbism)

- **Mechanism**: Lead inhibits **ALA dehydratase** and **ferrochelatase**, causing buildup of δ-ALA and protoporphyrin.
- **Clinical**: Anemia (due to impaired heme synthesis), basophilic stippling of RBCs, neurologic and GI symptoms in chronic exposure.
- **Diagnosis**: Elevated blood lead levels, increased zinc protoporphyrin.

Additional Heme-Related Issues

- **Sideroblastic Anemias**: Impaired incorporation of iron into protoporphyrin (e.g., genetic or acquired ALAS dysfunction) leading to ring sideroblasts in the marrow.
- **Drug-Induced Porphyrias**: Inducers of CYP450 can exacerbate or unmask acute porphyrias in susceptible individuals.

Metabolism and Fate of Heme

1. **Heme Degradation**
   - **Heme Oxygenase** cleaves heme ring to **biliverdin**, releasing CO and Fe^{2+}.
   - **Biliverdin reductase** reduces biliverdin to **bilirubin** (unconjugated, water-insoluble).
   - In the liver, bilirubin is **conjugated** with glucuronic acid (UDP-glucuronyl transferase) → excreted in bile.
2. **Clinical Correlates**
   - **Hyperbilirubinemia**: e.g., jaundice from hemolysis, reduced conjugation (Gilbert's syndrome, Crigler–Najjar), or biliary obstruction.

Concluding Remarks

Heme synthesis integrates multiple **mitochondrial** and **cytosolic** enzymes, ensuring a steady supply of heme for

oxygen transport (hemoglobin/myoglobin), **electron transfer** (cytochromes), and **redox reactions** (catalases, peroxidases). Dysregulation or enzymatic blockages—genetic (porphyrias) or acquired (lead poisoning)—lead to **toxic precursor accumulations** with distinctive clinical pictures (acute neurovisceral attacks, photosensitivity, liver dysfunction).

From a clinical standpoint, recognizing **porphyrias** and **lead poisoning** is critical, given their often protean presentations and potential triggers (certain medications, fasting, alcohol). Advances in **molecular diagnostics** have refined classification and management strategies (e.g., hemin infusions, phlebotomy in PCT, iron chelation), highlighting the interplay between basic biochemistry and translational medicine in addressing heme-related disorders.