Chapter 51

Manganese and Selenium

Overview

- Mn^{++} is associated with a wide variety of mammalian enzymes, including carboxylases, dehydrogenases, and transferases.
- Mn^{++} is best associated with mucopolysaccharide and lipopolysaccharide metabolism.
- Mn^{++} is absorbed from the small intestine at a rather low 3-4% efficiency, and is generally an abundant plant element.
- Mn^{++} is an additive in many pet food products.
- Mn^{++} is needed for normal bone metabolism.
- Se is an essential component of glutathione peroxidase, and is normally absorbed from the digestive tract at a rather high (50-90%) efficiency.
- The chemistry of Se appears to resemble that of sulfur.
- Some soils are Se-deficient, while others grow plants that when consumed can cause Se-toxicity.
- Se toxicity is associated with "blind staggers" and "alkali disease" in farm animals.
- Both vitamin E deficiency and Se deficiency lead to nutritional muscular degeneration, as well as other symptoms.

Manganese (Mn^{++})

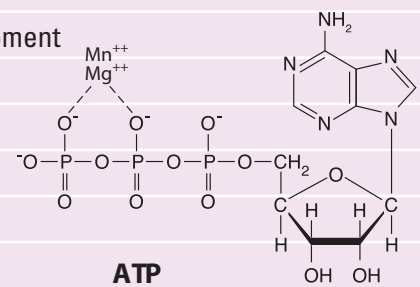
Manganese is associated with a wide variety of enzymes in several different areas of metabolism (**Table 51-1**). In contrast to several of the other trace elements, however, a deficiency in this mineral is uncommon in animals, and does not appear to have broad effects (probably because magnesium (Mg^{++}), the much more abundant intracellular divalent cation, can substitute for Mn^{++} in many of its various enzyme-related activities). The roles of this element in **mucopolysaccharide** and **lipopoly-saccharide** formation would appear, however, to be the most vital in animals (**Table 51-2**).

Manganese is considerably less abundant than Fe^{++}, Zn^{++}, Cu^{++}, Ca^{++}, or Mg^{++} in the body, and is absorbed from the small intestine at a rather low **3-4% efficiency** (**Fig. 51-1**). Intestinal absorption is **hindered** by **Ca^{++}**, **$PO_4^{\equiv}$**, **Fe^{++}**, and **phytate**, yet **aided** by **histidine** and **citrate**. Blood distribution is thought to be **aided** by **transferrin**, the same plasma protein that carries iron (see Chapters 48 and 50). Blood concentrations of Mn^{++}, however, are normally about **1-2%** that of Fe^{+++}, Zn^{++}, or Cu^{++}. Tissue concentrations are highest in the **pineal**, **pituitary**, and **lactating mammary glands**, which are generally higher than those found in bone, liver, and pancreatic tissue. Manganese concentrations are generally low in lung and muscle tissue. As with Fe^{++}, Zn^{++}, and Cu^{++}, normal excretion occurs via intestinal sloughed cells, bile, and pancreatic juice, with urinary concentrations normally being low unless excessive intake occurs.

Table 51-1

Manganese-Dependent Processes

Glycolysis	Mitochondrial superoxide dismutase
Citric acid cycle	(protect mitochondrial membranes)
Hepatic urea synthesis	Maintain connective tissue & cartilage
Hexose monophosphate shunt	Blood clotting
	Bone mineralization & demineralization
Production of:	Lactation
Mucopolysaccharides	Fetal development
Glycoproteins	Pancreatic function
Lipopolysaccharides	Brain function
Hyaluronic acid	Ear otolith development
Heparin	
Chondroitin sulfate	
Melanin	
Dopamine	
Lipids	



ATP

Table 51-2

Mn^{++}-Deficiency Symptoms

*Decreased mucopolysaccharide production	Pancreatic β-cell granulation
*Decreased lipopolysaccharide formation	Impaired lactation
Reduced glucose tolerance	Impaired fetal development
Defective otolith production	Hypocholesterolemia

*Primary

Rich **food sources** of **Mn^{++}** include nuts and whole grains, where the major portion is in the germ. Leafy vegetables are also good sources, where **Mn^{++}** is associated with a **thylakoid membrane binding protein** (the O_2-evolving complex) in the photosynthetic electron transport chain, and **Mg^{++}** is associated with the chlorophyll component of chloroplasts. Meats, fish, milk, and poultry are generally considered to be poor sources of Mn^{++}. For this reason Mn^{++} is usually added to feeds and pet food products.

