



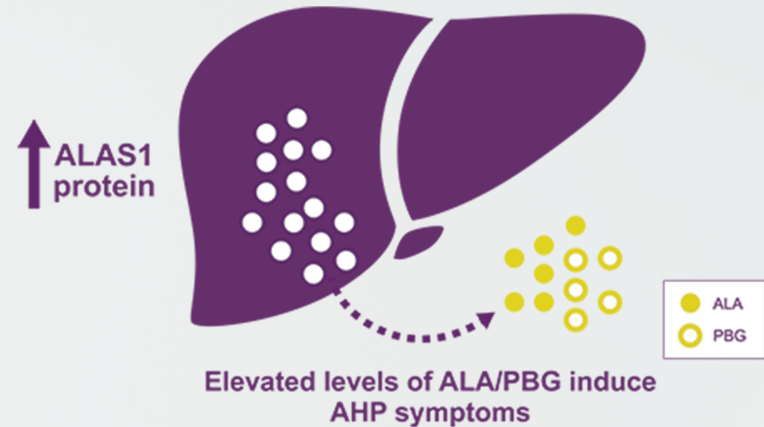
MODULE **02**

Pathophysiology of Acute Hepatic Porphyria (AHP)



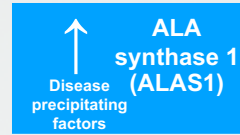
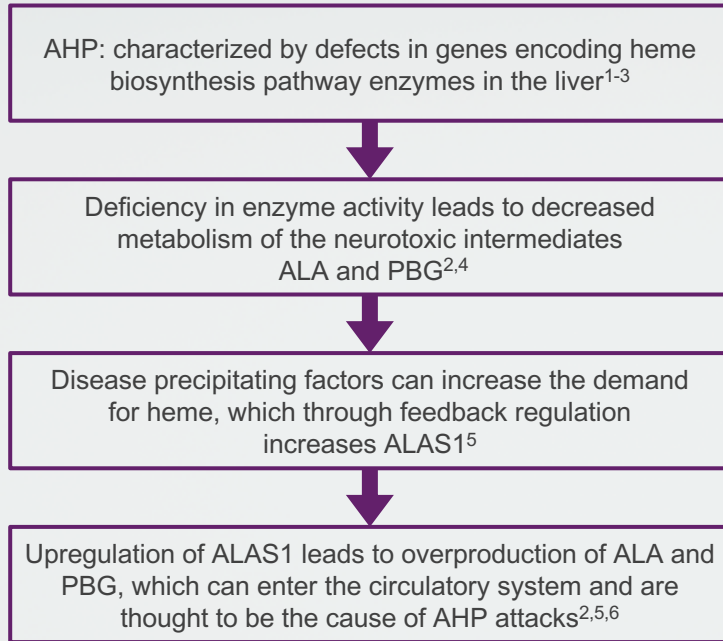
Introduction to the Pathophysiology of AHP

- Attacks are precipitated by events that either directly induce the enzyme aminolevulinic acid synthase 1 (ALAS1) or increase the demand for heme synthesis in the liver, and subsequently disinhibit ALAS1¹
- Upregulation of ALAS1 is the key contributor to elevated levels of the neurotoxic intermediates aminolevulinic acid (ALA) and porphobilinogen (PBG)^{1,2}
- Elevated levels of ALA and PBG are thought to be responsible for the neuropathologic effects in AHP and accompanying signs and symptoms^{1,2}
- AHP attacks and, for some patients, chronic symptoms are associated with widespread neurologic lesions, leading to dysfunction across the^{1,3}:
 - Autonomic nervous system
 - Central nervous system
 - Peripheral nervous system

