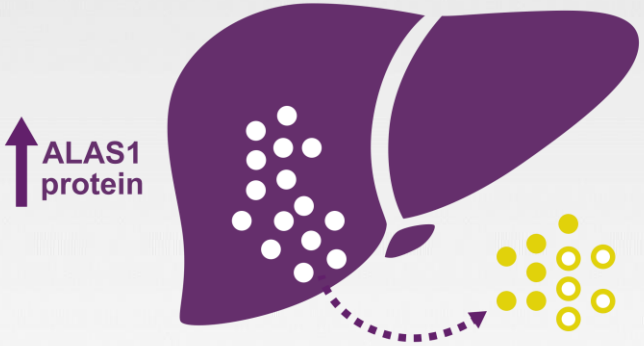
MODULE
02

Pathophysiology of Acute Hepatic Porphyria (AHP)

Alnylam PHARMACEUTICALS

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 ALAS1[1]
- 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



Elevated levels of ALA/PBG induce AHP symptoms

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

AHP: characterized by defects in genes encoding heme biosynthesis pathway enzymes in the liver[1-3]

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Deficiency in enzyme activity leads to decreased metabolism of the neurotoxic intermediates ALA and PBG[2,4]

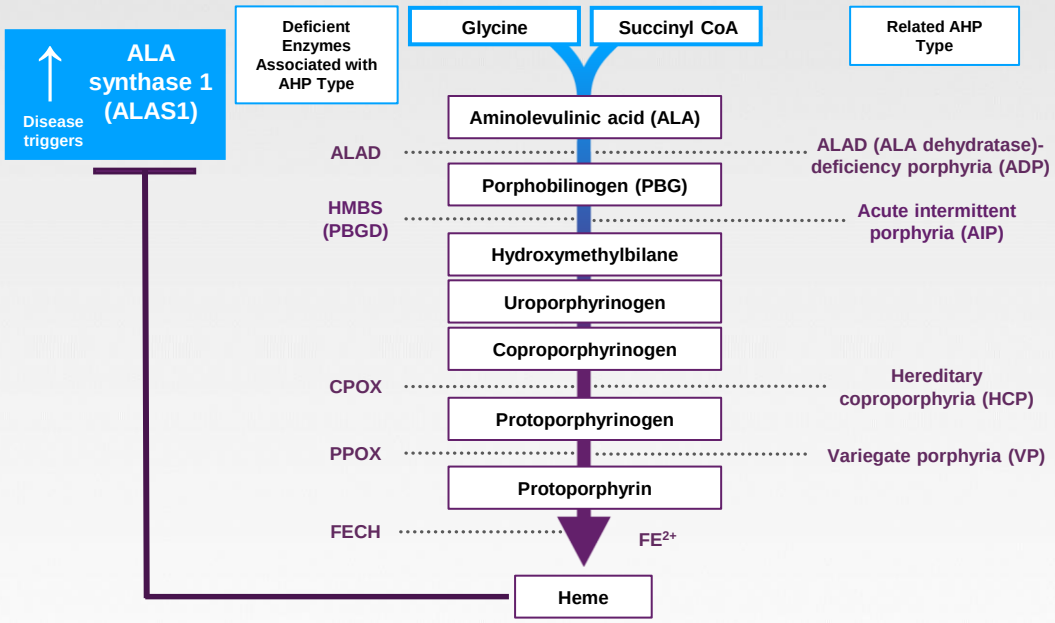
↓

Disease triggers can increase the demand for heme, which through feedback regulation increases ALAS1[5]

↓

Upregulation of ALAS1 leads to overproduction of ALA and PBG in the liver, which can enter the circulatory system and are thought to be the cause of AHP attacks and other disease manifestations[2,5,6]

The Pathway of Heme Biosynthesis[2,4]

