Porphyrias

Introduction

- The porphyrias are caused by deficiencies of enzymes[8] involved in heme biosynthesis which lead to blockade of the porphyrin pathway and subsequent accumulation of porphyrins and their precursors.
- Either genetic (autosomal dominant, autosomal recessive and X-linked) or acquired. → by Pb^{+} in ALA dehydratase & ferrochelatase
- Heterozygotes are asymptomatic in between acute attacks.
- Classified depending on site of overproduction and accumulation of porphyrin, overlapping features common

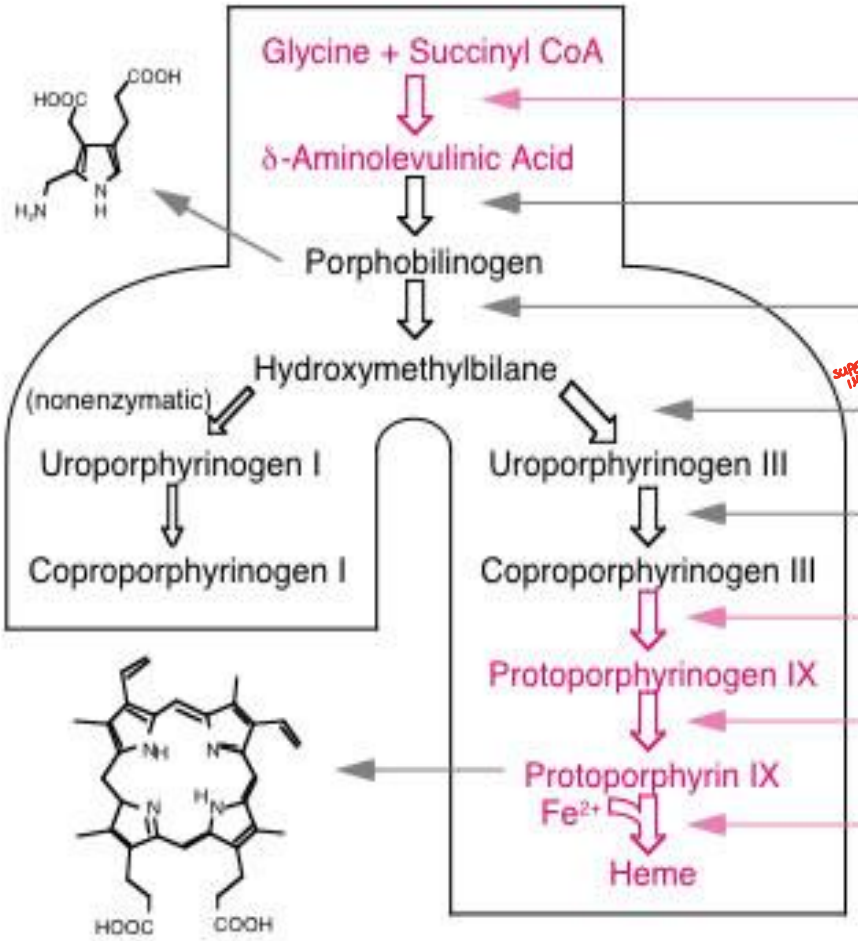
Hepatic — in liver

- Neurologic, mental disturbances → anxiety, Depression, Hallucinations
  - Neurovisceral manifestations
- Abdominal pain — Can't be treated by any NSAID, morphine is useful
- Extremity pain, paresthesias
- Motor neuropathy

Erythropoietic — in Bone marrow

- Cutaneous photosensitivity (long wave UV)
- light excites porphyrins in skins causing:
  1- Cell damage
  2- Hemolytic anemia

Heme Synthesis Pathway



Erythropoietec (BM):

- Uroporphyrinogen cosynthase coenzyme ⟶ Congenital erythropoietic porphyria
- Ferrochelatase enzyme ⟶ Erythropoietic protoporphyria

