



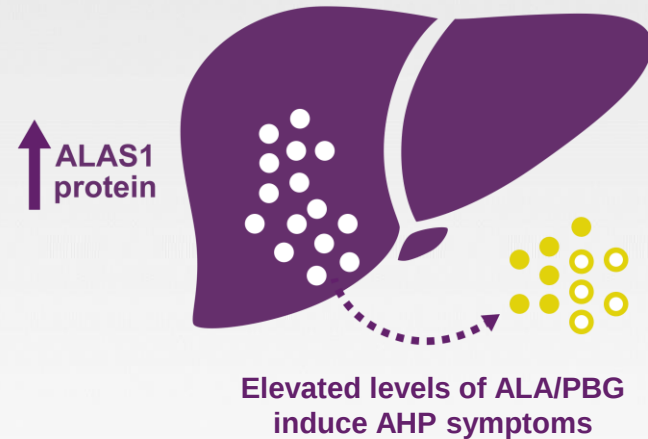
MODULE
02

Pathophysiology of Acute Hepatic Porphyrria (AHP)



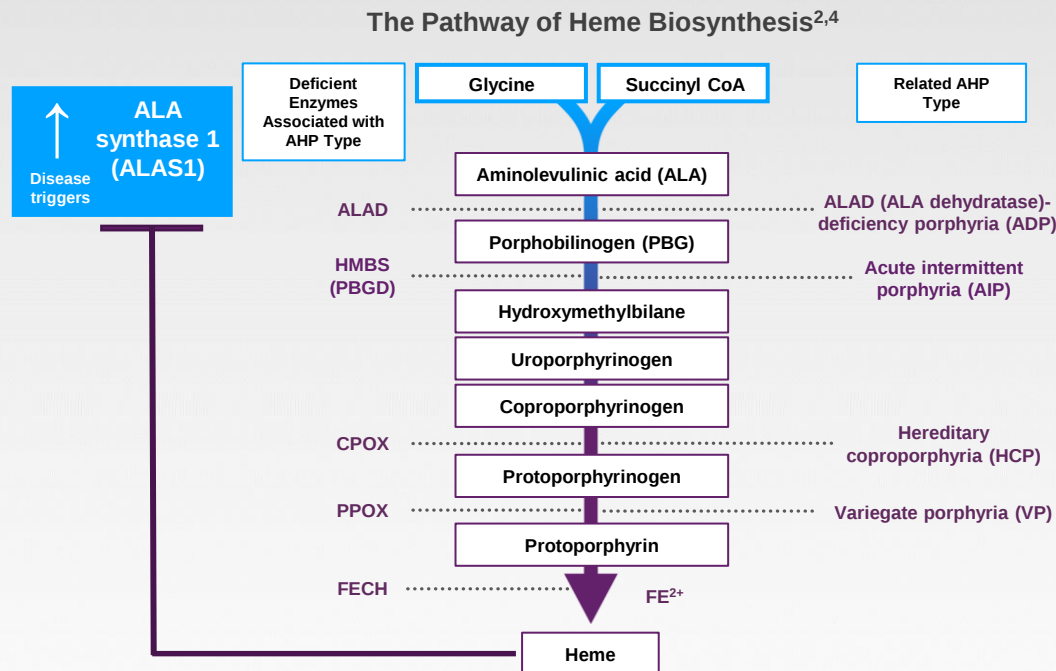
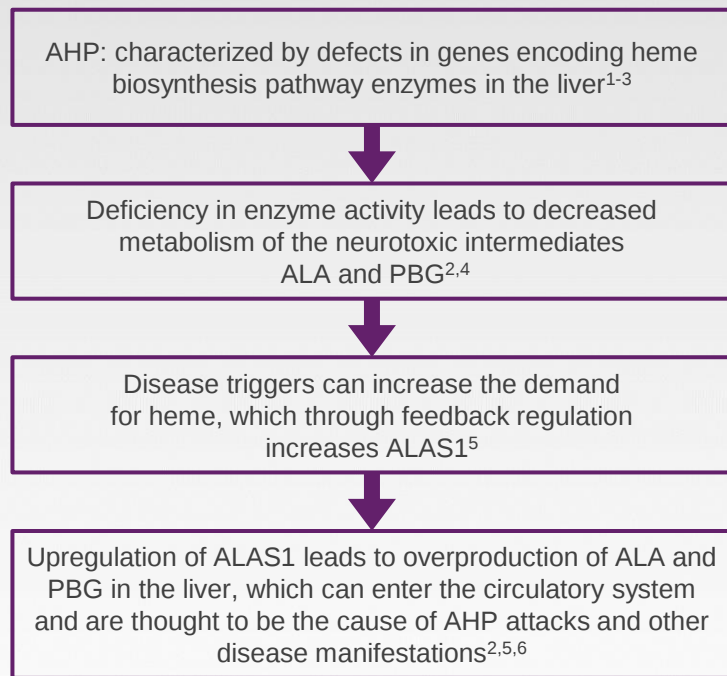
Introduction to the Pathophysiology of AHP

