Chapter 39

Vitamin C

Overview

- Vitamin C is a powerful reducing agent that participates in several important hydroxylation reactions.
- Na^{+}-coupled transporters help to facilitate entry of vitamin C into cells.
- Glial cells in the brain regenerate vitamin C from DHA.
- Vitamin C is needed for collagen, carnitine, catecholamine, and bile acid biosynthesis.
- Oxalate is a natural degradation product of vitamin C.
- Vitamin C uses Fe^{++} and Cu^{++} as cofactors, and it enhances intestinal Fe^{++} absorption.
- Vitamin C deficiency can result in "scurvy."
- Although most mammals can synthesize vitamin C from glucose, it cannot be formed in primates, fish, flying mammals, songbirds, or the guinea pig.
- Vitamin C is a natural preservative added to pet food products.

Water-soluble Vitamins

Vitamins are structurally unrelated organic compounds that function in small amounts as metabolic catalysts, usually in the form of coenzymes. **Water-soluble vitamins**, such as **vitamin C** (**ascorbate**) and the **B-complex vitamins**, are produced by plants and microorganisms; however, most are not synthesized at all or in sufficient amounts by animals to satisfy tissue requirements. Only modest stores of these vitamins are normally available in the mammalian organism, therefore, they need to be routinely supplied from food, fluids, or microorganisms inhabiting the digestive tract.

Vitamin C (Ascorbate)

"**Scurvy**", a **vitamin C deficiency** disease known since ancient times, was a particular problem for sailors in the 15th-19th centuries, who's diets were often less than adequate on the long voyages they endured. These men would develop swollen legs blotched with capillary hemorrhages, decaying peeling gums with loose teeth, decreased capacity to heal wounds, depression, anemia, and fatigue. **Infantile scurvy** (also known as **Barlow's syndrome or disease**), is associated with similar symptoms.

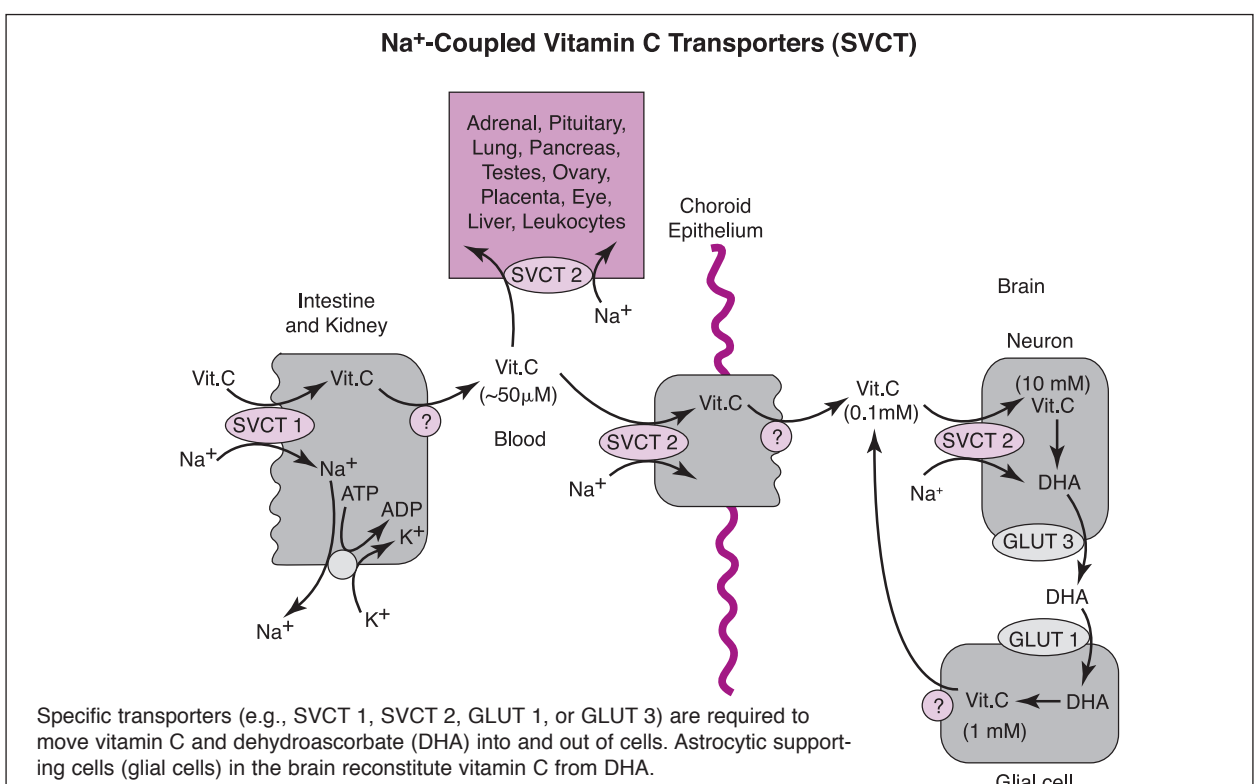
Although most vertebrates can synthesize vitamin C from glucose (see Chapter 29), it cannot be formed in **primates**, **fish**, **flying mammals**, **songbirds**, or the **guinea pig**. Therefore, these animals require it in their diet. This vitamin is found in both plant and animal foods, but is particularly prevalent in fruits and vegetables. Some bacteria also synthesize ascorbate.