Both **Mn^{++}** and **Mg^{++}** can serve as components of **ATP** or **ADP**, and as cofactors for several different types of enzymes, including carboxylases and decarboxylases, hydrolases and dehydrogenases, and transferases. Of particular significance are **pyruvate carboxylase**, **biotin carboxylase** and **acetyl-CoA carboxylase** (see Chapters 27, 42, and 56), and **isocitrate dehydrogenase** in the mitochondrial tricarboxylic acid cycle (see Chapter 34). The mitochondrial form of **superoxide dismutase**, which is thought to help protect mitochondrial membranes, is also associated with Mn^{++}, whereas the cytoplasmic form is best associated with Zn^{++} and Cu^{++}. Thus, Mn^{++}, which attains high levels in mitochondria, helps to reduce the oxidative stress associated with high mitochondrial O_2 consumption. **Arginase**,

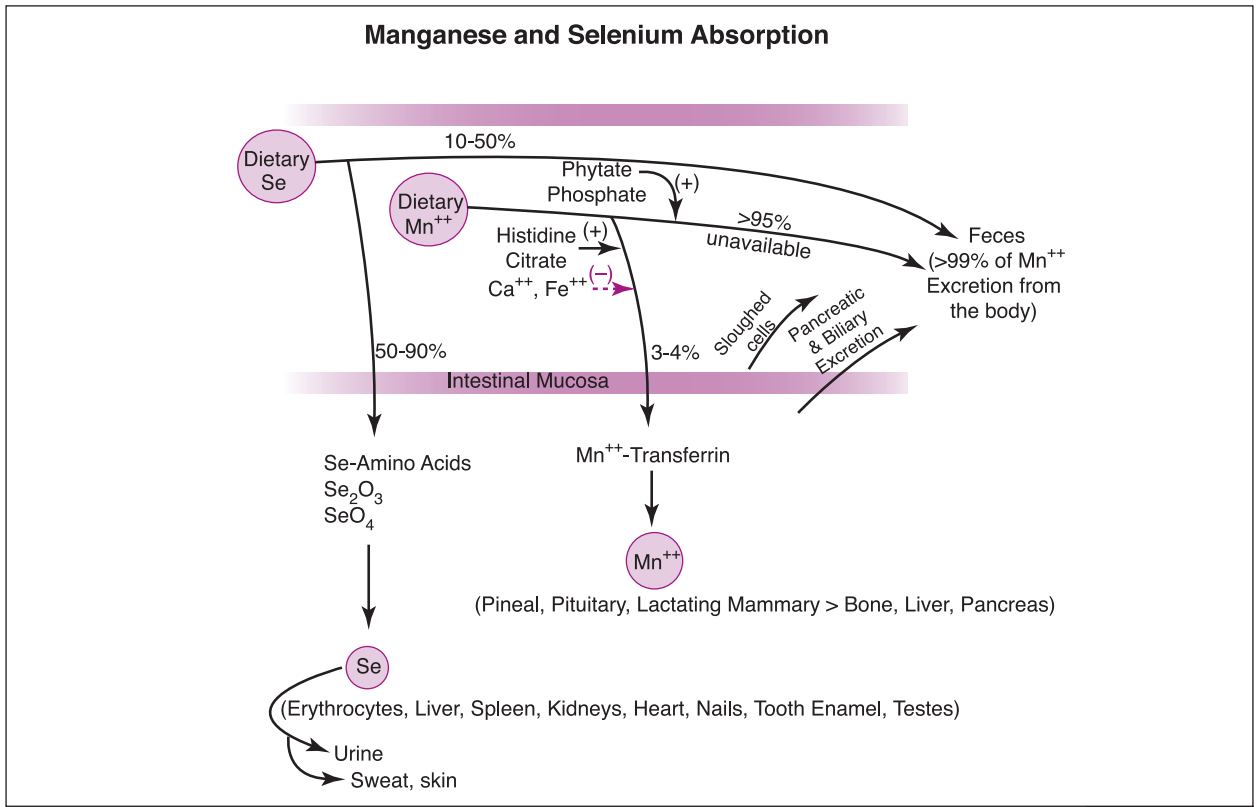


Figure 51-1

the terminal enzyme in urea production found in the cytoplasm of liver cells, also contains Mn^{++} (see Chapter 10). Other cytosolic Mn^{++}-containing enzymes are involved in the **hexose monophosphate shunt**, **glycolysis** (e.g., hepatic glucokinase; see Chapter 22), and **serine metabolism** (hydroxymethyl-transferase). This trace element is also associated with some of the enzymes of mucopolysaccharide, glycoprotein, and lipo-polysaccharide production, including **galactose transferase** and other membrane-bound glycosyltransferases. Manganese deficiency has negative effects on the production of **hyaluronic acid**, **chondroitin sulfate**, **heparin**, and other forms of mucopolysaccharide that are important for growth and maintenance of connective tissue, cartilage, and bone metabolism (see Chapter 19). Reports also indicate that Mn^{++} is involved with γ-carboxylation of the glutamate side chains of certain vitamin K-dependent proteins involved in blood clotting (see Chapter 47).