- Acute 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

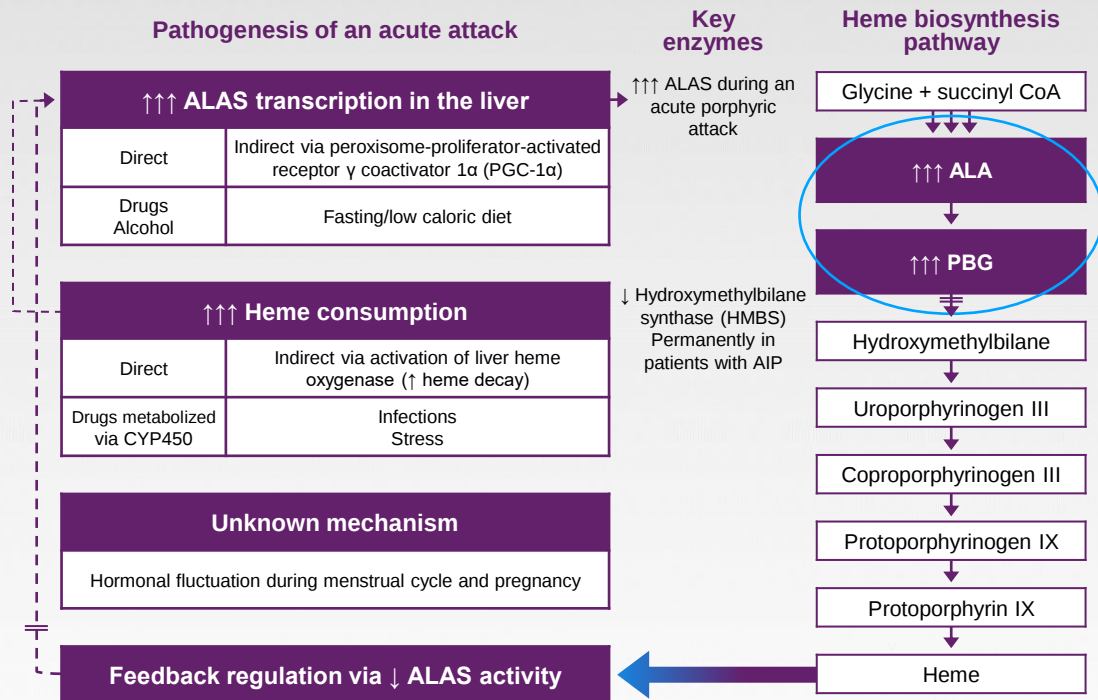


1. Besur S et al. *Metabolites*. 2014;4:977-1006. 2. Pischik E, Kauppinen R. *Appl Clin Genet*. 2015;8:201-214. 3. Szlendak U et al. *Adv Clin Exp Med*. 2016;25:361-368. 4. Bissell DM et al. *N Engl J Med*. 2017;377:862-872. 5. Balwani M et al. *Hepatology*. 2017;66:1314-1322. 6. Bissell DM, Wang B.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

