PORPHYRIAS
(Vampires and Crazy Kings)

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October 08-09, 2006 - Freiburg
PORPHYRIAS

Obscure diseases with confusing names considered only when the need for a diagnosis is desperate

(Antony McDonagh, 1997)
PORPHYRINS (TETRAPYRROLES) ARE THE PIGMENTS OF LIFE

Chlorophyll

Vitamin B12

Heme

Parent molecule: Uroporphyrinogen III
PORPHYRINS

“The compounds which make grass green and blood red” (Hans Fischer, 1930)

Porphyrlins are intermediates in the synthesis of heme (Fe-Protoporphyrin IXα)
HEMEPROTEINS

Hemoglobin
Myoglobin
Catalase
Mitochondrial cytochromes

Tryptophan dioxygenase
Nitric oxide synthase
Guanylate cyclase
Microsomal cytochromes P450
PORPHYRIAS

*Disorders resulting from partial deficiencies in enzymes of heme synthesis*
PORPHYRIAS

Disorders resulting from partial deficiencies in enzymes of heme synthesis

Intermittent Acute Porphyria: demonstration of a genetic defect in porphobilinogen deaminase

Heme synthesis pathway

Glycine → Succinyl-CoA → Aminolevulinic acid → Porphobilinogen → Copro-porphyrinogen III → Hydroxymethylbilane → Uro-porphyrinogen III → Protoporphyrinogen → Protoporphyrin → HEME

Enzymes:
- ALAS (Aminolevulinic acid synthase)
- ALAD (Aminolevulinic acid dehydratase)
- PBGD (Porphobilinogen deaminase)
- Uro-P Decarboxylase
- Uro-P Synthase
- Proto-P oxidase
- Ferrochelatase
PROPOSED NOMENCLATURE FOR PORPHYRIAS

Acute Porphyrias
- PBG-synthase deficiency
- PBG-deaminase deficiency
  (HMBS deficiency) (AIP)
- Copro’gen oxidase deficiency (HCP)
- Proto’gen oxidase deficiency (VP)
- Uro’gen III synthase deficiency (CEP)
- Uro‘gen decarboxylase deficiency (PCT)
- Ferrochelatase deficiency (EPP)

Cutaneous Porphyrias
PORPHYRIAS

CLINICAL MANIFESTATIONS

SUNLIGHT-INDUCED SKIN LESIONS
*(PHOTOSENSITIVITY)* DUE TO PORPHYRIN ACCUMULATION IN SKIN IN CUTANEOUS PORPHYRIAS

ATTACKS OF NEUROLOGIC DYSFUNCTION ASSOCIATED WITH ACCUMULATION OF THE PORPHYRIN PRECURSOR DELTA-AMINO-LEVULINIC ACID IN (INDUCIBLE) ACUTE PORPHYRIAS
PORPHYRIAS

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# SYMPTOMS AND SIGNS OF INDUCIBLE ACUTE PORPHYRIAS

<table>
<thead>
<tr>
<th>Gastrointestinal</th>
<th>Estimated incidence, %</th>
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</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>85 – 95</td>
</tr>
<tr>
<td>Vomiting</td>
<td>43 – 83</td>
</tr>
<tr>
<td>Constipation</td>
<td>48 – 84</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 – 12</td>
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<table>
<thead>
<tr>
<th>Neuropsychiatric</th>
<th></th>
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<tbody>
<tr>
<td>Pain in extremities, back, chest, etc.</td>
<td>50 – 70</td>
</tr>
<tr>
<td>Paresis</td>
<td>42 – 68</td>
</tr>
<tr>
<td>Respiratory paralysis</td>
<td>9 – 20</td>
</tr>
<tr>
<td>Mental symptoms (agitation, confusion, hallucinations)</td>
<td>40 – 58</td>
</tr>
<tr>
<td>Convulsions</td>
<td>10 – 20</td>
</tr>
</tbody>
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<tr>
<th>CV, autonomic NS</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Tachycardia</td>
<td>64 – 85</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>36 - 55</td>
</tr>
</tbody>
</table>

*Anderson et al., Ann. Int. Med. 142, 439-450, 2005*
# CHARACTERISTICS OF THE 4 INDUCIBLE ACUTE PORPHYRIAS
(combined prevalence ~5 cases / 100‘000 persons)

