

HEME METABOLISM (DR. OFFNER)

I. HEME BIOSYNTHESIS

A. Definitions

- i. Pyrrole
- ii. Tetrapyrrole: cyclical (heme); linear (bilirubin)
- iii. Porphyrinogen = reduced form of tetrapyrrole (colorless) – abbreviated “o’gen”
- iv. Porphyrin = oxidized form (color)

B. Outline of pathway

- i. Process by which glycine → heme = 8 steps:



*Uro’gen’s 4 isomers:

- 1) AP AP AP AP
- 2) AP PA AP PA
- 3) AP AP AP PA
- 4) AP AP PA PA

Only uro’gen III is biologically active.

C. Location

- i. Heme is synthesized in the bone marrow for immature red blood cells, and in the liver for cytochrome and other proteins
- ii. Location within cell:
 1. Steps 1, 6, 7, 8 occur in mitochondria
 2. Steps 2, 3, 4, 5 occur in cytoplasm

D. Regulation

- i. 4 separate checks and balances to ensure that no excess heme is being produced:
 1. Heme is a direct inhibitor of ALA synthase – no protein being made in cytoplasm → heme stays in mitochondrion and inhibits ALA synthase
 2. Heme can enter nucleus, bind to repressor protein, and stop transcription of ALA synthase
 3. Heme can prevent translation of ALA synthase in RNA
 4. Heme can prevent entry of ALA synthase into mitochondria

II. HEME CATABOLISM

Charles Gray – 1947 – discovered that pigments in blood are converted to bile pigment and excreted in stools. Actual mechanism not discovered until 30 years later.

A. Heme → bilirubin

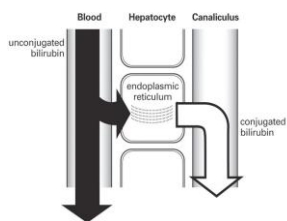
- i. Heme degradation (in mononuclear phagocytic system – spleen/ Kupffer cells):
 1. **Heme oxygenase** - cleaves alpha bridge, releases carbon – requires NADPH, O₂

HEME METABOLISM (DR. OFFNER)

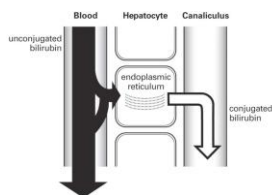
2. Molecule becomes linear → **biliverdin IX alpha** (green-blue)
3. **Bilirubin reductase** – reduces biliverdin IX alpha → **bilirubin IX alpha** (yel-orange)
 - ii. Bile pigment transport (through plasma)
 1. Bilirubin is completely insoluble – can't be directly put into bile
 2. BR complexed with **carrier albumin** – carries BR in blood to a hepatocyte
 3. Albumin is then recycled – can go pick up more bilirubin
- B. Conjugation (in hepatocyte):
 1. BR + 2 glucuronic acid (UDP) → **bilirubin diglucuronide (BRDG)**
 2. Enzyme = **bilirubin glucuronyl transferase (BRGT)**
 3. BRDG is now soluble → secreted into bile (via canaliculus)
- C. Excretion:
 - i. Bile enters small intestine, then large intestine:
 1. Bacterial enzyme **β-glucuronidase** → BRDG becomes bilirubin again
 2. Other enzymes: Bilirubin → **urobilinogen** → **stercobilin**
 - ii. Stercobilin excreted in feces
 - iii. Some urobilinogen reabsorbed → transported to kidney → **urobilin** – excreted in urine
- D. Some conjugated and some unconjugated BR leaks back into blood (trace amounts)

III. ABNORMALITIES IN HEME METABOLISM

A. Hyperbilirubinemias



- i. Increased bilirubin production
 1. Hemolysis caused by malaria, wrong blood transfusion → massive lysis of RBC's → greater amount of unconjugated bilirubin → hepatocyte unable to absorb and conjugate all of it
 2. Results in higher levels of both unconjugated and conjugated BR in blood (also more urobilinogen in urine)



