

Introduction and Clinical Aspects of Porphyria

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OUTLINE

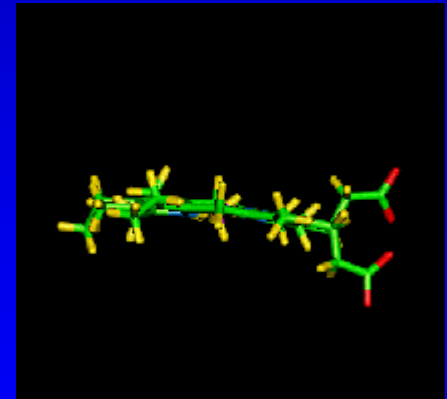
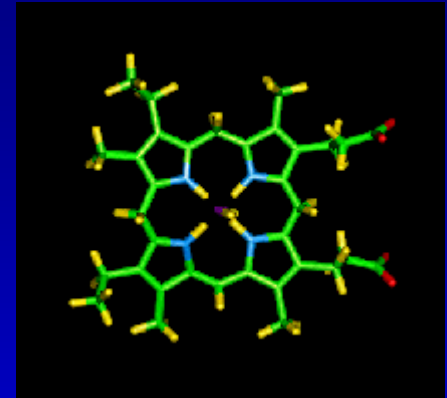
- Introduction
- The Acute Porphyrias
- Cutaneous porphyrias
 - Bullous porphyrias
 - Erythropoietic protoporphyria
- Cardiff Porphyria Services

Introduction

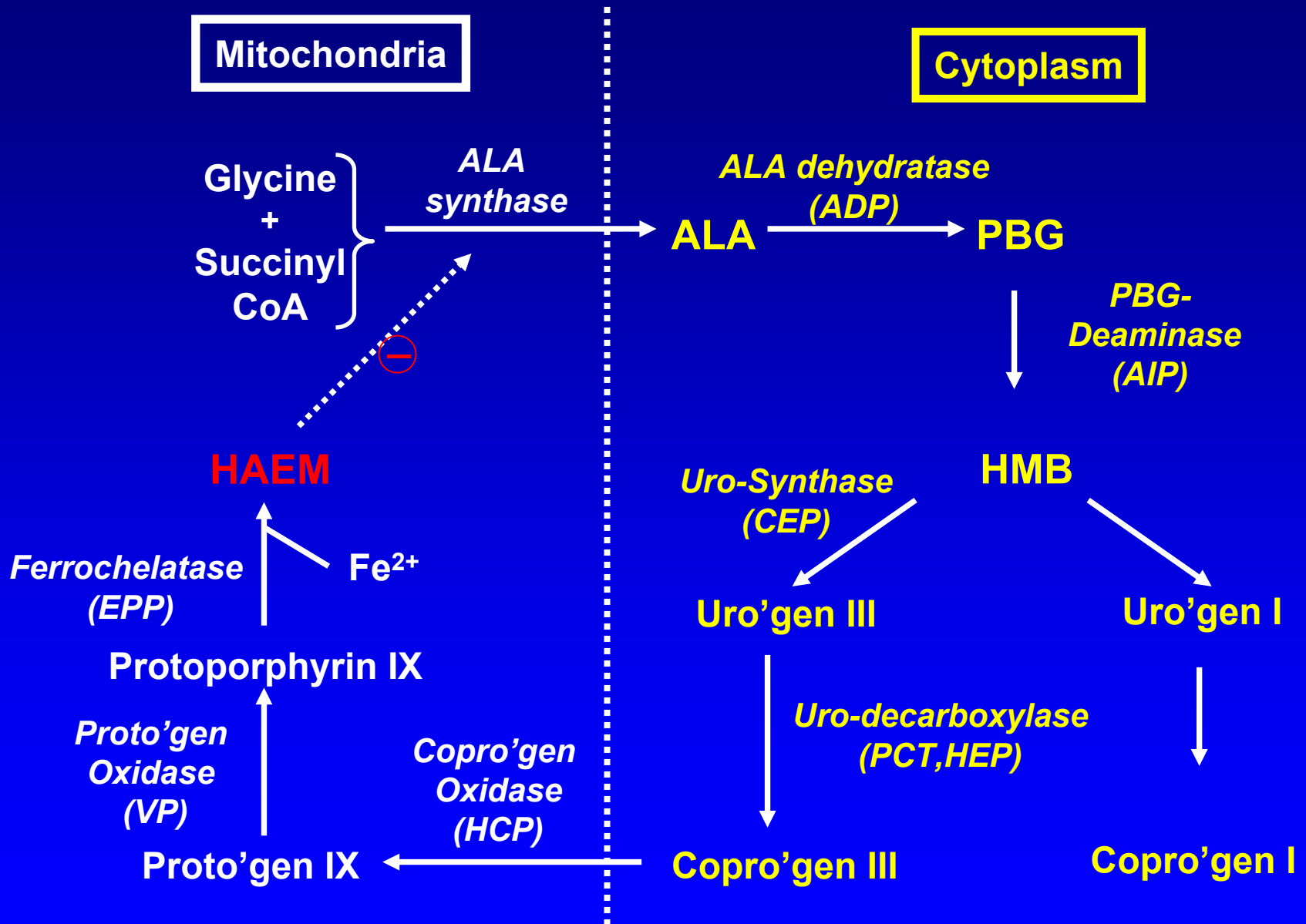
- Group of disorders of haem biosynthesis
- 7 different types
 - Acute porphyrias
 - Cutaneous Porphyrias
- Skin symptoms and or acute attacks