Classification of the Porphyrias

- Multiple ways to categorize porphyrias:
  - Hepatic (5) vs. Erythropoietic (2): organ in which accumulation of porphyrins and their precursors appears
  - Cutaneous vs. Non- cutaneous
  - Acute (4) and chronic (4) forms
- Acute:
  - ALA dehydratase deficiency porphyria (ALAD) → ALA - dehydratase
  - Acute intermittent porphyria (AIP) → Porphobilinogen deaminase
  - Hereditary coproporphyria (HCP) → Coproporphyrinogen oxidase
  - Variegate porphyria (VP) → Protoporphyrinogen oxidase
- Chronic:
  - Porphyria cutanea tarda (PCT) → Uroporphyrinogen decarboxylase
  - Erythropoietic protoporphyria (EPP) → Ferrochelatase
  - Congenital erythropoietic porphyria (CEP) → Uroporphyrinogen III cosynthase
  - Hepatoerythropoietic porphyria (HEP) Deficiency of both liver & bone marrow enzymes (SUPER IMPORTANT) → mixed

Porphyria categories

A- Bone Marrow

- *Erythropoietic protoporphyria → Ferrochelatase
- Congenital *erythropoietic porphyria → Uroporphyrinogen III cosynthase

B- Liver

- Porphyria cutanea tarda → Uroporphyrinogen decarboxylase
- Acute intermittent porphyria → Porphobilinogen deaminase
- Variegate porphyria → Protoporphyrinogen oxidase
- Hereditary coproporphyria → Coproporphyrinogen oxidase
- Hepatoerythropoietic porphyria * Mixed

Overview of the four acute porphyrias

- Four acute porphyrias cause acute, self-limiting attacks that lead to chronic and progressive deficits
- Symptoms of acute attacks increase the potential for misdiagnosis.
- Acute porphyrias are clinically indistinguishable during acute attacks, except the neurocutaneous porphyrias (1 variegate porphyria and 2 hereditary coproporphyria) can cause dermatologic changes But you cant make a differential diagnosis
- Acute attacks lead to an increase in PBG and ALA which can be detected in urine
  ↳porphobilinogen
- Diagnosis is difficult because of variable clinic course, lack of understanding about diagnostic process, and lack of a universal standard for test result interpretation

Genetic testing will give us accurate diagnosis

- Cutaneous features are not seen in acute intermittent porphyria or the very rare ALA dehydratase deficient porphyria.

- Erythropoietic protoporphyria and congenital erythropoietic porphyria are characterized by porphyrins produced mainly in the bone marrow.
- The reminder are primarily hepatic porhyrias.

- Excessive concentrations of porphyrins exposed to day-light generate free radicals, leading to cell membrane damage and cell death.

- The type of cellular damage depends on the solubility and tissue distribution of the porphyrins.

- Two main patterns of skin damage are seen in the porphyrias:
    1- accumulation of water soluble uro - and coproporphyrins leads to blistering.
    2- accumulation of the lipophilic protoporphyrins leads to burning sensations in the exposed skin.

Category	Type	Clinical presentation	Inheritance
Hepatic 5	ALA dehydratase deficiency → no cutaneous manifestations ⁺ Porphobilinogens ⁺	Acute attacks	Autosomal recessive
	Acute intermittent porphyria	Acute attacks	Autosomal dominant
	Porphyria cutanea tarda Uroporphyrinogen decarboxylase	Skin disease chronic	Usually acquired; a minority are inherited (autosomal dominant)
	Hereditary coproporphyria → water soluble ⇝ blistering	Skin disease, acute attacks	Autosomal dominant
	Variegate porphyria ↳ lipophilic ⇝ burning sensation	Skin disease, acute attacks	Autosomal dominant
Erythropoietic 2	Congenital erythropoietic porphyria uro ⇝ blistering	Skin disease chronic	Autosomal recessive
	Erythropoietic protoporphyria	Skin disease: specific presentation with immediate photosensitivity Chronic	Autosomal dominant: severe forms have complex inheritance

