Chapter 50

Copper

Overview

- Intestinal Cu^{++} absorption appears to be enhanced by dietary protein.
- Ceruloplasmin carries Cu^{++} in plasma, and also assists circulating transferrin in the reception of hepatic iron.
- Superoxide dismutase is the most abundant Cu^{++}-containing enzyme.
- Copper is a component of the mitochondrial electron transport chain.
- Copper is required for both catecholamine synthesis and degradation.
- Lysyl oxidase is a Cu^{++}-containing enzyme that aids in the crosslinking of elastin and collagen.
- Copper toxicity causes hepatic necrosis, methemoglobinemia, and hemolysis.
- Copper deficiency is associated with anemia, skin and hair depigmentation, CNS disturbances, and vascular degeneration.
- Wilson's-like disease is prevalent in Bedlington terriers.

Copper (**Cu^{++}**) is not as abundant as Zn^{++} or Fe^{++} in animals, however, disease states associated with Cu^{++} deficiency or Cu^{++} excess do exist. Like several other trace elements, the Cu^{++} content of the body is thought to be homeostatically regulated, with normally little storage of excess. High concentrations are found in **hair** and **nails**, but in terms of mass, the skeleton, muscle, liver, brain, and blood account for most of the Cu^{++} (although it is present in most all cells and tissues; **Table 50-1**).

Copper, like many other trace elements, is abundant in the germ of whole grains, therefore herbivores and omnivores usually show little or no evidence of Cu^{++} deficiency. Legumes, liver, and fish are also good dietary sources. Muscle meats (except duck) are generally less abundant in Cu^{++}.

Copper is normally absorbed at about **50% efficiency** from the upper small intestine by an energy-dependent process, and may compete with Zn^{++} and Fe^{++} for absorption. **Copper absorption** appears to be enhanced by dietary protein and amino acids. Evidence from studies in rats indicates that the concentration of **metallothionein** in mucosal cells determines how much Cu^{++} is free to proceed on into portal blood or stay behind attached to this small,

Table 50-1

Copper Content of Various Tissues

Bone > Muscle > Liver > Hair and Nails > Brain (substantia nigra) > Blood >
Kidney > Heart > Lung > Spleen

Data modified from Linder MC, 1991.

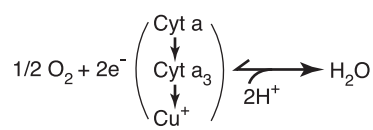
high-cysteine protein. Conditions that increase metallothionein production (such as a high Zn^{++} intake), decrease overall Cu^{++} transfer into blood (see Chapter 49).

Copper is initially bound to **albumin** in portal blood, where it is carried to the liver. Within hepatocytes, Cu^{++} is incorporated into **ceruloplasmin** and other proteins/enzymes (e.g., **metallothionein**, **superoxide dismutase**, **cytochrome c oxidase**), and some undergoes canalicular excretion into bile. Only small amounts are normally excreted into urine. Ceruloplasmin, like other plasma proteins made by the liver, moves into blood and transports Cu^{++} to cells throughout the organism. Incorporation of Cu^{++} into ceruloplasmin may be necessary for Cu^{++} homeostasis in primates, since Cu^{++} accumulates in the liver when there is inadequate ceruloplasmin synthesis (see **Wilson's disease** below).

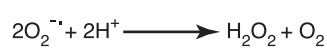
In addition to ceruloplasmin, Cu^{++} is associated with several intra- and extracellular enzymes (**Fig. 50-1**). **Cytochrome c oxidase**, the terminal component of the mitochondrial electron transport chain, transfers a pair of electrons from each of two cytochrome c molecules and a Cu^{++}-containing enzyme to O_2 (see Chapter 36). The cytochrome c

Reactions Catalyzed by Copper-Containing Enzymes

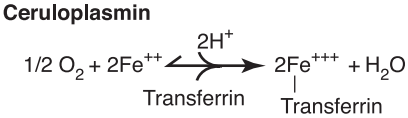
Cytochrome C Oxidase



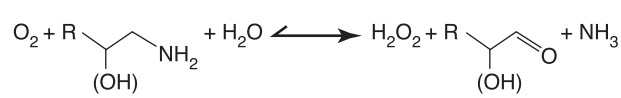
Superoxide Dismutase (SOD)



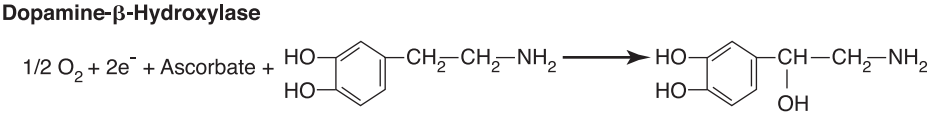
Ceruloplasmin



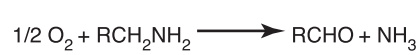
Lysyl Oxidase



Dopamine-β-Hydroxylase



Monoamine Oxidase (MAO)



Copper-containing enzymes catalyze several important reactions in the body. In copper deficiency, anemia ensues because of ceruloplasmin deficiency, deficiency of lysyl oxidase causes vasculature degeneration ascribable to a lack of elastin and collagen crosslinking, and dopamine-β-hydroxylase deficiency results in CNS disturbances. Apart from enzymatic functions, copper-proteins and copper-chelates may exert other less well understood actions in the body.

