Porphyrias

Introduction

-The porphyrias are caused by deficiencies of enzymes 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.
- Heterozygotes (autosomal recessive) are asymptomatic in between acute attacks.
- Clinical picture is classified depending on site of overproduction and accumulation of porphyrin, overlapping features common (differential diagnosis is very difficult)

Hepatic Porphyrias

↓

- Neurologic, mental disturbances
- Abdominal pain
- Extremity pain, paresthesias
- Motor neuropathy

Erythropoietic Porphyrias

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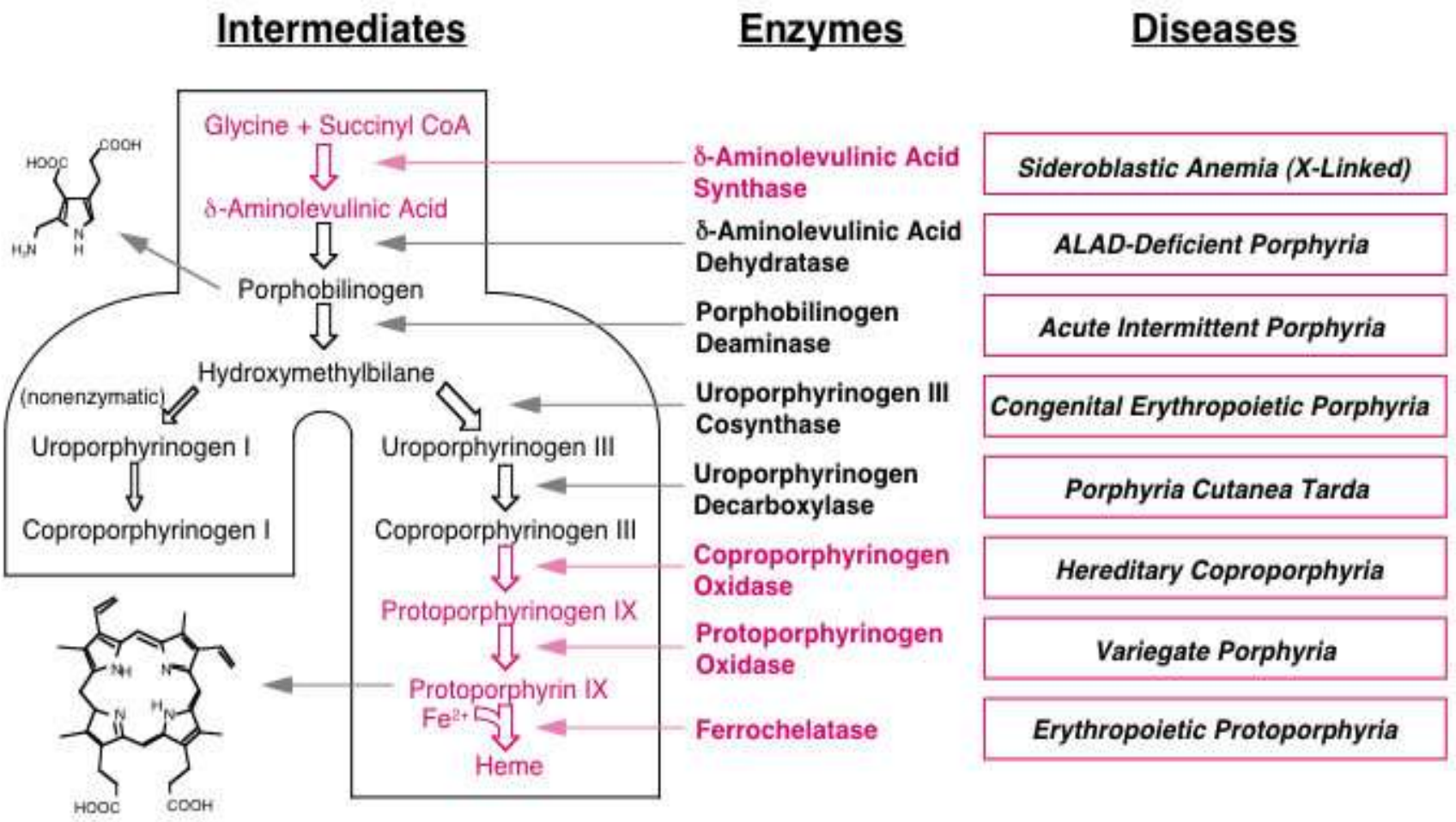
- Cutaneous photosensitivity (long wave UV)
- light excites porphyrins in skins causing:

1- Cell damage
2- Hemolytic anemia

Heme Synthesis Pathway



Classification of the Porphyrias

- Multiple ways to categorize porphyrias:
  - Hepatic vs. Erythropoietic: organ in which accumulation of porphyrins and their precursors appears
  - Cutaneous vs. Non- cutaneous
  - Acute and chronic forms

- Acute (requires more efficient diagnosis):
  - ALA dehydratase deficiency porphyria (ALAD)
  - Acute intermittent porphyria (AIP)
  - Hereditary coproporphyria (HCP)
  - Variegate porphyria (VP)