Triggers are a Significant Factor Involved in Many AHP Attacks

- AHP is a disease of low penetrance¹
 - Although the proportion of patients who develop overt clinical disease is ~1%, 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

Known Triggers and Pathogenesis of an Acute Attack in AIP⁴

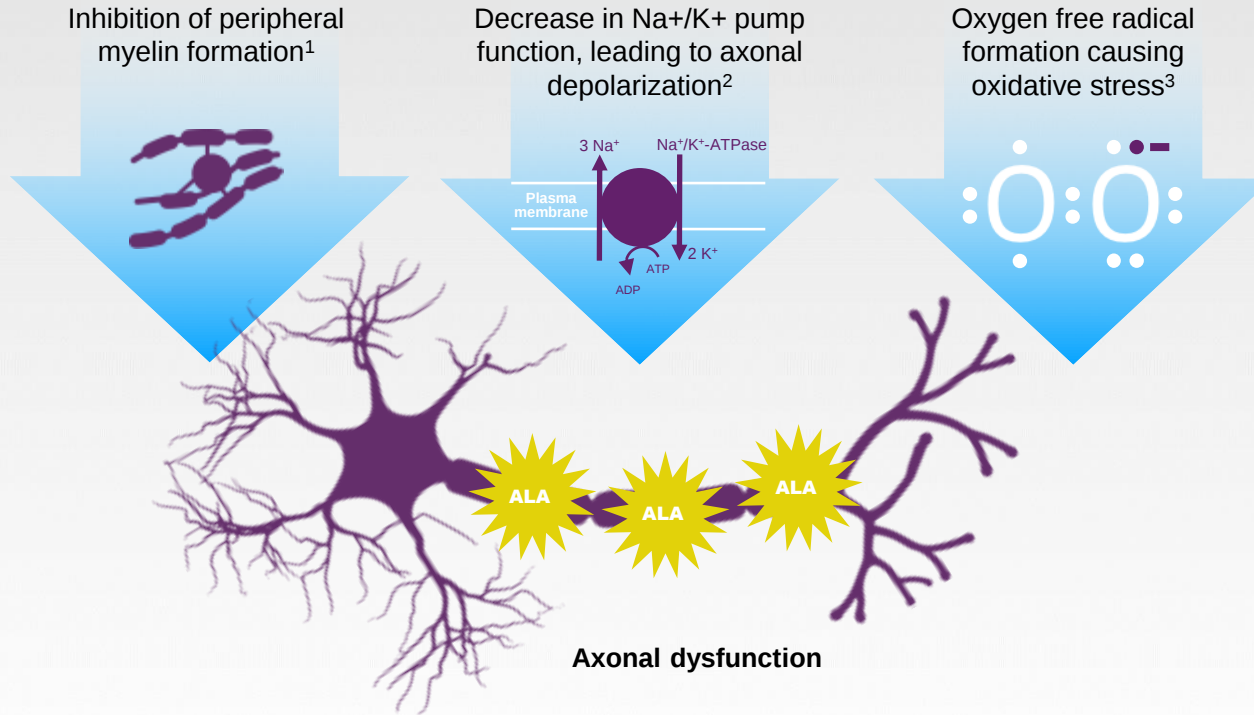


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1. Ventura P et al. *Eur J Intern Med*. 2014;25:497-505. 2. Whatley SD, Badminton MN. In: Adams MP et al. eds. *GeneReviews*. <https://www.ncbi.nlm.nih.gov/books/nbk11931/>. Published September 27, 2005. 3. Bissell DM et al. *N Engl J Med*. 2017;377:862-872.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

Three Proposed Pathophysiologic Mechanisms for Neurotoxicity by ALA Based on Existing Publications

ALA contributes to Axonal dysfunction in AHP



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.

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}

Triggers are a significant factor in many AHP attacks

- Low penetrance suggests the key role of environmental factors and possibly additional genetic modifiers in precipitating attacks³

Mechanisms of ALA neurotoxicity

- There are three proposed mechanisms for ALA 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

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.