Canine Copper-Associated Hepatitis

Karen Dirksen, DVM, PhD, Hille Fieten, DVM, PhD*

KEYWORDS

• Dog • Liver • Bedlington terrier • Labrador retriever • Wilson disease • *ATP7A* • *ATP7B* • *COMMD1*

KEY POINTS

- Canine copper-associated hepatitis shares similarities with human copper accumulation disorders.
- Copper-associated hepatitis is recognized in several dog breeds and differences exist in causal genes and inheritance patterns between breeds.
- Clinical signs are usually noted late in disease stage when severe liver damage due to hepatic copper accumulation is already present.
- D-Penicillamine (DPA) is the most commonly used chelator to treat hepatic copper accumulation and treatment is most effective in early stages of disease.
- A low-copper/high-zinc diet can help to prevent accumulation or reaccumulation of hepatic copper in dogs with complex forms of copper-associated hepatitis.

INTRODUCTION: PATHOPHYSIOLOGY OF COPPER HOMEOSTASIS AND CELLULAR COPPER METABOLISM

Copper Homeostasis

Copper is an essential trace element necessary for many vital functions in the body. Free copper is toxic, however, due to the potential to create reactive oxygen species. Therefore, copper uptake, distribution, and excretion are tightly regulated.[1] Dietary copper is predominantly absorbed in the small intestine. Copper uptake by the enterocyte is mainly mediated by copper transporter 1 (CTR1), a high-affinity copper transporter. The copper transporter ATPase copper transporting alpha (ATP7A) is located at the basal membrane of the enterocytes and facilitates copper transport into the portal circulation. In the portal blood, copper is predominantly bound to albumin and is delivered to the hepatocellular cytosol via apically located CTR1. The liver is the most important organ in copper metabolism and is responsible for copper storage,

Disclosure Statement: The authors have nothing to disclose.
Department of Clinical Sciences of Companion Animals, Faculty of Veterinary Medicine, Utrecht University, Utrecht, The Netherlands
* Corresponding author. Yalelaan 108, 3584 CM, Utrecht, The Netherlands.
E-mail address: H.Fieten@uu.nl

Vet Clin Small Anim ■ (2016) ■–■
http://dx.doi.org/10.1016/j.cvsm.2016.11.011 **vetsmall.theclinics.com**

redistribution to other tissues and organs, and excretion of excess copper via the biliary system. The kidneys excrete a small proportion of excess body copper.

Cellular Copper Metabolism

After copper enters the hepatocytes, it is immediately bound by proteins to prevent oxidative damage (**Fig. 1**). Copper scavengers, including the small proteins metallothionein (MT) and glutathione (GSH), are the first to bind and store copper. Special delivery proteins, the copper chaperones, ensure safe handover of copper to their destination molecules.[2] Cyclooxygenase (COX)17 is the copper chaperone for cytochrome C oxidase (CCO), which resides in the inner mitochondrial membrane. CCO is the terminal enzyme in the mitochondrial respiratory chain and thus plays a crucial role in aerobic energy metabolism. The copper chaperone for superoxide dismutase (CCS) shuttles copper to superoxide dismutase (SOD1), which is an important protein in the defense against oxidative stress. Antioxidant 1 copper chaperone (ATOX1) is the copper chaperone for the copper transporters, ATP7A and ATPase, copper transporting, beta (ATP7B). Both ATPases reside in the trans-Golgi network (TGN) under normal copper conditions. When intracellular copper concentrations are rising, they move away from the TGN to their respective destinations. In the TGN, ATP7B loads 6 copper atoms onto the ferroxidase ceruloplasmin (CP), which is secreted into the circulation.[3] CP is the main copper transport protein in the blood. Under elevated copper conditions, ATP7B traffics to a lysosomal or apical membrane-associated cellular component and facilitates excretion of excess copper into the bile.[4] Previously, the main role of ATP7A was presumed to be copper uptake in the intestines, but recently hepatocellular ATP7A was demonstrated to have an important role in mobilizing and redistributing hepatic copper stores in case of peripheral copper deficiency.[5] The copper metabolism (Murr1) domain containing 1 (COMMD1) protein interacts with the amino

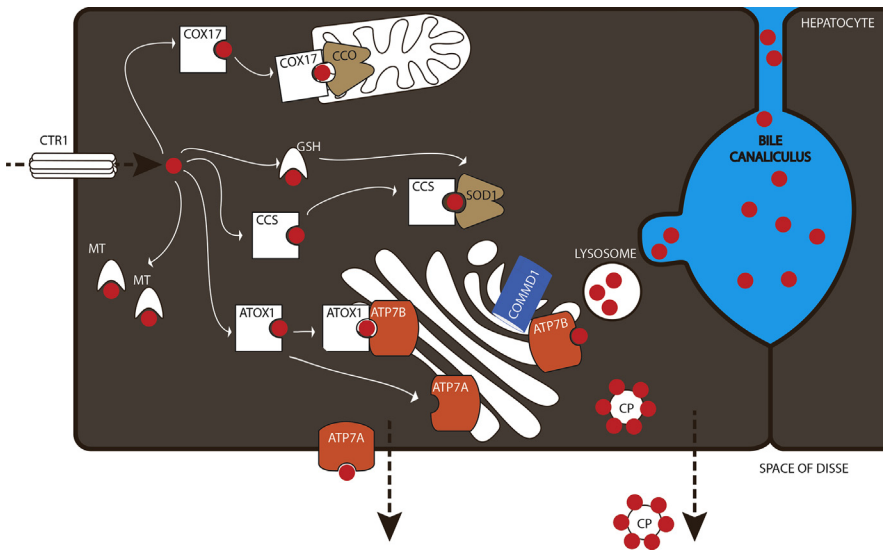

Fig. 1. Hepatocellular copper metabolism. Copper enters the cell via CTR1 and is immediately bound by MTs and/or GSH to prevent oxidative stress. The chaperones COX17, CCS, and ATOX1 transfer copper to their respective destination molecules CCO, SOD1, and ATP7A/ATP7B. ATP7A and ATP7B function in the export of copper to the blood (ATP7A and ATP7B) or to the bile (ATP7B). COMMD1 interacts with both ATPases.