- Chronic:
  - Porphyria cutanea tarda (PCT)
  - Erythropoietic protoporphyria (EPP)
  - Congenital erythropoietic porphyria (CEP)
  - Hepatoerythropoietic porphyria (HEP)

Porphyria categories

A- Bone Marrow

- Erythropoietic protoporphyria
- Congenital erythropoietic porphyria

B- Liver

- Porphyria cutanea tarda
- Acute intermittent porphyria
- Variegate porphyria
- Hereditary coproporphyria
- Hepatoerythropoietic porphyria

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 (variegate porphyria and hereditary coproporphyria) can cause dermatologic changes

** صعب نميز بين الأربعة الـ acute بس اسهلهم نميز بين VIP & HCP لانهم عندهم + neurological cutaneous manifestation، بس بنفس الوقت صعب نميز بين الاثنين.

- Acute attacks lead to an increase in **PBG** and **ALA** which can be detected in urine.
- Diagnosis is difficult because of **variable clinic course**, **lack of understanding about diagnostic process**, and **lack of a universal standard for test result interpretation**

- 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	ALA dehydratase deficiency	Acute attacks	Autosomal **recessive**
	Acute intermittent porphyria	Acute attacks	Autosomal dominant
	Porphyria cutanea tarda	Skin disease	Usually acquired; a minority are inherited (autosomal dominant)
	Hereditary coproporphyria	Skin disease, acute attacks	Autosomal dominant
	Variegate porphyria	Skin disease, acute attacks	Autosomal dominant
Erythropoietic	Congenital erythropoietic porphyria	Skin disease	Autosomal **recessive**
	Erythropoietic protoporphyria	Skin disease: specific presentation with immediate photosensitivity	Autosomal dominant: severe forms have complex inheritance

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	Photocutaneous	↑ 7- carboxylate porphyrin (U) and isocoproporphyrin (F)
Hereditary coproporphyria	Photocutaneous and neurovisceral	↑ ALA, PBG and coproporphyrin (U) and coproporphyrin (F)
Variegate porphyria	Photocutaneous and neurovisceral	↑ ALA, PBG (U) and protoporphyrin (F)
Erythropoietic protoporphyria	Photocutaneous	↑ protoporphyrin (F & E) and in plasma

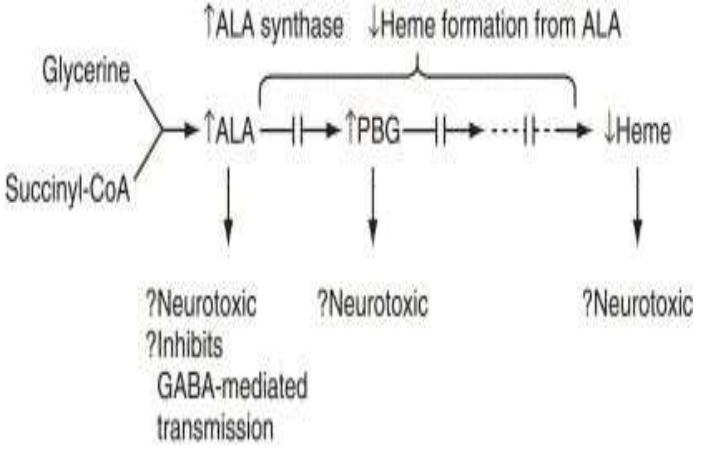
Acute intermittent porphyria

- 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:
  - 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
- Treat any infection.
- Pain control with Morphine
- Treat sympathetic hyperactivity with propranolol.
- 300-400 grams of carbohydrates per day.
- IV heme at 3-5 mg/kg/day.

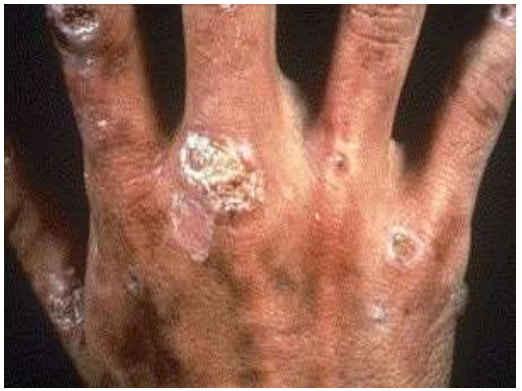


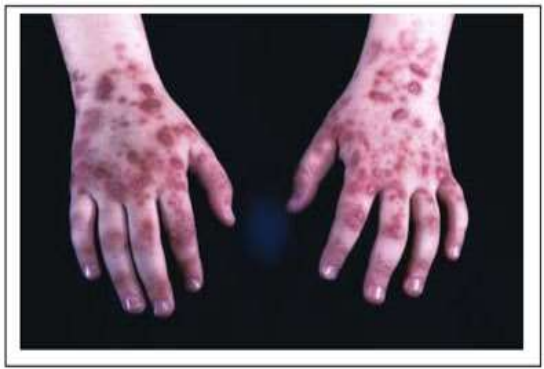
Porphyria cutanea tarda

- Most common porphyria which causes skin manifestations
- Deficiency of hepatic urodecarboxylase
- 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
- Precipitants frequently include alcohol, estrogen and iron

Treatment:

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





Erythropoietic protoporphyria

- 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)

- 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.