The connection between Mn^{++} and bone metabolism in rats indicates that both **osteoblastic** and **osteoclastic** activities are reduced in Mn^{++}-deficiency, resulting in osteoporosis and osteopenia (reduced bone cell number). Manganese also appears to be involved in melanin and dopamine production, in lipid biosynthesis (i.e., acetyl-CoA carboxylase), and in the formation of membrane phosphatidylinositol. Manganese deficiency can cause hypocholesterolemia, which may be due to a need for Mn^{++} by cholesterolgenic enzymes. It is also associated with nucleic acids, and, as indicated above, a portion is present in the mineral compartment of bone.

Selenium (Se)

Selenium is an essential component of **glutathione peroxidase**, a rather ubiquitous enzyme in mammalian tissues, that plays a role in the detoxification of peroxides and free radicals (see Chapter 30). These peroxides and free radicals can exert damaging effects on cell membranes of erythrocytes, hepato-

cytes, and other tissues in Se deficiency. While **vitamin E** appears to be the first line of defense against peroxidation of unsaturated fatty acids contained in cell membrane phospholipids, **catalase** and **glutathione peroxidase** constitute the second line of defense (see Chapter 46).

The chemistry of Se appears, in some regards, to resemble that of **sulfur**. Glutathione peroxidase is a 4-subunit enzyme with one Se per subunit in the form of **Se-cysteine**, required for activity. Other mammalian proteins containing Se-cysteine include 3 in the testes involved with spermatogenesis, and a **deiodinase** found in many thyroid hormone target cells that converts tetraiodothyronine (T_4) to the more active triiodothyronine (T_3) (**Table 51-3**). It is possible that Se-methionine, the main form of Se in plants, is sometimes incorporated into mammalian proteins in place of sulfur-containing methionine, and this insertion may be random and nonspecific.

From **50-90%** of dietary Se can be **absorbed** from the small intestine, with plant sources making it more readily available. Once absorbed, the highest tissue concentrations are found in erythrocytes, the liver, spleen, kidneys, heart, nails, tooth enamel, and the testes (see **Fig. 51-1**). Unlike Mn^{++}, Se is lost from the body primarily via urine in the form of di- and trimethylselenonium compounds.

Soils, and therefore their pastures, vary widely in their Se content. In general, soils derived from rocks of recent origin (e.g., the granitic and pumice sands of New Zealand), are notably Se deficient, as are soils in Finland, England, parts of Australia and China, and in the Pacific northwest and eastern seaboards of the USA. Alkaline soil encourages plants to absorb Se, yet a high sulphur content competes for absorption sites with Se in both plants and animals. The Se content of pastures is usually lowest in the spring when rainfall is heavy.

Table 51-3

Selenium-Dependent Processes

Cell membrane protection
Peroxide detoxification
Conversion of T_4 to T_3
Retard tumor development
Spermatogenesis

Selenium Deficiency

Both **vitamin E deficiency** and **Se deficiency** lead to nutritional muscular degeneration (i.e., **white muscle disease**; see Chapter 46). Additional symptoms of Se deficiency are included in **Table 51-4**. Within the past few years there has been increasing interest in the role of deficiencies of specific nutritional components in the etiology of myocardial cell destruction. The most important of these appears to be the amino acid **taurine** (see Chapters 3 and 62), and **carnitine**, the compound required to shuttle long-chain fatty acids across mitochondrial membranes (see Chapter 55). Vitamin E deficiency and Se deficiency are also associated with acute **myocardial necrosis** in farm animals, as well as in experimental dogs. There may also be other connections between Se deficiency and cardiovascular disease. The mechanism may involve increased aggregability of platelets and production of thromboxane A_2 (TXA_2), with less production of prostacyclin (PGI_2) from vascular endothelial cells (see Chapters 68 and 69 for more information on the functions of these eicosanoids). Heavy neonatal mortality in farm animals, chronic diarrhea in calves, infertility due to fetal resorption in ewes, and dietetic hepatosis in swine are complications that reportedly respond to dietary supplementation with this element.

Lastly, the possibility that adequate Se intake may prevent or retard tumor formation indicates a need for an optimal Se intake in both humans and animals.