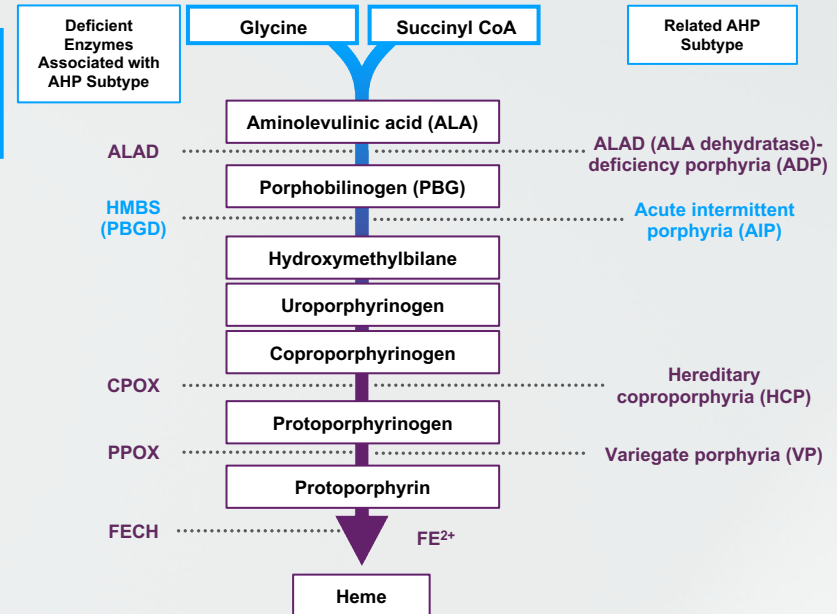


1. Puy H et al. *Lancet*. 2010;375:924-937. 2. Bissell DM, Wang B. *J Clin Transl Hepatol*. 2015;3:17-26. 3. Szlendak U et al. *Adv Clin Exp Med*. 2016;25:361-368.

Mechanisms for the Increase in ALA and PBG by Key Regulating Enzyme ALAS1



The Pathway of Heme Biosynthesis^{2,4}

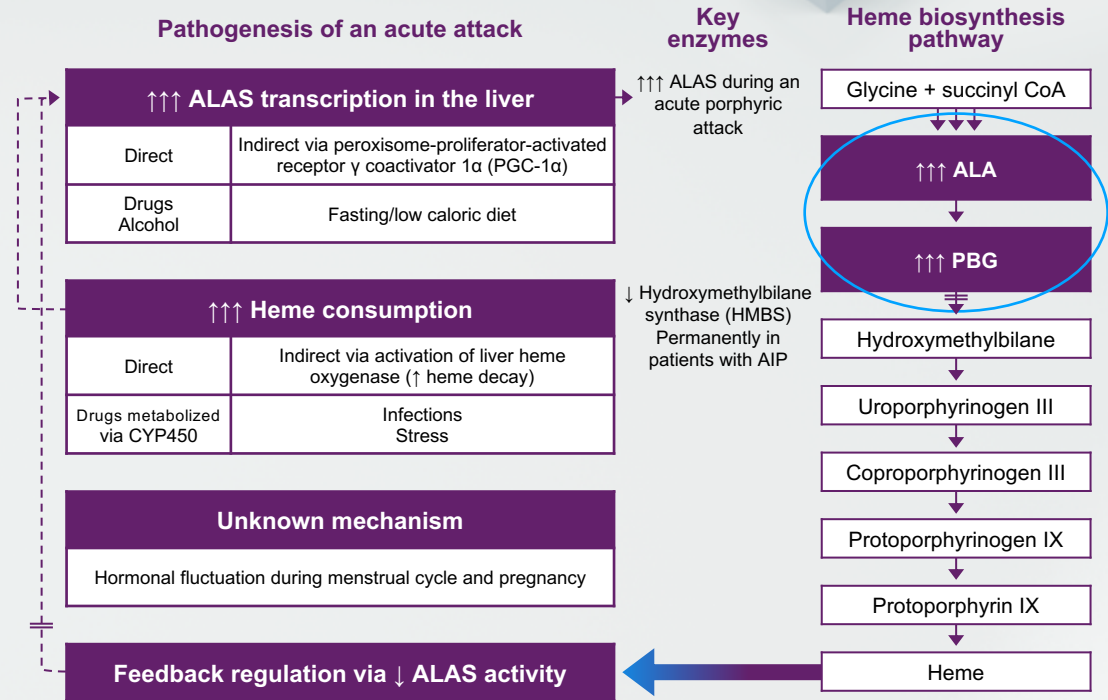


1. Besur S et al. *Metabolites*. 2014;4:977-1006. 2. Pischik E, Kauppinen R. *Appl Clin Genet*. 2015;8:201-214. 3. Szlendak U et al. *Adv Clin Exp Med*. 2016;25:361-368. 4. Bissell DM et al. *N Engl J Med*. 2017;377:862-872. 5. Balwani M et al. *Hepatology*. 2017;66:1314-1322. 6. Bissell DM, Wang B. *J Clin Transl Hepatol*. 2015;3:17-26.