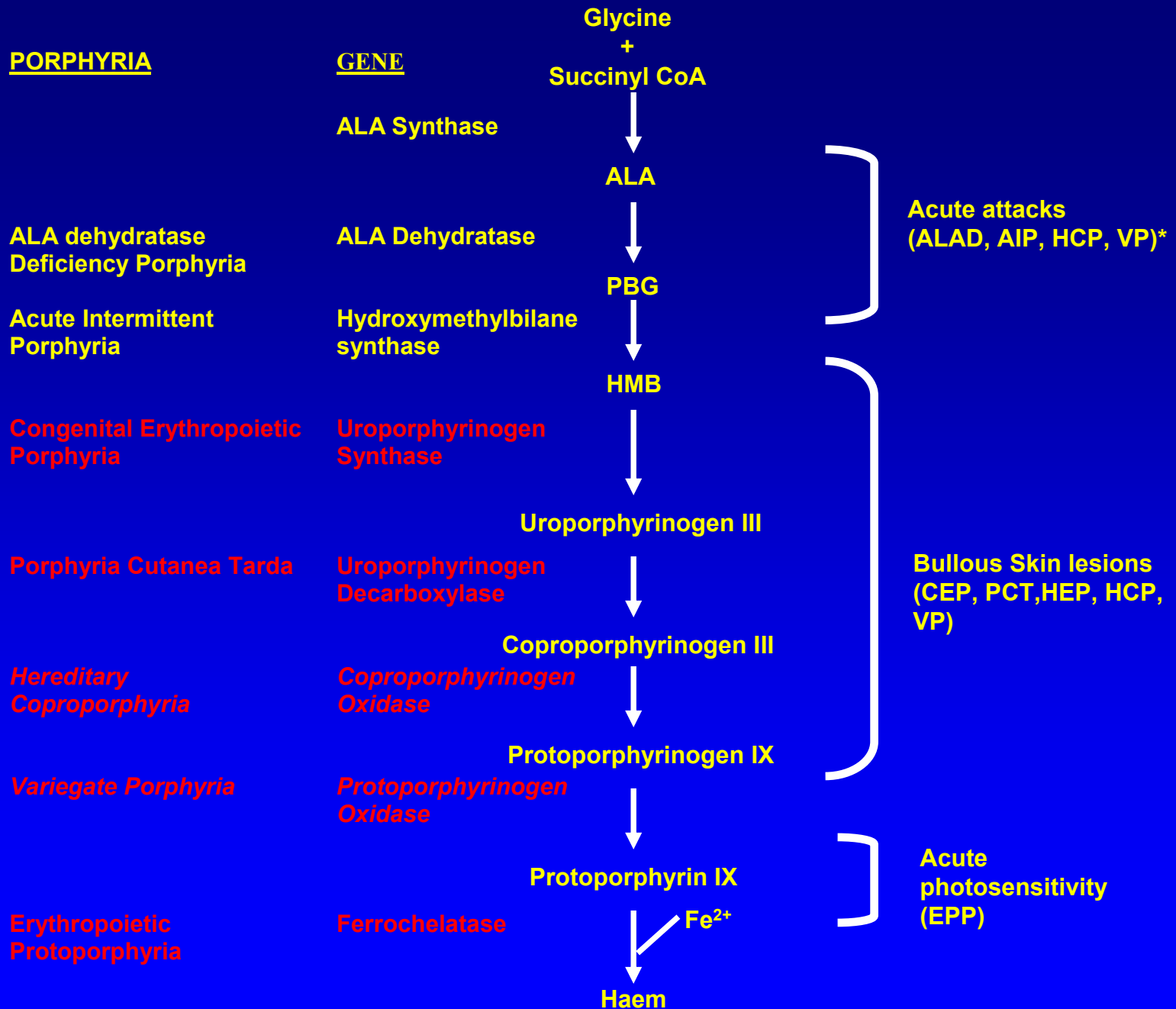
Haem Biochemistry

- Synthesised in all tissues
 - 80% for haemoglobin
 - 20% for enzymes (CytP450, catalase, peroxidase, tryptophan pyrrolase)
- 8 enzymes in pathway
- Intermediates (porphyrinogens) unstable
- Porphyrinogens oxidise to porphyrins



Haem Biosynthesis Pathway





Secondary causes of increased porphyrins

- Urine Coproporphyrin
 - Liver disease, drugs, fever, alcohol
- Faeces Protoporphyrin
 - Constipation, GIT bleed, dietary (meat)
- Blood Increased Zinc protoporphyrin
 - Lead poisoning, iron deficiency
- Plasma
 - Renal failure, cholestasis