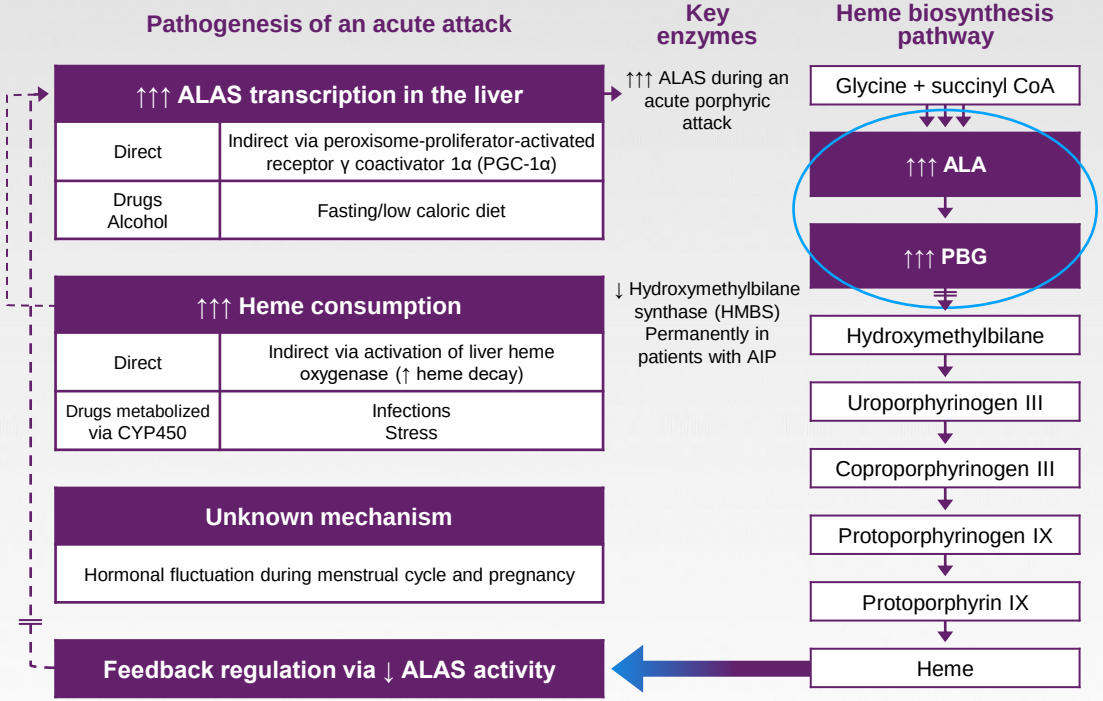


1. Besur S et al. *Metabolites.* 2014;4:977-1006. **2.** Pischik E, Kauppinen R. *Appl Clin Genet.* 2015;8:201-214. **3.** Szlendak U et al. *Adv Clin Exp Med*. 2016;25:361-368. **4.** Bissell DM et al. *N Engl J Med.* 2017;377:862-872. **5.** Balwani M et al. *Hepatology.* 2017;66:1314-1322. **6.**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

Triggers are a Significant Factor Involved in Many AHP Attacks

- AHP is a disease of low penetrance[1]
  - Although the proportion of patients who develop overt clinical disease is ~1%, manifest disease can be associated with debilitating and even life-threatening attacks[1]
  - Because penetrance is relatively low, not all family members with a mutation for the disease will develop clinical disease[2]
- Low penetrance suggests the key role of environmental factors and possibly genetic modifiers in precipitating attacks[3]

Known Triggers and Pathogenesis of an Acute Attack in AIP[4]



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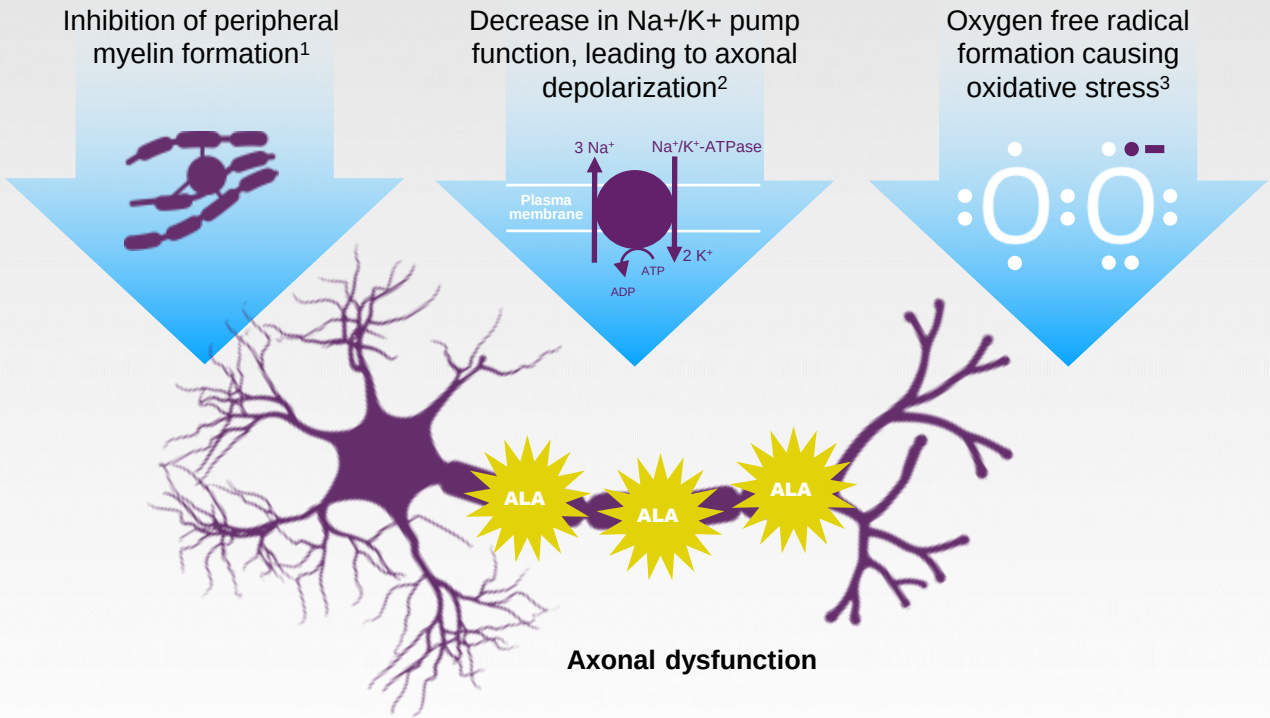
1. Ventura P et al. *Eur J Intern Med.* 2014;25:497-505. **2**. Whatley SD, Badminton MN. In: Adams MP et al. eds. *GeneReviews.* https://www.ncbi.nlm.nih.gov/books/nbk11931/. Published September 27, 2005. **3.** Bissell DM et al. *N Engl J Med.* 2017;377:862-872. **4.** Pischik E, Kauppinen R. *Appl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

Mechanisms of ALA neurotoxicity

- There are three proposed mechanisms for ALA leading to axonal dysfunction[4-6]
  - Inhibition of myelin formation[4]
  - Decrease in Na+/K+ pump function, leading to axonal depolarization[5]
  - Oxygen free radical formation causing oxidative stress[6]

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.