<table>
<thead>
<tr>
<th>Disease Abbreviation</th>
<th>Inheritance</th>
<th>Deficient Enzymes</th>
<th>Enzyme Activity (%)</th>
<th>Known Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute intermittent porphyria (AIP)</td>
<td>Autosomal dominant</td>
<td>Porphobilinogen-deaminase (HMBS)</td>
<td>~50</td>
<td>227</td>
</tr>
<tr>
<td>Hereditary coproporphyria (HCP)</td>
<td>Autosomal dominant</td>
<td>Coproporphyrinogen oxidase</td>
<td>~50</td>
<td>36</td>
</tr>
<tr>
<td>Variegate porphyria (VP)</td>
<td>Autosomal dominants</td>
<td>Protoporphyrinogen oxidase</td>
<td>~50</td>
<td>120</td>
</tr>
<tr>
<td>ALA-dehydratase deficient porphyria (ADP)</td>
<td>Autosomal recessive</td>
<td>ALA dehydratase (porphobilinogen synthase)</td>
<td>~5</td>
<td>7</td>
</tr>
</tbody>
</table>

*Anderson et al., Ann. Int. Med. 142, 439-450, 2005*
PRECIPITATION OF ATTACKS IN ACUTE PORPHYRIAS

- **DRUGS**
- HORMONAL CAUSES
- INFECTION
- CALORIC RESTRICTION
- HEAVY SMOKING (?)
- ALCOHOL
- UNKNOWN
HEPATIC ACUTE PORPHYRIAS

QUESTIONS

- WHAT CAUSES NEUROLOGICAL DYSFUNCTION?
- HOW DO DRUGS, FASTING AND HORMONES PRECIPITAE PORPHYRIA?
- WHAT ARE MECHANISMS OF APPARENTLY BENEFICIAL EFFECTS OF CARBOHYDRATES AND HEME?
Attacks are always associated with hepatic ALAS1

**Hypothesis**

All triggering factors directly upregulate ALAS1 at the transcriptional level

1. How do drugs increase ALAS1?
2. How does fasting increase ALAS1?
3. What factors determine the liver specific ALAS1 induction?
4. What else potentially activates ALAS1 and therefore trigger attacks?
Porphobilinogen deaminase deficiency in mice causes a neuropathy resembling that of human hepatic porphyria

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Nature Genetics
Vincent
INDUCTION OF ALAS IN PBGD-knockdown MICE

Urinary excretion of ALA during phenobarbital treatment

ALA (µmol/µmol creatinine)

Day

T1/T2 (male, n=2)
T1/T2 (female, n=2)
control (n=2)
Drug-Response Elements of ALAS1

Fraser, D. J. et al. (2002) *J Biol Chem*
Fraser, D. J. et al. (2003) *J Biol Chem*
Xenosensors CAR and PXR mediate Drug Induction of ALAS1

Nuclear Hormone Receptor Family of Transcription Factors

Drug

CAR/PXR

- 16kb

CYP3A
CYP2B
UGT1A1

ALAS1

Fraser et al. 2002, 2003; Podvinec et al. 2004

Negative feedback regulation of ALAS1 by heme amplifies the response to drugs of ALAS1 in acute porphyrias
INDUCTION OF ALAS IN PBGD-knockdown MICE

Urinary excretion of ALA during phenobarbital treatment

ALA (µmol/µmol creatinine)

Day

T1/T2 (male, n=2)
T1/T2 (female, n=2)
control (n=2)
What Triggers the Fasting Response?

** p < 0.01 fasted vs fed control
Cell 122: 505-515, 2005

The mediator of the fasting response of ALAS1 is PGC-1α
PGC-1α

Peroxisome Proliferator Activator Receptor γ Coactivator 1-α

Versatile co-activator

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<tr>
<th>TISSUE</th>
<th>FUNCTION</th>
<th>TFs</th>
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<tbody>
<tr>
<td>Liver</td>
<td>Gluconeogenesis</td>
<td>HNF4α, GR, FOXO1</td>
</tr>
</tbody>
</table>
PGC-1α acts via FOXO1 and NRF1

Fasting response is blunted in the absence of PGC-1α

Handschin et al. (2005)
Bile acids induce human ALAS1
(Anne-Kathrin Peyer)

Cultures of Primary Human Hepatocytes

Human Liver Slice
(MG Elferink, GM Groothuis, Diana Jung)
Transcriptional Effects on ALAS1

Fasting

Glucagon → cAMP

HNF4α

PGC1α

FXR

CAR

PXR

Xenobiotics

Endobiotics

Bile Acids

ALA, PBG ↑

ALAS1

Acute Neurovisceral Crisis
CONCLUSIONS

Induction of neurovisceral attacks in acute porphyrias:

*Drug-effects on ALAS1 are mediated by the xenosensors CAR and PXR*

*Bile acids induce ALAS1 via activation of FXR*

( clinical importance not known )

*Fasting effects on ALAS1 are mediated via PGC-1α*
HEPATIC ACUTE PORPHYRIAS

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