Chapter 48

Iron

Overview

- Iron is the most abundant trace element in mammalian organisms.
- The principal function of iron in the body involves oxygen transport.
- Only 3-6% of the iron present in the diet is normally absorbed by the intestine.
- Iron absorption is an active process, with most absorption occurring in the upper part of the small intestine.
- Cobalt, zinc, copper, and manganese compete, somewhat, with iron for intestinal absorption.
- Unless bleeding occurs, iron is not easily excreted from the body.
- Iron, which is continually interconverted between the ferric and ferrous state, can cause free radical formation.
- Iron toxicity results in pancreatic and liver damage, which is exacerbated in vitamin E deficiency.
- Young, fast-growing animals are vulnerable to iron deficiency.
- Most metalloflavoproteins contain iron.

Trace Elements

The mammalian organism normally contains and incorporates most all of the elements in the periodic table. The twenty-six most important can be subdivided into "**macrominerals**" (i.e., minerals required in comparatively large amounts in the diet), "**trace elements**" (i.e., microminerals), and "**ultra trace elements**" (those that are almost undetectable in body fluids and tissues; **Table 48-1**). Each trace element is physiologically important, with symptoms of both deficiency and toxicity occurring. Among the ultra trace elements, **lead** and **arsenic** toxicities are most frequently encountered in animals.

The trace elements are known to be essential for good health and reproduction, and each has well-defined actions. For example, they may serve as cofactors in enzymatic reactions, components of body fluids (electrolytes), sites for binding of oxygen (in transport), and structural components of nonenzymatic macromolecules. Although exceptions exist, most tend to concentrate in the germ of seeds and grains, where the highest concentrations of the B-complex vitamins are found. A discussion of the metabolism of each trace element can be found in the following five chapters, with many of their interactions, relations to disease, deficiency, and toxicity symptoms identified.

Iron (Fe)

Iron is the most abundant trace element in mammalian organisms, and one of the two most abundant in nature. Approximately **70%** of that present in the body is normally asso-

Table 48-1

Common Elements of the Body

Macrominerals	Trace Elements	Ultra Trace Elements
Calcium (Ca)	Iron (Fe)	Chromium (Cr)
Phosphorus (P)	Zinc (Zn)	Fluorine (F)
Magnesium (Mg)	Copper (Cu)	Nickel (Ni)
Sodium (Na)	Manganese (Mn)	Boron (B)
Chloride (Cl)	Selenium (Se)	Molybdenum (Mo)
Potassium (K)	Iodine (I)	Arsenic (As)
Sulfur (S)	Cobalt (Co)	Vanadium (V)
		Bromine (Br)
		Silicon (Si)
		Lead (Pb)
		Lithium (Li)
		Tin (Sn)

ciated with hemoglobin (Hb; see Chapter 32). Lesser amounts are associated with the heme-containing **cytochromes** and **iron-sulfur proteins** of electron transport (see Chapter 36), and the enzymes of hepatic drug metabolism (i.e., those involving the **cytochrome P_{450} system**). Also, the widely distributed enzyme of DNA synthesis (**ribonucleoside diphosphate reductase (RDR)**) contains iron (see Chapter 16), as do several enzymes involved in the metabolism of biogenic amines (e.g., **tyrosine** and **tryptophan hydroxylases** that initiate formation of DOPA and serotonin, respectively). The **myeloperoxidase** of leukocytes is an iron-containing enzyme involved in bacterial killing, and the liver heme enzymes, **catalase** and **tryptophan oxygenase**, also contain iron. Many flavoprotein enzymes contain either molybdenum or iron as essential cofactors. These **metalloflavoproteins** are widespread, and participate in many important oxidation/reduction reactions (see Chapter 40).