Remember :-

* Acute form : 1- ALA - Dehydratase deficiency ⟶ ALA - dehydratase (porphobilinogen synthase)
2- Acute intermittent porphyria ⟶ Porphobilinogen deaminase
3- Hereditary coproporphyria ⟶ Coproporphyrinogen oxidase
4- Variegate porphyria ⟶ Protoporphyrinogen oxidase

* Chronic form: 1- Congenital erythropoietic porphyria ⟶ Uroporphyrinogen III cosynthase
2- Erythropoietic porphyria ⟶ Ferrochelatase
3- Porphyria cutanea tarda ⟶ Uroporphyrinogen decarboxylase
4- Hepatoerythropoietic porphyria

* Erythropoietic : 1- Congenital erythropoietic porphyria ⟶ Uroporphyrinogen III cosynthase
2- Erythropoietic porphyria ⟶ Ferrochelatase

* Liver : 1- Acute intermittent porphyria ⟶ Porphobilinogen deaminase
2- Porphyria cutanea tarda ⟶ Uroporphyrinogen decarboxylase
3- Hereditary coproporphyria ⟶ Coproporphyrinogen oxidase
4- Variegate porphyria ⟶ Protoporphyrinogen oxidase
5- Hepatoerythropoietic porphyria

Diagnosis

- Overlapping, may be difficult to determine exactly
- Check plasma, urine, stool porphyrin excretion

Porphyria	**Symptoms**	**Diagnostic findings** **U= Urine, F=Feces, E=Erythrocytes**
ALA dehydratase deficiency	Neurovisceral	↑ ALA (U)
Acute intermittent porphyria	Neurovisceral	↑ ALA and PBG (U)
Congenital erythropoietic porphyria	Photocutaneous	↑ uroporphyrin I and coproporphyrin I (U & E)
Porphyria cutanea tarda blistering	Photocutaneous	↑ 7- carboxylate porphyrin (U) and isocoproporphyrin (F)
Hereditary coproporphyria blistering	Photocutaneous and neurovisceral	↑ ALA, PBG and coproporphyrin (U) and coproporphyrin (F)
Variegate porphyria burning sensation	Photocutaneous and neurovisceral	↑ ALA, PBG (U) and protoporphyrin (F)
Erythropoietic protoporphyria	Photocutaneous	↑ protoporphyrin (F & E) and in plasma

Acute intermittent porphyria → Porphobilinogen deaminase

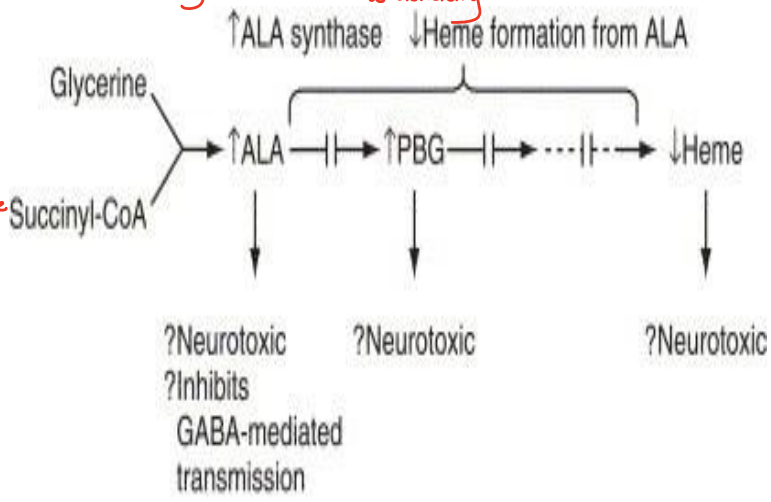
* porphobilinogen → no cutaneous symptoms

- Prevalence of 5-10 per 100,000 and thought to be higher in psychiatric populations
- More frequent in women than men.
- Heterozygotes are asymptomatic between acute attacks.
- Risk factors for exacerbation include medications, diet, weight loss, surgery, infection, menstrual hormones, smoking
- Common symptoms include: neurovisceral symptoms
  - Abdominal pain.
  - Tachycardia, arrhythmia.
  - Orthostatic hypotension.
  - Psychiatric symptoms including anxiety, depression, hallucinations and paranoia
  - Peripheral neuropathy