Table 51-4
Selenium

Se-Deficiency Symptoms	Se-Toxicity Symptoms
Growth retardation	"Blind Staggers" or "Alkali
Cataract formation	Disease" in ruminant animals
Decreased spermatogenesis	Neurological damage
Placental retention	Rough hair
Myositis	Alopecia
Muscular degeneration	Hoof abnormalities
Cardiomyopathy	GI Disorders

Selenium Toxicity

Selenium poisoning can occur in areas where soils are derived from particular rock formations containing a high content of Se. It has been recorded in certain areas of North America, Ireland, Israel, Canada, and parts of Australia and South Africa. Acute Se-toxicity is known colloquially as "**blind staggers,**" because affected animals appear to be blind, wander aimlessly (often in circles), and display head pressing. The appetite may be depraved, with abdominal pain evident. The terminal stage is one of paralysis with death due to respiratory failure. Essentially the same picture can be produced by the experimental oral dosing of sheep with sodium selenite. Chronic poisoning ("**alkali disease**"), is reportedly manifested by dullness, emaciation, lack of vitality, stiffness, and lameness. In cattle, horses, and mules, the hair at the base of the tail and switch is lost, and in pigs there may be general alopecia. There are also hoof abnormalities, with deformity or separation and sloughing of the hooves reported in several species. Newborn animals whose dams have received diets containing an excess of Se may also be born with congenital hoof deformities.

In summary, Mn^{++} and Se are two important dietary trace elements associated with several metabolic processes. However, since Mg^{++} can substitute for Mn^{++} in many of these processes, Mn^{++} deficiency symptoms are uncommon. In contrast, dietary Se deficiency can lead to significant muscular degeneration as well as other debilitating conditions.

Manganese is considerably less abundant than other divalent cations in the body, and is absorbed from the digestive tract at a rather low efficiency. Both Mn^{++} and Mg^{++} serve as cofactors for several different types of enzymes, particularly **carboxylases** and **decarboxylases.**

Selenium is an essential component of **glutathione peroxidase,** a rather ubiquitous enzyme that participates in the detoxification of peroxides and free radicals, it is a component of the **deiodinase** that converts thyroxine (T_4) to its more active form (T_3), it is a component of three different enzymes involved in **spermatogenesis,** and it may retard tumor development. In contrast to the low intestinal absorption efficiency of Mn^{++} (3-4%), the absorption efficiency of Se is quite high (50-90%). While Se is lost from the body primarily via urine, most Mn^{++} exits the body in feces. Selenium poisoning may occur in areas of the world where soils are rich in this trace element, and affected animals may exhibit classic symptoms of "blind staggers." This syndrome, also known as "alkali disease," occurs because alkaline soils encourage plants to absorb Se at a high rate.

OBJECTIVES

- Compare the normal intestinal absorption efficiency of Mn^{++} to that of Fe^{++}, and identify factors that could enhance or hinder Mn^{++} absorption.
- Identify the second most abundant intracellular cation, and explain its relationship to Mn^{++}.
- Explain how Mn^{++} is transported in plasma, identify tissues containing the most Mn^{++}, and indicate how Mn^{++} usually exits the organism.
- Show how Mn^{++} and ATP are structurally related, and discuss the involvement of Mn^{++} and/or Mg^{++} in cytoplasmic and mitochondrial energy metabolism.
- Summarize the Mn^{++}-dependent processes of the body, and recognize the signs and symptoms of Mn^{++} deficiency.
- Indicate how Se is involved in peroxide and free radical detoxification (see Chapters 30 & 46).
- Contrast the efficiency of intestinal Se absorption to that of the other trace elements, and identify areas of the world where Se-deficient and Se-rich soils exist.
- Compare signs and symptoms of Se deficiency to those of vitamin E, and recognize the causes and effects of "blind staggers," or "alkali disease."

QUESTIONS

1. Which one of the following divalent cations is known to substitute for Mn^{++} in many of its various enzyme-related activities?

a. Ca^{++}
b. Fe^{++}
c. Cu^{++}
d. Zn^{++}
e. Mg^{++}

2. Which one of the following is a Mn^{++}-dependent process?

a. Ear otolith development
b. Peroxide detoxification
c. Conversion of T_4 to T_3
d. Spermatogenesis
e. Retard tumor development

3. Most Mn^{++} is normally excreted from the body through:

a. Feces.
b. Urine.
c. Respiration.
d. Sweat.
e. Hair loss.

4. Which one of the following is a Mn^{++}-deficiency symptom?

a. Growth retardation
b. Cataract formation
c. Decreased mucopolysaccharide production
d. Placental retention
e. Cardiomyopathy

5. Selenium is an essential component of:

a. Catalase.
b. Vitamin E.
c. Vitamin C.
d. Glutathione peroxidase.
e. Superoxide dismutase.

6. Select the TRUE statement below regarding selenium (Se):

a. Acidic soil encourages plants to absorb Se.
b. Se-deficiency causes "blind staggers" in farm animals.
c. Spermatogenesis is a Se-dependent process.
d. Se-toxicity is associated with cataract formation.
e. Se-deficiency is associated with hoof abnormalities.

7. Selenium chemistry resembles that of:

a. Manganese.
b. Sulfur.
c. Zinc.
d. Copper.
e. Cobalt.

8. Most Se is normally excreted from the body through:

a. Feces.
b. Urine.
c. Sweat.
d. Hair loss.
e. Respiration.

Answers

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