Although **70%** of iron in the body is associated with **Hb**, highly variable amounts are associated with **ferritin**, a multisubunit protein present in all cells, but especially those of the liver, spleen, and bone marrow. Another **3-5%** is bound to muscle **myoglobin**, **hemosiderin** (a granular protein-iron complex and breakdown product of ferritin), and the heme-containing **cytochromes** (**Fig. 48-1**). Most iron in plasma is transported bound to a β_1-globulin known as **transferrin**, or **siderophilin**. The movement of

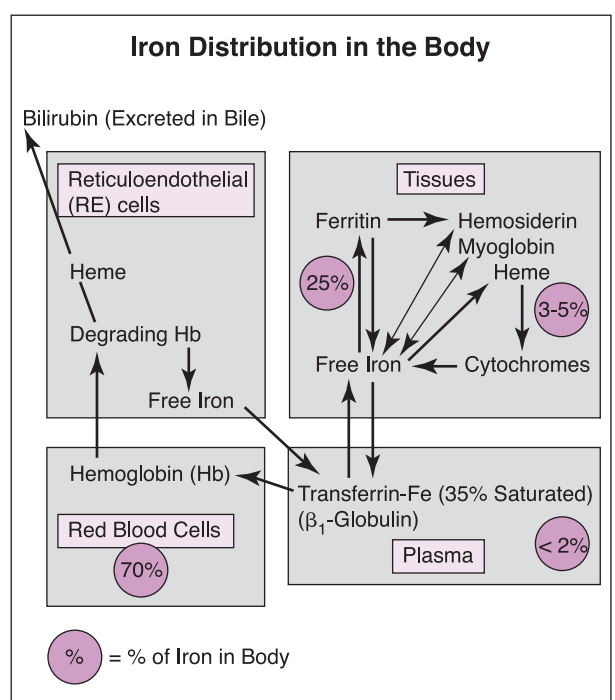

Figure 48-1

iron from hepatic storage sites to transferrin involves **ceruloplasmin**, a protein which carries about 60% of Cu^{++} in plasma (see Chapter 50). Normally, transferrin is about 35% saturated with iron. When heme is degraded to bilirubin by reticuloendothelial cells, the iron is normally recycled (see Chapter 33).

From its association with these specific proteins, it is clear that the principal functions of iron in the body involve **oxygen transport** within blood and muscle, and **electron transfer** in relation to energy metabolism. It is also intimately involved in **cell proliferation**, the production and disposal of **oxygen radicals** (and hydrogen peroxide (H_2O_2); see Chapter 30), systemic **hormone action**, and in some aspects of **immune defense**.

Iron has the capacity to accept and donate electrons readily, interconverting between the **ferric** (**Fe^{+++}**) and **ferrous** (**Fe^{++}**) states. This capability makes it a useful component of cytochromes, oxygen-binding molecules (e.g., Hb and myoglobin), and many enzymes. However, iron can also damage tissues by catalyzing conversion of **H_2O_2** to **free-radicals** that attack cell membranes, proteins, and DNA. Organisms generally have difficulty excreting iron from the body, and therefore deal with this problem by tightly regulating the iron concentration of their internal fluids (through protein sequestration), and by carefully controlling iron absorption from the intestinal tract.

The amount of ingested iron absorbed from the gut ranges normally from about **3-6% of the amount ingested**. Iron is more readily absorbed in the ferrous state, but most dietary iron is in the ferric form. No more than a trace of iron is normally absorbed in the stomach, but gastric **HCl** helps to dissolve iron from bound protein so that it can be absorbed by the small intestine. The importance of this function is indicated by the fact that iron deficiency anemia is a troublesome and frequent complication of partial gastrectomy. **Ascorbic acid** (**vitamin C**) and other reducing agents in the diet also help to facilitate conversion of iron from the ferric to ferrous state (see Chapter 39).

Heme is also absorbed by the small intestine using an **HCP-1** transporter (not shown in **Fig. 48-2**), and the Fe^{++} that it contains is released inside mucosal cells. Other dietary factors, such as **phytic acid**, **phosphates** and **oxalates**, can reduce iron availability by forming insoluble compounds with it. Pancreatic juice, because of its alkaline nature, also tends to reduce iron absorption.

