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Vitamin C in Human Health and Disease

Effects, Mechanisms of Action, and New Guidance on Intake

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Preface

More than 30 years have been passed since I first made vitamin C part of my life. I think it was my great good fortune to be introduced to vitamin C as a medical doctor, for I have been able to lead a healthier life by regularly taking large amounts of vitamin C. In addition, I have performed countless experiments on vitamin C using animals, especially gulo(−/−) mice, which, like humans, cannot synthesize this vitamin. These experiments, published in some 40 papers in recognized international journals over the last few decades, have served to identify the effects of vitamin C on each of the human body systems, including the cardiovascular, nervous, gastrointestinal, immune, endocrine, and respiratory systems, and have sometimes even elucidated the detailed mechanisms involved.

In most scientific books, chapters are co-authored, but I have chosen to write this book as the sole author because I dare to declare myself a "vitamin C specialist". Moreover, throughout my career I have lectured on the structure of the human body as an anatomy professor, and I consequently believe that I have a deep understanding of the whole human body.

I do not regard this book as purely scientific. Medicine is an empirical science. In the treatment of the sick, endless scientific endeavors aim to clarify the treatment mechanisms, but in many cases the treatment is successful without knowing the exact mechanism of action. Indeed, it is virtually impossible to reveal the mechanisms of all treatments for all diseases because clinical experimentation using humans is extremely limited. The purpose of the book is, therefore, not merely to assemble the relevant scientific evidence but to enhance the health of people across the world by explaining why vitamin C should be taken regularly and by describing the precise amount of vitamin C to take each day and how to take it.

As I have just mentioned, this book is intended to promote human health through the proper use of vitamin C. In this context, each body system/organ-oriented chapter begins with a very brief description of structure because understanding of the human body must precede discussion of measures to benefit human health. Thereafter, the effects of vitamin C on each system or organ are described based mainly on the results that I have obtained during my studies. Of course, I have done my utmost to ensure that the scientific basis for taking vitamin C is sound by fully reviewing and taking into account the research results of other international scientists.

I want to let every reader know that the most important point of the book is the presentation of a new proposal on *the optimal dose of vitamin C,* which is currently 60 mg or more. Although the recommended dose has increased over the years, for too long insufficient detailed consideration has been devoted to the actual importance of vitamin C in maintaining good health. Furthermore, I wish to emphasize that the purpose of regular vitamin C use is not merely to prevent scurvy, but to actively prevent fatal diseases such as cancer, vascular diseases, and so on, which have become the fate of so many people in the modern world.

Above all, I want to glorify God, who has deepened enlightenment and inspiration during my writing of this book and share joy with my family, wife and daughter. And then, I would like to express my sincere gratitude to the many people who have supported me through their continuous prayers for successful publication. Especially, CEOs, Changhyon Cho and Byung-Jo Yim, who supported me with the grant for the research of vitamin C as well as helped me publish the book of vitamin C for the first time in my life. Furthermore, I cannot help but notice that there were so many people helping me with this book. Professor Kwang-Ho Lee, who informed me of the importance of vitamin C for the first time more than 30 years ago; Dr. Daeho Cho, who performed vitamin C research in my lab for the first time; Drs. Dong-Hoon Jin and Jae Seung Kang, who have greatly improved and enriched vitamin C research both quantitatively and qualitatively, providing many scientific data referred to in the book; all my beloved PhD students, who have contributed to the study of vitamin C without complaint; Mr. Yong Ho Yeo, CEO of Paramark, and Mr. Sae Young Chung, who helped to edit the figures for the book; Ms. Sunjoo Kim, who made many of the illustrations by herself; and Ms. Young-jin Oh, my secretary, who has handled all the prepublication chores, including compilation of the manuscripts and procurement of permission to use illustrative material from other publications. I also express my thanks to Ms. Yim, the former publishing editor, and Dr. Sue Lee and Ms. Emmy Lee, the publishing editors of Springer, Biomedical Sciences for their active support.

Finally, I am sincerely grateful to the many people who have listened to my recommendations through my lectures, the mass media, or social network sites directly or indirectly, waiting for this book to be published while taking a high dose of vitamin C over the past 30 years.

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Chapter 1
Introduction

History of Vitamin C Discovery

There have been many episodes of vitamin C deficiency, known as scurvy, throughout human history, for example, a scurvy-like disease written down on papyruses (1550 BC) and a Greek physician's (Hippocrates) description of scurvy-like symptoms (400 BC); however, only the core episodes that provide living evidence on the importance of vitamin C in maintaining life are summarized and described chronologically in this chapter (Table 1.1).