Induction of ALAS1 by Precipitating Factors is the Key Factor Involved in AHP Attacks

- AHP is a disease of low penetrance¹
 - Although the proportion of patients who develop overt clinical disease is <20%, manifest disease can be associated with debilitating and even life-threatening attacks¹
 - Because penetrance is relatively low, not all family members with a mutation for the disease will develop clinical disease²
- Low penetrance suggests the key role of environmental factors and possibly genetic modifiers in precipitating attacks³

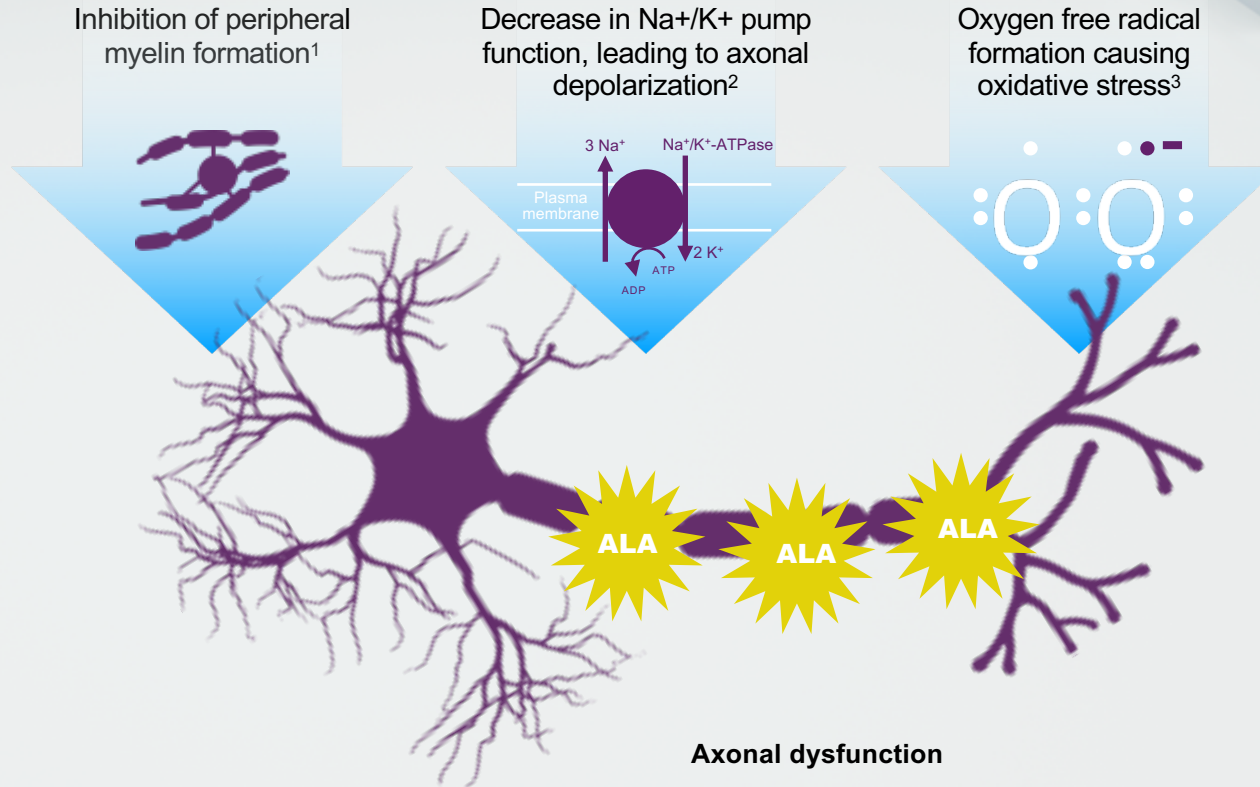
Precipitating Factors and Pathogenesis of an Acute Attack in AIP⁴



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1. Ventura P et al. *Eur J Intern Med*. 2014;25:497-505. 2. Whatley SD, Badminton MN. In: Adams MP et al. eds. *GeneReviews*. <https://www.ncbi.nlm.nih.gov/books/nbk11931/>. Published September 27, 2005. 3. Bissell DM et al. *N Engl J Med*. 2017;377:862-872. 4. Pischik E, Kauppinen R. *Appl Clin Genet*. 2015;8:201-214.