Iron absorption is an active process, with most absorption occurring in the **upper part of the small intestine**. Other mucosal cells can transport iron, but the duodenum and adjacent jejunum contain most of the carriers. **Cobalt**, **Zn^{++}**, **Cu^{++}**, and **Mn^{++}** appear to **compete**, somewhat, with **Fe^{++}** for intestinal absorption (see Chapters 49-52).

Iron must cross two membranes to be transferred across the absorptive epithelium of the small intestine (**Fig. 48-2**). Each transmembrane transporter is coupled to an enzyme that changes the oxidation state of iron. The **apical transporter** has been identified as **DMT-1**, and acts in concert with a recently identified **ferric reductase**. The **basolateral transporter** requires **hephaestin**, a **ferroxidase-type** protein that converts iron back to the ferric state.

The erythropoietic factor that regulates iron absorption is thought to be **erythropoietin** (**EPO**), a glycoprotein hormone of 165 amino acids. Erythropoietin blood levels rise in such conditions as anemia or pregnancy, and its half-life in the circulation is about 5 hours. This hormone also stimulates the bone marrow to produce red cells, however, it takes about 2-3 days to realize this effect since red cell maturation is relatively slow. In adult animals, about 85% of EPO originates from the kidneys (endothelial cells of peritubular capillaries), and 15% from the liver. During fetal life, the major site of both EPO and red cell production is the

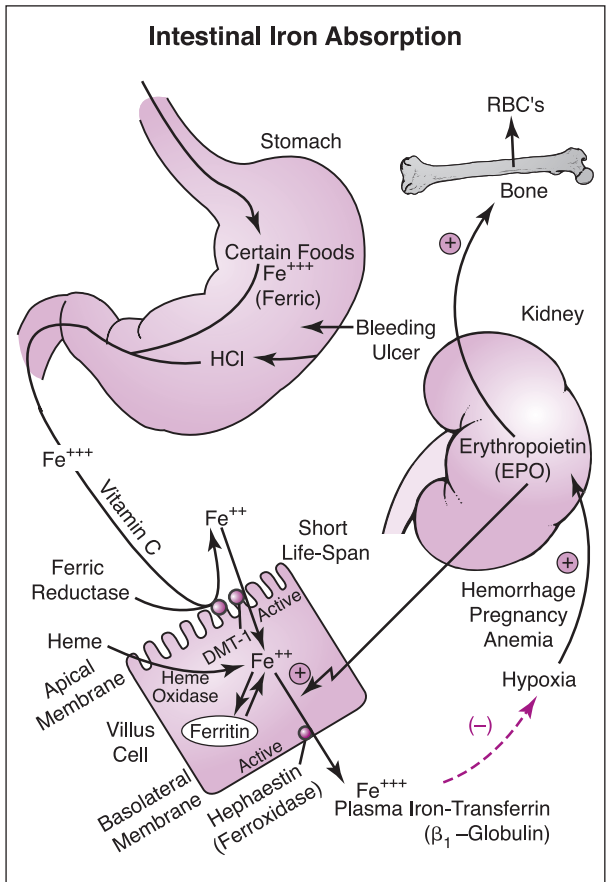

Figure 48-2

liver. However, in some forms of adult kidney disease, the liver cannot compensate for loss of EPO synthesis, and anemia develops.

Iron Toxicity

If more iron is absorbed than excreted, **iron overload** results. Large ferritin and hemosiderin deposits are associated with **hemochromatosis**, a syndrome characterized by pigmentation of the skin, pancreatic damage with diabetes ("**bronze diabetes**"), cirrhosis, a high incidence of hepatic carcinoma, and gonadal atrophy. Hemochromatosis can be produced by prolonged, excessive iron intake, as well as by a congenital disorder in which the mucosal regulatory mechanism behaves as if iron deficiency were present, and absorbs iron at a high rate ("idiopathic hemochromatosis"). Hereditary hemochromatosis is, unfortunately, a common genetic disorder of humans.