Clinical features

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

- Hypersplenism. - Hemolytic anemia. - Thrombocytopenia

Treatment

- Superactivated charcoal - Hypertransfusion
- Splenectomy - Bone marrow transplantation

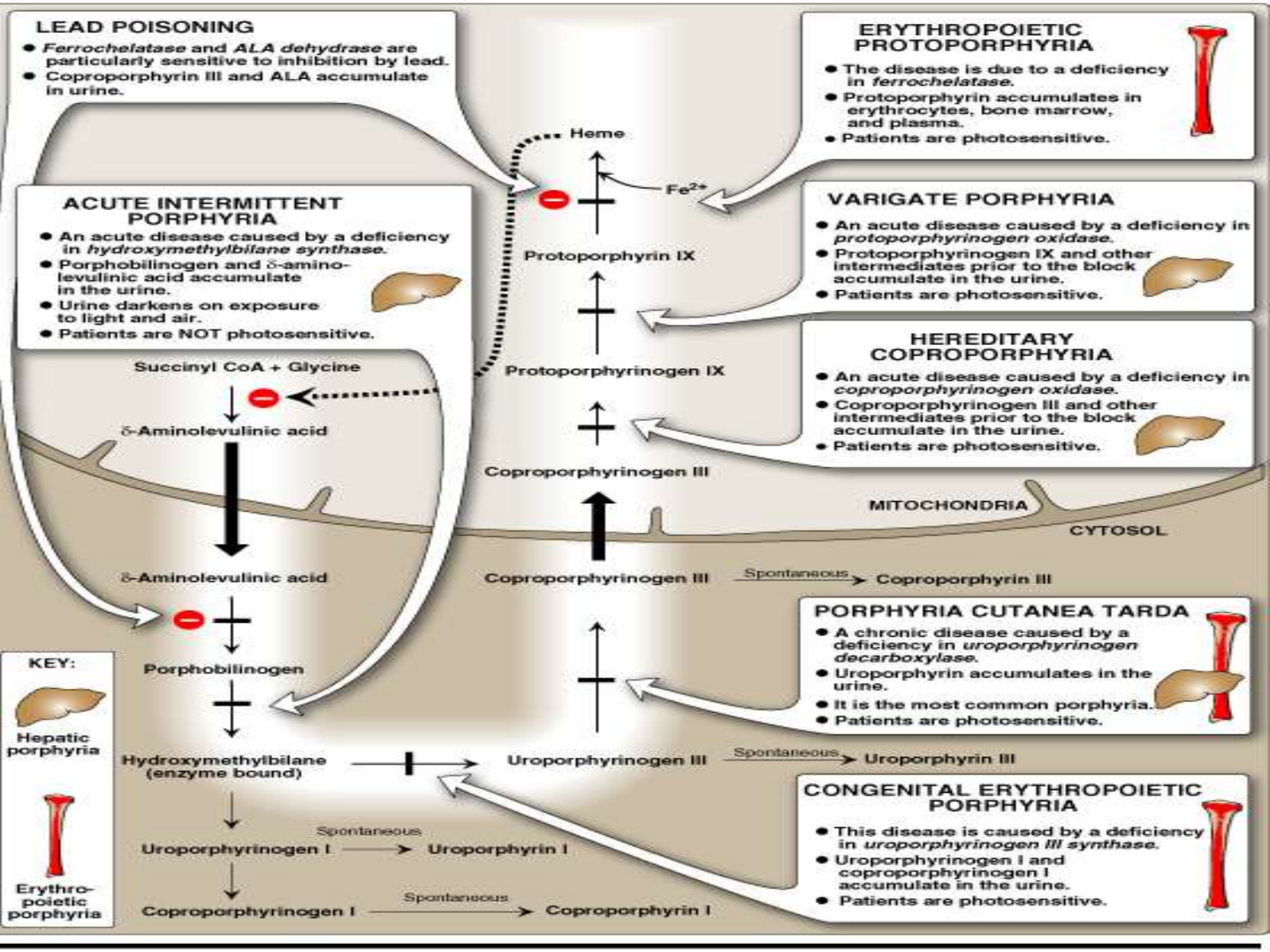
Pseudoporphyria

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

Neurotoxicity mechanisms

(ALA can be subjected to autoxidation and make free radicals)

- 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) (then interact with GABA receptor so it can cause CNS manifestation)
- Another hypothesis: unsaturation of hepatic tryptophan pyrrolase secondary to liver heme deficiency leads to altered tryptophan delivery to CNS → ↑ tryptophan excretion. (tryptophan can be converted to Serotonin and Vitamin D_3)


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