Diagnosis: Caused by a deficiency of* PBG deaminase resulting in an accumulation of PBG and ALA

Treatment:

- Discontinue all unnecessary or potentially harmful drugs as Sulfa drugs, barbiturates, ACEI, Antiepileptics and Antifungals * Sometimes you have to stop these medications due to the interaction between the intermediate resulting from PBG deaminase deficiency
- Treat any infection.
- Pain control with Morphine NSAIDs are not useful
- Treat sympathetic hyperactivity with propranolol.
- 300-400 grams of carbohydrates per day. IMPORTANT! to inhibit ALA synthase
- IV heme at 3-5 mg/kg/day.



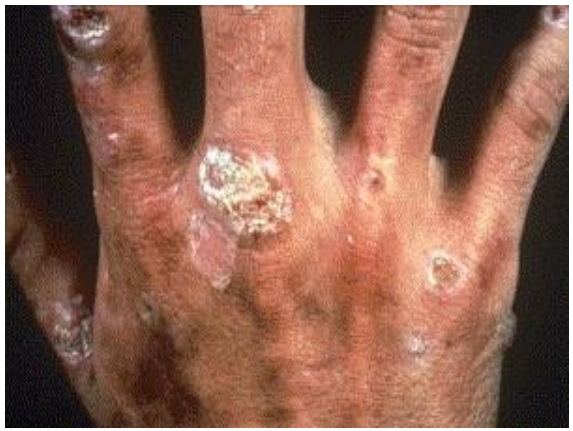
* photocutaneous manifestations
* Chronic

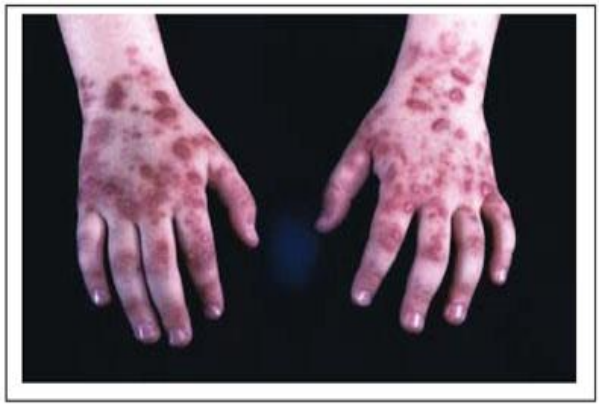
Porphyria cutanea tarda → Uroporphyrinogen decarboxylase

- Most common porphyria which causes skin manifestations
- Deficiency of hepatic urodecarboxylase → uro + copro → blistering
- Cutaneous photosensitivity → fluid filled vesicles on sun exposed areas, friable skin, wounds heal slowly and hyperpigmentation on face
- No neurologic manifestations
- Higher incidence of hepatocellular carcinoma * in liver
- Precipitants frequently include alcohol, estrogen and iron
  ↳ more frequent among females

Treatment:

- Avoid sunlight, use sunscreen
- Chloroquine or hydroxychloroquine to form complexes with porphyrins to enhance excretion → inhibition of ALA synthase
- Superactivated charcoal
- β- carotene may increase tolerance of sunlight through Vitamin A. Strengthen the skin





Erythropoietic protoporphyria

* Ferrochelatase
* chronic

- It is the most common childhood porphyria.
- It is usually evident by 2 years of age.
- Protoporphyrin levels are elevated because of deficient activity of *ferrochelatase enzyme.