Regardless of whether vitamin C is derived through the diet or from biosynthesis in liver (as in **rodents**), or the kidneys (as in **reptiles**),

specific transport mechanisms are required to move it into dependent tissues (**Fig. 39-1**). Ascorbate enters cells via **Na^+-coupled vitamin C transporters** (**SVCT 1** or **SVCT 2**), and cellular efflux occurs by as yet undescribed mechanisms. The oxidized form of vitamin C (i.e., **dehydroascorbate (DHA)**; **Fig. 39-2**), is thought to exit and enter cells via glucose transporters (**GLUT 3** and **GLUT 1**, respectively; see Chapter 22). In the CNS, **glial cells** (i.e., astrocytic supporting cells) **regenerate vitamin C** from **DHA** via **reduced glutathione** (**GSH**) oxidation, and then vitamin C is transported back into neurons (see Chapter 90). Neurons exhibit a high level of oxidative metabolism, and thus require protection by this important water-soluble vitamin.

At the molecular level, ascorbate is a **powerful reducing agent**, like the fat-soluble **vitamin E** (Chapter 46), and as such possesses general importance as an antioxidant, thus affecting the body's "redox" potential (i.e., the relative states of oxidation/reduction of other water-soluble substances inside and outside of cells). It is used as a natural **preservative** in pet food products, and is sometimes given to **cats** as a treatment to reverse the **methemoglobinemia** associated with **acetaminophen toxicity** (see Chapters 29 and 30). The physiologic importance of vitamin C as an antioxidant has been documented in **pond turtles**, which possess particularly high concentrations of vitamin C in the **brain** (Rice ME, et al, 1995). These animals exhibit a high tolerance for O_2 depletion during **diving**, and vitamin C may help to prevent oxidative damage to neurons during the reoxygenation period following a hypoxic dive.

Other notable reactions involving ascorbate include **hydroxylations** using molecular oxygen (O_2), that also use either **Fe^{++}** or **Cu^{++}** as a cofactor (**Table 39-1**). Here, ascorbate is thought to play either of two roles: **1**) as a direct source of electrons for the reduction of



Specific transporters (e.g., SVCT 1, SVCT 2, GLUT 1, or GLUT 3) are required to move vitamin C and dehydroascorbate (DHA) into and out of cells. Astrocytic supporting cells (glial cells) in the brain reconstitute vitamin C from DHA.