The Acute Hepatic Porphyrrias

Autosomal dominant

Low penetrance (90% asymptomatic)

Life threatening neurovisceral attacks

Porphyria Type	Prevalence	Clinical Presentation
Acute intermittent Porphyria (AIP)	Commonest 1-2:100,000	Acute neurovisceral attack
Hereditary coproporphyrria (HCP)	Rarest <1:250,000	i. Acute attack only (72%) ii. Skin lesions only (7%) iii. Both 21%
Variegate porphyria (VP)	1:250,000	i. Acute attack only (20%) ii. Skin lesions only (59%) iii. Both (21%)

Acute Attacks

Females>males (5:1)

Rare before puberty

Symptoms/signs

Abdominal pain, Vomiting, constipation

Psychiatric symptoms (anxiety, confusion, hallucinations)

Hypertension, tachycardia,

Convulsions:

Motor neuropathy: Mild→severe (paralysis)

Hyponatraemia

Treatment:

Withdraw precipitating factor

Symptomatic (opiates, anti-emetics etc)

IV fluids (10% dextrose in N saline)

Intravenous haematin (Haem arginate)

Start treatment early (<24 hours)

Problems: Thrombophlebitis

Prognosis:

Good, even with profound motor neuropathy

Management: Prevention

Family studies to identify relatives at risk

Avoid Known Precipitants:

Sex hormones

Unsafe drugs

WMIC consensus “Safe list” (BNF = UNSAFE)

www.porphyria-europe.com

Alcohol, infection, dieting

THE CUTANEOUS PORPHYRIAS

- Bullous porphyrias
 - PCT (HEP)
 - CEP
 - HCP and VP
- Acute photosensitivity: - EPP

The Bullous Porphyrias

- Skin lesions identical
- Clues in clinical history
 - Age of presentation
- Require biochemical investigation to distinguish
- Essential for appropriate management
 - Definitive treatment (PCT, CEP)
 - Risk of acute attack (VP, HCP)
 - Family studies (VP, HCP)

Bullous Porphyrias: Clinical Manifestations

- Fragile skin
- Vesicles, bullae
- Hypertrichosis
- Other:
 - Milia,
 - hyper/hypopigmentation
 - scarring alopecia
 - sclerodermoid plaques

Porphyria Cutanea Tarda

- Commonest porphyria (1:25,000)
- Types
 - Acquired (Type I) 80%
 - Familial (Type II) 20%
 - (HEP= homozygous familial PCT)
- Males 60% Females 40%

PCT: Pathogenesis

- Inhibition of hepatic enzyme (UroD)
- Exact mechanism unknown
- Involves iron (>80% hepatic siderosis)
- Predisposing factors
 - Alcohol
 - Prescribed oestrogens
 - Hepatitis C, HIV
 - Genetic haemochromatosis
 - (Renal failure)

PCT: Management

- Avoid sunlight
- Withdraw precipitants
- Check hepatitis, transferrin saturation, HFE genotype
- Choose definitive treatment
 - Venesection
 - Low dose chloroquine
- Long term follow-up
 - Monitor liver function (hepatocellular carcinoma)
 - Monitor for relapse

Congenital Erythropoietic Porphyria

- Autosomal recessive
- Defect in uroporphyrinogen III cosynthase
- Variable phenotype: Infancy to adulthood
- Clinical Manifestations
 - Extreme photosensitivity, scarring, mutilation
 - Hypertrichosis
 - Erythrodontia
 - Haemolytic anaemia, splenomegaly

CEP: Treatment

- General
 - Avoid sunlight
 - Treat infections
 - Blood transfusion (+ DFO)
- Specific
 - Bone Marrow Transplantation
 - (Gene therapy)

Erythropoietic protoporphyria (EPP)

- Autosomal dominant, incomplete penetrance
- ~ 1:150,000
- Ferrochelatase activity 10-40%
- Mean age of onset 1 year (range 4/12 - 12 years)
- Mean age at diagnosis 12 years!
- Acute photosensitivity due to free protoporphyrin
 - 80% from bone marrow
 - 20% from liver

EPP: Clinical

Acute	Burning pain, oedema, relieved by cold “like a candle flame under skin”
Chronic	Linear scarring, thickened skin

Management

Sunlight avoidance

Beta-carotene,

Narrow band UV (311-313 nm)

Regular follow-up

Complications

Liver dysfunction: Mild → fulminant liver failure → transplant

Anaemia

Cardiff SAS Porphyria Service

- Established by Professor George Elder
- Deputy Director: Dr Sharon Whatley
- Diagnosis of all types of porphyria
 - Biochemical testing (metabolites, enzymes)
 - Mutational analysis
- Clinical service: Adult Metabolic Clinic: Acute porphyrias
Dermatology Clinic: Cutaneous porphyrias
- Teaching
- Research interests
 - Epidemiology and genetics of EPP
 - Mitochondrial targeting of enzymes
 - Late onset erythropoietic porphyrias