Congenital erythropoietic porphyria (Gunther's disease)

* Uroporphyrinogen III casynthase
* chronic

- It is a very rare autosomal recessive disorder.
- Patients usually present during infancy and rarely present in adult life with milder forms.
- It is caused by elevation of both water-soluble and lipid-soluble porphyrin levels due to deficiency of uroporphyrinogen III ~~synthase enzyme~~. casynthase coenzyme

Clinical features

+ labratory test to support the genetic examinations

uro : → hydrophilic

- Very severe photosensitivity with phototoxic burning and blistering leading to burning sensation in the light exposed parts.
- Hypersplenism. - Hemolytic anemia. - Thrombocytopenia

Treatment

- Superactivated charcoal
- Splenectomy
- Hypertransfusion
- Bone marrow transplantation

Pseudoporphyria

- In certain settings patient develop blistering and skin fragility identical to PCT with the histological features but with normal urine and serum porphyrins. some manifestations
- This condition called → pseudoporphyria.
- Most commonly* due to medications especially NSAIDs and tetracycline.
- Some patients on hemodyalisis develop a similar PCT-like picture. ↗ porphyria cutanea tarda

Neurotoxicity mechanisms Pb^+

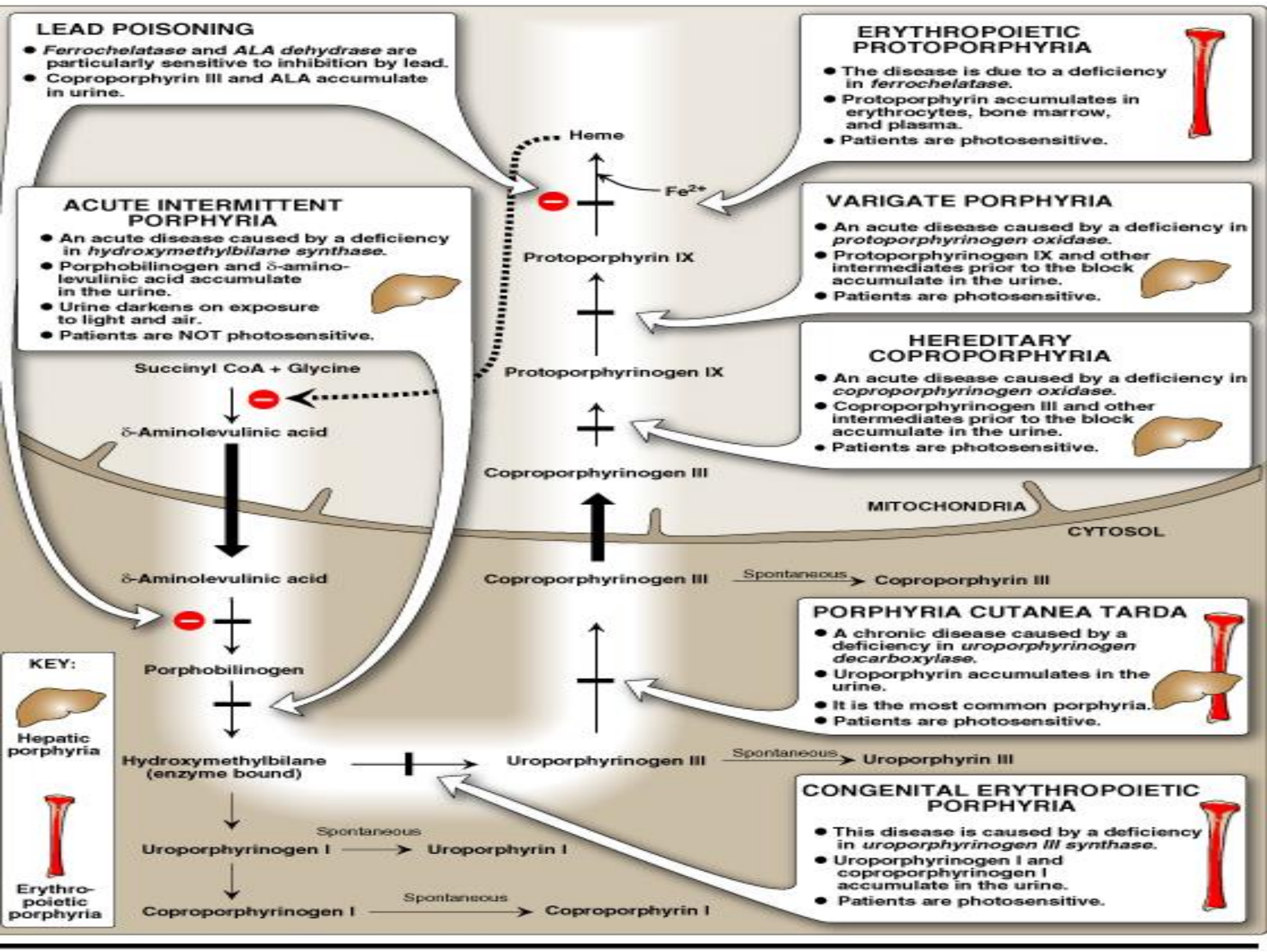
- Most current thinking focuses on accumulations of toxic metabolites.
- ALA and PBG are neurotoxins.
- ALA may be a false transmitter for GABA, it also blocks one of ATPases (perhaps a sodium pump).
- Another hypothesis: unsaturation of hepatic tryptophan pyrrolase ↗ Containing heme secondary to liver heme deficiency leads to altered tryptophan delivery to CNS → ↑ tryptophan excretion.