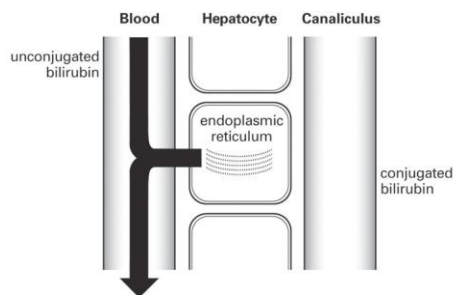
- i. Decreased bilirubin uptake
 1. Impairment of unconj BR's ability to enter hepatocyte → more unconj. BR in blood (still some conjugated but not more)

- i. Impaired conjugation
 1. More unconj BR in blood; less to no conj BR (fatal if none)
 2. Due to gene mutations:
 - a. Gilbert's Syndrome

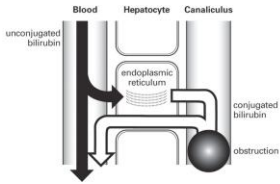
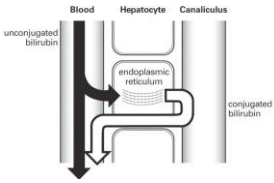
- i. Common: ~10% pop
- ii. Mutation in promoter region of BRGT gene
- iii. asymptomatic, or higher levels of unconj BR in blood

b. Crigler-Najjar Syndrome

- i. Rare
- ii. Mutations in coding region → nonfunc protein



HEME METABOLISM (DR. OFFNER)



- iii. Type I – homozyg → complete lack of protein → fatal or if found in utero can get liver transplant
- iv. Type II – hetero – reduced levels of protein

iv. Defective Secretion (Dubin-Johnson's syndrome)

- 1. Transporter is somehow defective → conj BR “regurgitated” into blood

v. Biliary Obstruction

- 1. BR enters hepatocyte, conjugated, but can't enter bile → reenters blood
- 2. Also some BR would enter urine → dark-colored urine

B. Neonatal Jaundice

- i. ~60% of infants have some degree of jaundice
- ii. Maternal circulation clears BR before birth → infant does not start expressing BRGT until 5-14 days after birth
- iii. Unconj BR can accumulate, cross into brain (blood-brain barrier not yet est)
- iv. Buildup = kernicterus = neurotoxic
- v. Treatment: fluorescent light absorbed by BR → broken down into nontoxic products that can be excreted without conjugation

C. Porphyrrias Diseases

i. Overview

- 1. 1-10 in 10000 affected – can be rare or common, depending on area
- 2. Defects are in 1 allele of heme biosynthetic enzyme (3-8) → inactivation → 50% activity (homozygous is very rare)

1 2 3 4 5 6 7 8
succinyl CoA → ALA → PBG → bilane → uro'gen III → copro'gen III → proto'gen IX → protoporphyrin IX → heme

ii. Types of porphyrias

Step	Disease	Enzyme	Inheritance (Autosomal)	Hepatic/ Erythropoetic
3	Acute intermittent porphyria (AIP)	PBG deaminase	Dominant	Hepatic
4	Congenital Erythropoetic Porphyria (CEP)	Urogen III Cosynthase	Recessive	Eryth.
5	Porphyria Cutanea Tarda (PCT)	Uro'gen III decarboxylase	Dominant	Hepatic
6	Hepatic Coproporphyrin (HCP)	Copro'gen III decarboxylase	Dominant	Hepatic
7	Variegate porphyria (VP)	Proto'gen IX dehydrogenase	Dominant	Hepatic
8	Erythropoetic protoporphyrin (EP)	Ferrochelatase	Dominant	Eryth.

iii. Example: variegate porphyria

- 1. Defect in proto'gen IX dehydrogenase → 50% activity → less protoporphyrin IX but still sufficient heme to shut off pathway
- 2. During an attack, not enough heme:
 - a. Heme being used in liver to make cytochromes
 - b. No longer heme to shut off ALA synthase

HEME METABOLISM (DR. OFFNER)

- c. All products prior to step 7 build up:
 - i. ALA and PBG are directly neurotoxic; 'ogens → porphyrins → can generate free radicals, oxidative damage
 - ii. Abdominal pain
 - iii. Neuropsychiatric symptoms
 - iv. Red urine as these elements are secreted
 1. ALA – copro III water soluble → excreted in urine
 2. Copro – protoIX lipid sol → excreted in feces
3. Treatment: give slightly modified heme → can shut off ALA synthesis without degrading as easily → intermediates are excreted