Proposed Pathophysiologic Mechanisms for Neurotoxicity by ALA Based on Existing Publications



1. Felitsyn N et al. *J Neurochem.* 2008;106:2068-2079. 2. Lin CS-Y et al. *Clin Neurophysiol.* 2011;122:2336-2344. 3. Meyer UA et al. *Semin Liver Dis.* 1998;18:43-52.

Clinical Evidence for the Role of ALA and PBG in Acute Intermittent Porphyrria (AIP)-Associated Attacks

Background

- A retrospective analysis of 23 consecutive patients with porphyria-like symptoms from Taiwan
- AIP documented in 12 patients based on history of past attacks, clinical manifestations, precipitating factors, elevated urinary ALA and PBG levels, and molecular genetic defects

Results

- All 12 patients with AIP-associated neuropathies had motor paresis during or after a severe attack with CNS manifestations
- Urinary ALA and PBG levels were elevated during or after the attack in all 12 patients with AIP

Electrophysiological Findings and 24-Hour Urine ALA and PBG Levels in 12 Patients with AIP

Patient Type	Motor Nerve Conduction Velocity and Electromyography	ALA Level (mg/day)*	PBG Level (mg/day)*
AIP patients with motor nerve abnormalities (n=7)	Motor axonal polyneuropathy involving upper extremities	38.6	136.9
	Asymmetric motor neuropathy prominently involving both radial and left peroneal nerve	34.3	78.9
	Axonal motor polyneuropathy	63.9	52.1
	Absence of all sensory and motor action potentials	20.8	70.0
	Axonal motor neuropathy	87.3	3.9
	Bilateral radial neuropathy	198.1	35.0
	Bilateral radial motor neuropathy	38.0	38.0
AIP patients with normal findings (n=5)	Normal	7.7-318.6	11.4-154.7

*Reference range for 24-hour urinary ALA=0.3-7.4 mg/day and PBG=0-2 mg/day.

Summary

Pathophysiology of AHP

- Attacks and, for some patients, chronic symptoms are associated with widespread neurologic lesions, leading to dysfunction across the autonomic, central, and peripheral nervous systems^{1,2}
- Elevated levels of the neurotoxic intermediates ALA and PBG are thought to be responsible for the neuropathologic effects^{2,3}

Mechanisms of ALA neurotoxicity

- ALA is especially thought to be neurotoxic, with various proposed mechanisms leading to axonal dysfunction⁴⁻⁶
 - Inhibition of myelin formation⁴
 - Decrease in Na⁺/K⁺ pump function, leading to axonal depolarization⁵
 - Oxygen free radical formation causing oxidative stress⁶

Clinical evidence for the role of ALA and PBG in AHP attacks

- In 12 patients retrospectively diagnosed with AHP, urinary ALA and PBG levels were elevated during or after attacks in all patients⁷
- Other studies have shown that PBG and ALA are elevated during and after AHP attacks^{8,9}

1. Szlendak U et al. *Adv Clin Exp Med*. 2016;25:361-368. 2. Puy H et al. *Lancet*. 2010;375:924-937. 3. Bissell DM, Wang B. *J Clin Transl Hepatol*. 2015;3:17-26. 4. Felitsyn N et al. *J Neurochem*. 2008;106:2068-2079. 5. Lin CS-Y et al. *Clin Neurophysiol*. 2011;122:2336-2344. 6. Meyer UA et al. *Semin Liver Dis*. 1998;18:43-52. 7. Kuo H-C et al. *Eur Neurol*. 2011;66:247-252. 8. Gouya L, et al. EXPLORE: A Prospective, Multinational, Natural History Study of Patients with Acute Hepatic Porphyrria with Recurrent Attacks. *Hepatology*. 2020; May;71(5):1546-1558. Poster. 9. Marsden JT, Rees DC. *J Clin Pathol*. 2014;67:60-65.