Figure 39-1

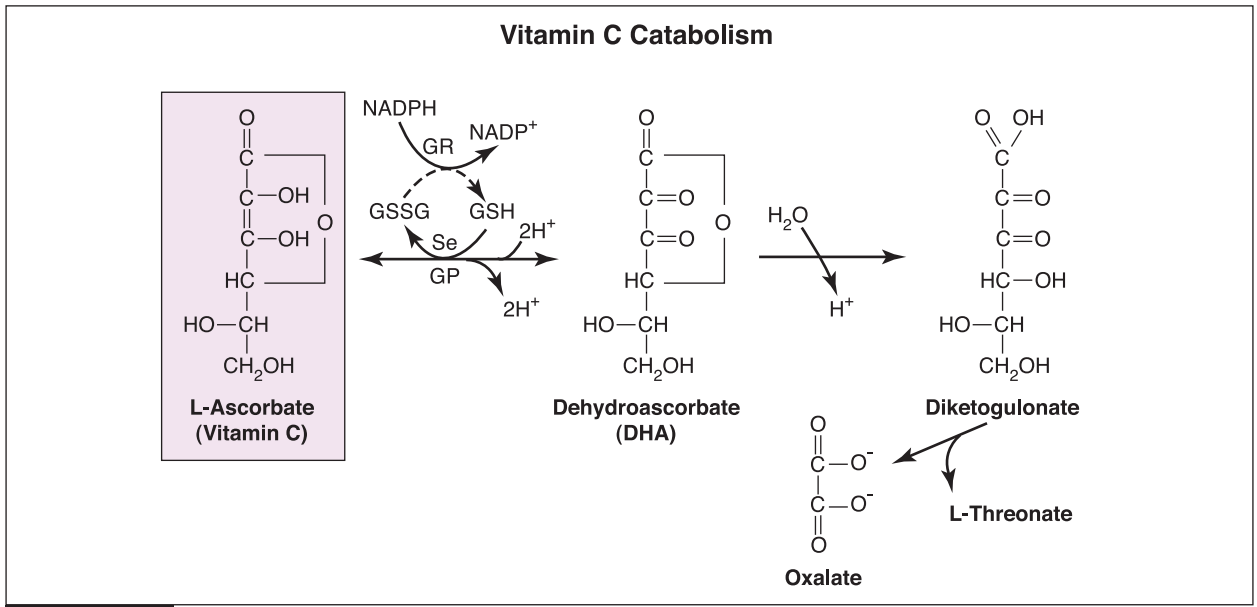


Figure 39-2

O_2 (e.g., as a cosubstrate), or **2**) as a protective agent for maintaining **Fe^{++}** or **Cu^{++}** in their reduced states. Particularly important are hydroxylations involving **hydroxyproline** and **hydroxylysine** formation during collagen biosynthesis in **connective tissue** (primarily in bone and ligaments, **Fig. 39-3** and Chapter 3). The formation of collagen is important during growth and development, when collagen fibers are constantly being laid down and also removed. Once physical maturity is achieved, there is relatively little collagen turnover (one of the few proteins in the body for which this may be said). An exception is healing from

Table 39-1

Actions of Vitamin C

- Powerful reducing agent ("Antioxidant").
- Enhance intestinal Fe^{++} absorption.
- Reduce cataract formation.
- Enhance leukocyte activity.
- Participate in Cu^{++}-dependent amidation reactions in polypeptide hormone biosynthesis (e.g., GH, CT, and MSH).
- Participate in the amidation of C-terminal glycine residues in the brain by Cu^{++}-dependent enzymes.
- Act as a carrier of sulfate groups in glycosaminoglycan formation (the "ground substance" between cells in all organs).
- Participate in hydroxylation reactions using O_2 (with Fe^{++} or Cu^{++} as cofactors).
  a. Hydroxyproline and hydroxylysine formation during collagen biosynthesis.
  b. Carnitine biosynthesis from lysine and S-adenosylmethionine.
  c. Dopamine hydroxylation during catecholamine biosynthesis.
  d. Hydroxylation of steroid hormones, aromatic drugs, and carcinogens in liver microsomes.

