

Title: Hepatoerythropoietic Porphyria *GeneReview* – Pathophysiology

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Excess iron may contribute to UROD inhibition by providing an oxidative environment that is apparently required for generating a UROD inhibitor [Ryan Caballes et al 2012]. Hepatic hepcidin expression has been shown to regulate iron homeostasis and likely plays a role in development of PCT; however, the role that hepcidin plays in PCT development has not been clearly defined [Ajioka et al 2008].

Alcohol and its metabolites may induce the enzymes ALAS1 and CYP2E1, generate reactive oxygen species that contribute to oxidative damage, cause mitochondrial injury, deplete reduced glutathione and other antioxidant defenses, increase endotoxin production, and activate Kupffer cells leading to inflammation. In addition, alcohol has been found to impair iron-mediated expression of hepatic hepcidin and to decrease hepatic expression of hepcidin, which may help lead to increased iron in hepatocytes [Harrison-Findik et al 2006, Harrison-Findik et al 2007].

Smoking may increase oxidative stress in hepatocytes and induce hepatic CYP1A2 (which is important in the development of uroporphyrin in rodent models).

Hepatitis C is associated with excess fat, some iron accumulation, mitochondrial dysfunction, and oxidative stress in hepatocytes – all of which may contribute to the development of PCT. Dysregulation of hepcidin may contribute to iron accumulation in hepatitis C [Fujita et al 2008, Nishina et al 2008].

Estrogens can generate reactive oxygen species in some experimental systems; however, the mechanism by which they are a susceptibility factor has not been established. Estrogen mimetics (e.g., tamoxifen) have been shown to be associated with PCT in several cases. The liver is the site of estrogen metabolism; first pass kinetics leads to a much higher hepatic concentration of estrogen and may also contribute to an increased oxidative environment in some individuals [Bulaj et al 2000].

References

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