Figure 50-1

oxidase complex contains heme iron as part of cytochromes a and a_3, and during electron transfer, the Cu^{++}-containing enzyme changes charge on reduction from +2 to +1.

The most abundant Cu^{++}-containing enzyme is **superoxide dismutase (SOD)**, which also contains Zn^{++} (see Chapter 49). This enzyme is concerned with the disposal of potentially damaging superoxide anions throughout the body (see Chapter 30).

Ceruloplasmin, which carries about **60% of Cu^{++} in plasma**, is also a weak, yet broad-based oxidase. It functions in copper transport, and in **antioxidant** defense as an extracellular scavenger of superoxides and other oxygen radicals. Serum Cu^{++} concentrations and ceruloplasmin are often increased in inflammatory conditions, indicating a positive role for these agents in the healing process and in connective tissue repair. Many types of cell-mediated inflammatory processes are propagated by the production of superoxide anions and other oxygen radicals. Ceruloplasmin, playing the role of a free-radical scavenger, is thought to help combat these processes.

Ceruloplasmin also plays a role in allowing the flow of **iron** from storage sites in the liver to **transferrin**, for transport to bone marrow and other sites (see Chapter 48). Specifically, **ceruloplasmin** is necessary for **oxidation** of **Fe^{++}** (which leaves ferritin where it is stored), **to Fe^{+++}** in order to allow attachment to plasma transferrin (see **Fig. 50-1**). In Cu^{++}-deficient rats that accumulate liver Fe^{++}, studies have shown that infusion (or liver perfusion) of ceruloplasmin causes release of liver iron to circulating transferrin. This finding helps to explain the similar symptomatology of Fe^{+++} and Cu^{++}-deficiency anemias, although energy availability for hematopoiesis, through oxidative phosphorylation and cytochrome c oxidase, may also be rate-limiting.

Another important Cu^{++}-containing enzyme is **lysyl oxidase**, which is secreted by connective tissue cells to aid in the crosslinking of elastin and collagen. This enzyme is essential for the health and maintenance of connective tissue and blood vessels, for in its absence, vascular degeneration occurs (**Table 50-2**).

Dopamine-β-hydroxylase is a Cu^{++}-containing, vitamin C-dependent enzyme needed for catecholamine production in the brain, adrenal medulla, and sympathetic postganglionic neurons (see **Fig. 50-1**). In addition to catecholamine production, one enzyme involved in the degradation of catechola-

Table 50-2

Copper

Deficiency Symptoms	Toxicity Symptoms
Anemia	Acute
Osteopenia	Hemolysis
Hypercholesterolemia	Methemoglobinemia
Neutropenia	Hepatic necrosis
Vascular degeneration	Wilson's-like disease
Skin and hair depigmentation	Chronic hepatitis and cirrhosis
CNS disturbances	Lethargy
Decreased immune function	Ascites
Hyperextension of distal phalanges	Weight loss
	Jaundice

mines, namely **monoamine oxidase** (**MAO**), also contains Cu^{++}. Two isozymes of MAO have been described, **MAO-A** in neural tissue, and **MAO-B** in extraneural tissue (i.e., effector cells, the liver, stomach, kidney, and intestine). Monoamine oxidase inhibitors are drugs that would obviously prolong the action of the monoamines (namely serotonin, histamine, and the catecholamines, (dopamine, norepinephrine, and epinephrine)), including those in the CNS, and have thus been used to treat depression.

Apart from enzymatic functions, Cu^{++}-proteins and Cu^{++}-chelates are thought to possess other less well understood roles. For example, nonsteroidal antiinflammatory drugs like aspirin exert their actions as Cu^{++}-chelates, and Cu^{++} deficiency is associated with immune dysfunction (see **Table 50-2**). Other Cu^{++}-chelates are thought to possess limited anticancer activity, and Cu^{++} may play a role in the development of blood vessels and capillaries (i.e., angiogenesis).

Copper Deficiency

Although rare, **Cu^{++} deficiency** in the dog has been associated with hyperextension of the distal phalanges, and tissue Cu^{++} decreases in hair (with depigmentation), liver, kidney, and heart muscle (see **Table 50-2**). Osteopenia, lameness, and bone fragility have also been reported in dogs on Cu^{++}-deficient diets. Additional symptoms of Cu^{++}-deficiency include an anemia similar to that seen in Fe^{++}-deficiency, neutropenia, and a degeneration of the vasculature ascribable to lack of elastin and collagen crosslinking (via lysyl oxidase). In rats, CNS disturbances, probably due to alterations in catecholamine production and degradation, and hypercholesterolemia have been associated with Cu^{++}-deficiency.