Chelated iron in concentrations of 0.1 to 15% can be found in some commercial plant foods, and iron supplements are frequently present in the home. Although low levels of Fe^{+++} can be found in bile, pancreatic juice, and urine, it should be noted that **a distinctive feature of iron metabolism is the absence of a specific mechanism for iron excretion from the body (unless bleeding occurs)**.

Iron Deficiency

Iron-deficiency anemia is an important syndrome in many animals leading to weakness and lethargy due to decreased O_2 transport to tissues. It can result from dietary deficiency of absorbable iron, or from chronic blood loss through parasitism or hemorrhage. Blood that is reabsorbed from a body cavity or tissue pocket typically recycles the iron.

Young, fast-growing animals are particularly vulnerable to iron deficiency since they have a high demand for iron-containing compounds, and lack reserves. A major contributing factor is the low level of iron in milk, although colostrum is normally high in this mineral. For example, **piglets** housed in buildings that allow no access to earth usually require supplemental iron if anemia is to be avoided, but iron toxicity can result, especially if vitamin E deficiency coexists. Numerous gastrointestinal disturbances are also associated with iron deficiency, where there is an increased incidence of diarrhea and malabsorption.

In summary, iron has the capacity to readily interconvert between the ferric and ferrous states, which makes it a valuable component of the cytochromes and O_2 -binding molecules. Seventy percent of that in the body is usually associated with Hb, with the remainder associated with myoglobin, ferritin and transferrin, and with various enzymes and heme-containing molecules. The amount of iron absorbed from the digestive tract is normally about 3-6% of that injested, and following absorption this

trace element is highly conserved and reutilized. Excessive iron absorption results in **hemochromatosis**, and iron deficiency results in **anemia**.

OBJECTIVES

- Describe all steps involved in intestinal iron absorption, discuss the control and efficiency of this process, and identify the ways in which iron circulates in blood.
- Discuss the quantitative and qualitative partitioning of iron in various pools of the body.
- Identify relationships between iron and NDP reduction, and between iron and catecholamine biosynthesis (see Chapters 16 & 39).
- Show how the copper-binding protein, ceruloplasmin, is involved with iron transport.
- Understand iron's involvement in the production and disposal of free radicals, and in O_2 transport and electron transfer (see Chapters 30, 32 & 36).
- Recognize the trace elements that compete with iron for intestinal absorption.
- Compare intestinal iron efficiency to that of other trace elements, and understand why hemochromatosis is a common human genetic disorder.
- Contrast iron-deficiency anemia to other causes of anemia.

QUESTIONS

1. Approximately what percentage of iron ingested is normally absorbed by the intestine?
a. 5%
b. 28%
c. 50%
d. 70%
e. 95%

2. The apical transporter for iron in the small intestine:
a. Is known as hephaestin.
b. Will transport iron only in the ferric (Fe^{+++}) state.
c. Is a ferroxidase.
d. Is known as ferritin.
e. Acts in concert with a ferric reductase.

3. Most iron in plasma is normally:
a. Bound to albumin.
b. Bound to myoglobin.
c. Bound to transferrin.
d. Filtered by the kidneys.
e. Contained in the cytochromes.

4. Select the TRUE statement below regarding iron:
a. Hemochromatosis is a form of iron-deficiency anemia.
b. A distinctive feature of iron metabolism is the absence of a specific mechanism for excretion from the body.
c. Intestinal iron absorption is largely a passive process.
d. Iron is normally excreted from the body as a component of bilirubin, a heme decomposition product.
e. The majority of iron in plasma is normally bound to erythropoietin.

5. The principal function of iron in the body involves:
a. Acid/base balance.
b. Blood pressure regulation.
c. Lipoprotein clearance from the circulation.
d. Oxygen transport.
e. Insulin biosynthesis and release.

6. Which one of the following is a macromineral?
a. Iron
b. Vanadium
c. Phosphorus
d. Zinc
e. Cobalt

7. Approximately what percentage of iron in the body is normally associated with hemoglobin?
a. 5%
b. 28%
c. 50%
d. 70%
e. 95%

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