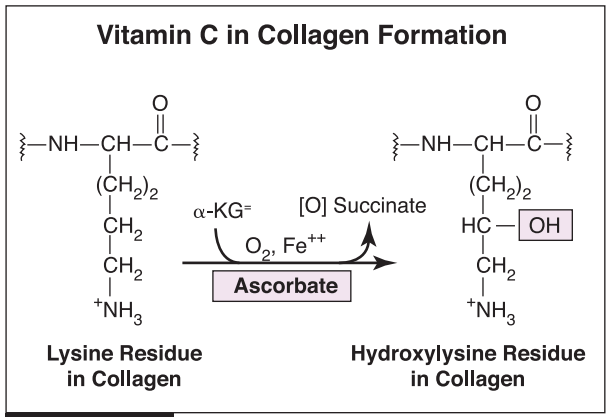


Figure 39-3

tissue injury and scar formation.

Ascorbate has a secondary function in connective tissue metabolism as a carrier for sulfate groups needed in **glycosaminoglycan** formation (chondroitin sulfate, dermatan sulfate, etc.; see Chapter 29). These compounds help to form the gel matrix (or "**ground substance**") between cells in all organs. There would seem to be an obvious connection between these needs for ascorbate in connective tissue metabolism, and the basic symptoms of **scurvy** above.

Although vitamin C supplementation is not considered to be essential in dogs, megadoses of ascorbate fed to the bitch during pregnancy, and provided to the offspring until young adulthood, have been associated with reducing the incidence of **canine hip dysplasia** in animals considered genetically at risk for this condition.

Ascorbate is also used in the biosynthesis of **carnitine** from lysine and S-adenosylmethionine (see Chapters 55 and 57). Carnitine is involved in the transport of long-chain fatty acids across mitochondrial membranes.

Ascorbate is active in **hepatic microsomal drug metabolism**. Both endogenous and exogenous **steroids** are hydroxylated and conjugated in the liver, as are certain nonsteroidal drugs (e.g., barbiturates) and suspected carcinogens. The resulting hydroxylation makes these compounds more water-soluble, and thus more likely to be excreted from the body through bile or urine. For example, the first step in hepatic **bile acid** formation from cholesterol (7-α-hydroxycholesterol formation; see Chapter 62) is activated by vitamin C, and **guinea pigs** exhibiting ascorbate deficiency decrease their biliary excretion of bile acids. It has also been shown that rats exposed to toxic polychlorinated biphenyls (PCBs) greatly increase their need for vitamin C.

This vitamin is also concentrated in **leukocytes**. Deficiencies in leukocyte ascorbate concentrations have been reported in some diabetics, leading to a decreased capacity for wound repair and response to infection. Indeed, the enhanced response of neutrophils to chemotactic stimuli, and enhanced proliferation of lymphocytes in response to mitogens, may be related to their vitamin C content. The ascorbate in leukocytes may prevent autoxidation of the oxygen-radical forming system integral to their function, as well as modulate their production of leukotrienes (see Chapters 68 and 69). A propensity for **cataract** formation has also been linked to low ascorbate (and vitamin E) bioavailability, perhaps from a relative lack of reducing equivalents. Ascorbate is normally concentrated in the aqueous humor (see **Fig. 39-1**).

Ascorbate also plays an important role in **biogenic amine** (i.e., **catecholamine**) biosynthesis in the **adrenal medulla**, **central** (**CNS**), and **sympathetic** (**SNS**) **nervous systems** (**Fig. 39-4**). Indeed, the highest concentrations of this vitamin are usually found in these locations. Vitamin C serves as a cosubstrate in the **hydroxylation of dopamine to norepinephrine**, catalyzed by the enzyme **dopamine β-hydroxylase**. Catecholamines are associated with the ability of animals to deal with stress, and they help to mobilize glycogen and triglyceride for energy purposes (see Chapter 23 and 70).