Although Cu^{++}-deficiency can occur from a deficient diet or from deficient parenteral feeding, excess loss of Cu^{++} through renal dialysis can also occur. Unexplained observations have been made in experimental animals that excessive fructose (or sucrose) intake may exacerbate Cu^{++}-deficiency.

Copper Toxicity

Acute Cu^{++}-toxicity can follow ingestion of $CuSO_4$ solutions used as fungicides, algicides, and sheep foot-baths. Copper is corrosive to mucus membranes of the digestive tract, and causes hepatic necrosis, methemoglobinemia, and hemolysis (see **Table 50-2**).

Hepatic Cu^{++} accumulation can be associated with significant hepatic injury in animals, resulting in **chronic hepatitis** and **cirrhosis**. It is one of the few well-documented causes of chronic hepatitis in the dog. Certain breeds, including the West Highland white terrier (WHWT), Doberman pincher, American and English cocker spaniel, keeshond, Skye terrier, standard poodle, and Labrador retriever appear to have higher mean values for hepatic Cu^{++} than other breeds. An inherited metabolic defect in biliary Cu^{++} excretion causes chronic hepatitis in **Bedlington terriers**. A similar disorder occurs in WHWTs, however it is not identical, and is of lower magnitude. Because Cu^{++} is normally excreted in bile, hepatic Cu^{++} accumulation can also theoretically occur secondary to any cholestatic disorder.

In affected dogs, Cu^{++} is initially sequestered in hepatic lysosomes, and hepatic damage is reportedly minimal. However, with progressive accumulation of Cu^{++}, hepatic injury appears to become significant. The disease has been recognized in Bedlington terriers around the world, but primarily occurs in the United States, where the **prevalence** has been reported as **over 60%**. This disorder is similar in many respects to **Wilson's disease** in humans, and both disorders are transmitted by an autosomal recessive inheritance. Dogs,

however, do not apparently show evidence of CNS or corneal Cu^{++} accumulation, and plasma Cu^{++} and ceruloplasmin concentrations are reportedly normal in affected dogs (rather than decreased, as in Wilson's disease of humans).

OBJECTIVES

- Contrast and compare the normal copper content of various body tissues.
- Identify the protein of intestinal mucosal cells that regulates copper absorption, and the primary plasma protein that binds this trace element.
- Recognize six important cellular reactions catalyzed by copper-containing enzymes.
- Explain the dual role of ceruloplasmin in copper and iron transport, and the dual role of copper in catecholamine production and degradation.
- Identify and explain the copper deficiency symptoms.
- Discuss common causes of acute copper toxicity in animals, and explain the symptoms.
- Contrast and compare the causes and symptoms of Wilson's disease in humans to hepatic copper accumulation in Bedligton terriers.

QUESTIONS

1. Which one of the following exocrine secretions of the body is the major route for Cu^{++} elimination?
a. Saliva
b. Pancreatic juice
c. Bile
d. Sweat
e. Urine

2. Approximately 60% of Cu^{++} in circulating plasma is normally complexed with:
a. Albumin.
b. Fibrinogen.
c. Transferrin.
d. Ceruloplasmin.
e. Lysyl oxidase.

3. What is the most abundant Cu^{++}-containing enzyme in the body?
a. Hexokinase
b. Superoxide dismutase
c. Glutathione reductase
d. Monoamine oxidase
e. PEP carboxykinase

4. Which one of the following Cu^{++}-containing compounds helps to transfer hepatic iron to circulating transferrin?
a. Cytochrome c oxidase
b. Superoxide dismutase
c. Ceruloplasmin
d. Lysyl oxidase
e. Dopamine-β-hydroxylase

5. Which one of the following symptoms is best associated with Cu^{+}-deficiency?
a. Hypocholesterolemia
b. Polycythemia
c. Hepatitis
d. Polyuria
e. Vascular degeneration

6. Hepatic Cu^{++} accumulation resulting in hepatitis and cirrhosis is best associated with:
a. Ponies.
b. Female cats.
c. Dairy cows.
d. Goats.
e. Bedlington terriers.

7. Select the TRUE statement below regarding copper:
a. Copper is normally absorbed from the upper small intestine by an energy-dependent process.
b. Amino acids are known to compete with copper for intestinal absorption.
c. Copper is normally associated with intracellular enzymes, but not extracellular enzymes.
d. Activation of lysyl oxidase, a Cu^{++}-containing enzyme, causes vascular degeneration.
e. Unlike catecholamine synthesis, catecholamine degradation involves a Cu^{++}-containing enzyme.

ANSWERS
1. c
2. d
3. b
4. c
5. e
6. e
7. a