neurotransmitters which are produced by tryptophan : Serotonin, Melatonin * Both are excitatory NT

Pb^+ → binds to Zn^+ in the active site in ALA-dehydratase enzyme
↳ - inhibition of the enzyme
- accummalation of ALA
↳ displace GABA → ↑ free radicals

tryptophan pyrrolase is also used in the production of NAD^+ & $NADP^+$

no neurotransmitters
no $NADP^+$ / NAD^+
} CNS manifestations


LEAD POISONING
Ferrochelatase and ALA dehydrase are particularly sensitive to inhibition by lead.
Coproporphyrin III and ALA accumulate in urine.
ERYTHROPOIETIC PROTOPORPHYRIA
The disease is due to a deficiency in ferrochelatase.
Protoporphyrin accumulates in erythrocytes, bone marrow, and plasma.
Patients are photosensitive.
Heme
Fe2+
ACUTE INTERMITTENT PORPHYRIA
An acute disease caused by a deficiency in hydroxymethylbilane synthase.
Porphobilinogen and δ-amino-levulinic acid accumulate in the urine.
Urine darkens on exposure to light and air.
Patients are NOT photosensitive.
Protoporphyrin IX
VARIGATE PORPHYRIA
An acute disease caused by a deficiency in protoporphyrinogen oxidase.
Protoporphyrinogen IX and other intermediates prior to the block accumulate in the urine.
Patients are photosensitive.
Succinyl CoA + Glycine
Protoporphyrinogen IX
HEREDITARY COPROPORPHYRIA
An acute disease caused by a deficiency in coproporphyrinogen oxidase.
Coproporphyrinogen III and other intermediates prior to the block accumulate in the urine.
Patients are photosensitive.
δ-Aminolevulinic acid
Coproporphyrinogen III
MITOCHONDRIA
CYTOSOL
δ-Aminolevulinic acid
Coproporphyrinogen III
Spontaneous
Coproporphyrin III
PORPHYRIA CUTANEA TARDA
A chronic disease caused by a deficiency in uroporphyrinogen decarboxylase.
Uroporphyrin accumulates in the urine.
It is the most common porphyria.
Patients are photosensitive.
KEY:
Hepatic porphyria
Erythro-poietic porphyria
Porphobilinogen
Hydroxymethylbilane (enzyme bound)
Uroporphyrinogen III
Spontaneous
Uroporphyrin III
CONGENITAL ERYTHROPOIETIC PORPHYRIA
This disease is caused by a deficiency in uroporphyrinogen III synthase.
Uroporphyrinogen I and coproporphyrinogen I accumulate in the urine.
Patients are photosensitive.
Spontaneous
Uroporphyrinogen I
Uroporphyrin I
Spontaneous
Coproporphyrinogen I
Coproporphyrin I