Vitamin C has also been found to participate in Cu^{++}-dependent amidation reactions in **poly-**

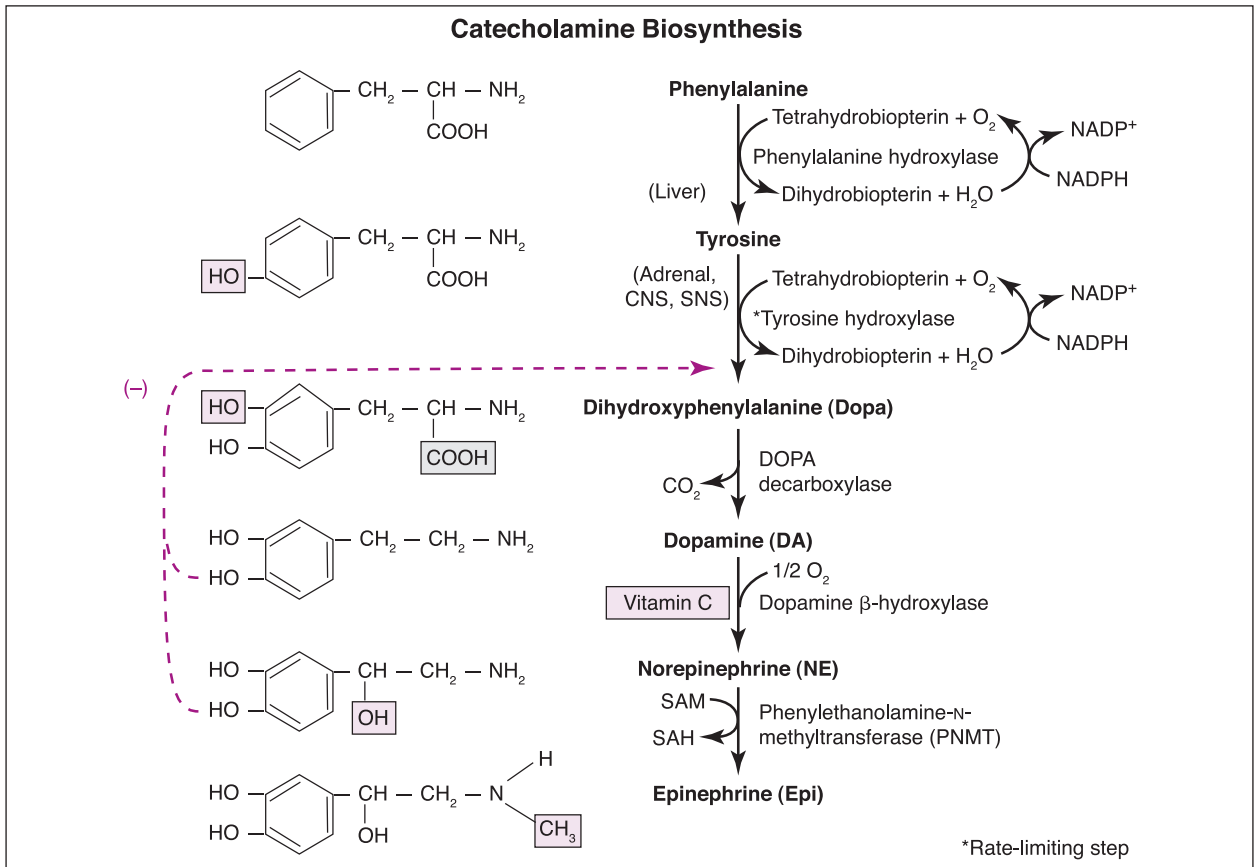


Figure 39-4

peptide hormone biosynthesis (e.g., growth hormone (GH), calcitonin (CT), and melanocyte stimulating hormone (MSH)), and it may be necessary for the evocation of increased numbers of cell surface **acetylcholine receptors** by muscle cells responding to nerve stimuli. This vitamin plays a role in Fe^{++} metabolism, by enhancing conversion of dietary iron from the **ferric** (**Fe^{+++}**) to **ferrous** (**Fe^{++}**) state. Since iron is more readily absorbed from the intestine in the **Fe^{++}** state, vitamin C helps to facilitate its absorption (see Chapter 48). Ascorbate may also be involved in the mobilization of stored Fe^{++}, especially from hemosiderin in the spleen. While a modest intake of vitamin C may be beneficial, excessive intake has a propensity to cause iron overload (i.e., **hemochromatosis**), which can be debilitating.

The capacity of this vitamin to **chelate Ca^{++}** may mean it has a function as well in bone mineral metabolism. In this regard, animal experiments point to a role for this vitamin in **tooth formation**. In dog breeds predisposed to **Cu^{++} hepatotoxicosis** (e.g., Bedlington terriers), discouraging intestinal absorption of Cu^{++} through chelation has been attempted with high oral doses of vitamin C (see Chapter 50). Results of these studies, however, have not been encouraging.

A major pathway of ascorbate catabolism is to **oxalate** (see **Fig. 39-2**). It has been estimated that under normal circumstances, approximately one-third of **urinary oxalate** may be derived from ascorbate catabolism. Large doses of vitamin C (ascorbic acid) will enhance urine acidity, which promotes conversion of urate into **uric acid**, and **oxalate** into **oxalic acid**. Vitamin C overload could also promote formation of **calcium oxalate** kidney stones in susceptible animals.

OBJECTIVES

- Compare the action of intestinal SVCT 1 to that of SGLT 1 (see Chapter 38).
- Explain how and where vitamin C is oxidized and reduced in the CNS.
- Show how vitamin C is transported across the blood-CSF barrier, and how it is transported into and out of neurons and glial cells of the brain (see Chapter 90).
- Summarize the metabolic actions of vitamin C in the body, and recognize the signs and symptoms of scurvy.
- Identify five important hydroxylation reactions where vitamin C acts as a cofactor.
- Describe the role of vitamin C in intestinal iron absorption.
- Explain the proposed relationship between ascorbate overload and urolithiasis.
- Describe all steps in the biosynthesis of epinephrine from phenylalanine, and include the enzymes, intermediates and cofactors involved.

QUESTIONS

1. Vitamins typically act as _____ in the reactions they participate in?

a. Enzymes
b. Coenzymes
c. Substrates
d. Energy sources
e. Hormones

2. Which one of the following animals cannot synthesize vitamin C from glucose?

a. Horse
b. Rat
c. Dog
d. Guinea pig
e. Goat

3. Vitamin C is known to participate in which reaction type?

a. Carboxylation
b. Dehydration
c. Hydration
d. Hydroxylation
e. Decarboxylation

4. Vitamin C is known to participate in the biosynthesis of all of the following, EXCEPT:

a. Bile acids.
b. Collagen.
c. Epinephrine.
d. Carnitine.
e. Cholesterol.

5. Absorption of which one of the following from the digestive tract is thought to be enhanced by vitamin C?

a. Iron
b. Glucose
c. Amino acids
d. Medium-chain fatty acids
e. Lactate

6. Vitamin C is known to be concentrated in all of the following locations, EXCEPT:

a. Sympathetic, post-ganglionic neurons.
b. Skeletal muscle.
c. Central nervous system.
d. Leukocytes.
e. Adrenal medulla.

7. Which one of the following is a normal degradation product of vitamin C?

a. Oxalate
b. Dopamine
c. Lactate
d. Ascorbate
d. Acetyl-CoA

8. Select the TRUE statement below regarding vitamin C:

a. It cannot be regenerated in the body.
b. It enters cells via Na^+-coupled transporters.
c. It cannot cross the blood-brain-barrier.
d. It donates reducing equivalents directly to the mitochondrial electron transport chain.
e. Large doses of this vitamin will alkalinize the urine.

9. Glutathione (GSH) participates in dehydroascorbate reduction:

a. True
b. False

ANSWERS

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