What Is Vitamin C?

Vitamin C is a representative of the water-soluble vitamins. Another representative of that group is vitamin B, which now is known to be a complex composed of several subfractions, such as B6, B12, riboflavin, niacin, biotin, folic acid, and so on. Considering that both vitamins are commonly water-soluble, what are the basic differences between vitamins B and C? There is no doubt that they must have their own functions. Traditionally, vitamin B deficiency has been called beriberi, while vitamin C deficiency has been called scurvy. The interesting difference between them is that people rarely die of beriberi as long as they are normally fed in their routine life. Actually, no reports on deaths from vitamin B deficiency have been documented in human history because they usually die of starvation in advance just before they die of beriberi. However, in the case of vitamin C, it is very different. People can die of vitamin C deficiency, and actually, many people have died from it even though they are regularly fed. The medieval history of Europe and especially the British marine history, during which people could not help but use marine transportation for long-distance travel, tell us that many young marine soldiers died without any cause during the voyage to the land under British occupation even though

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Table 1.1 Brief chronicle on vitamin C discovery

1550 BC. A scurvy-like disease, thought to be treated by eating onions, is written down on papyruses
400 BC. Hippocrates, a Greek physician, known to be the "father of modern medicine" describes scurvy-like symptoms: fetid breath, lax gums, and bleeding from the nose
1499 AD. When Vasco da Gama came back to Lisbon, Portugal, from the Arabian Sea, he lost 116 out of 170 of his crew despite knowing that citrus fruits could treat scurvy
1535 AD. While struggling against scurvy caused by the extremely cold winter on the St. Lawrence River, Canada, French explorers Jacques Cartier and Daniel Knezevic were advised by native Indians to drink plant tea from the needles of the arbor vitae tree to prevent death from scurvy during the winter
1753 AD. James Lind, British naval surgeon, made the report "A Treatise on the Scurvy" after the first controlled in vivo experiment (1747), using 12 men, who were suffering from scurvy. They were divided into six groups, each of which were given different regimens with a basic diet. Among them, the citrus fruit feeding group showed the most remarkable recovery from scurvy
1795 AD. Gilbert Blane, a British naval physician, advised the admiralty to eat citrus fruits on board ships as a routine diet. Thereafter, scurvy has been forever eliminated from the British navy
1802 AD. The British government established a law which mandates every ship to load citrus fruits on board before any voyage for any reason
1880 AD. Since the establishment of the law mandating every sailor eat citrus fruits on board ships, British sailors had to eat citrus fruits on board ship to prevent scurvy. However, because they preferred lime among the citrus fruits such as lemons, oranges, and limes, British sailors were called "limeys"
1907 AD. Axel Holst and Theodor Frølich, two Norwegian physicians studying shipboard beriberi, had a serendipitous finding from guinea pigs in which the scurvy-like condition was caused when they were fed only food consisting of grains and flour and that condition was cured when the test animals were fed fresh vegetables. This became the starting point of intensive scientific research on scurvy
1912 AD. The vitamine is named by combining "vital" and "amines" because it was thought that all these materials were vital as well as chemical amines. Although the "e" was deleted after it was proven that some of these compounds are not amines, the word vitamin is used popularly as a generic name for them
1928 AD. Hungarian biochemist Albert Szent-Györgyi isolated an organic reducing substance, hexuronic acid, from animal adrenal glands and suspected it to be an antiscorbutic factor. However, he could not prove it to be an antiscorbutic factor
1932 AD. Charles Glen King isolated vitamin C in his laboratory at the University of Pittsburgh and concluded that it was the same as "hexuronic acid." However, he could not determine its chemical structure
1933 AD. British chemist Walter Haworth deduced the molecular structure of hexuronic acid and renamed it ascorbic acid
1937 AD. Albert Szent-Györgyi was nominated as a laureate of the Nobel Prize in Medicine for his discovery of vitamin C, and Walter Haworth shared that year's Nobel Prize in Chemistry for his work with carbohydrates and for his part on the vitamin C synthetic work
In 1970s AD. Linus Pauling, who is the only person ever to receive two unshared Nobel Prizes (Chemistry in 1954 and Peace in 1962), made vitamin C popular for health promotion and disease control, by writing books on the effects of vitamin C for health promotion including *Vitamin C, the Common Cold, and the Flu* and *Cancer and Vitamin C*

(continued)

Table 1.1 (continued)

End of 1970 AD. Linus Pauling established the Linus Pauling Institute of Science and Medicine, where many scientists continue to perform research on the roles of vitamin C most vigorously in the world
1994 AD. Linus Pauling died of pancreatic cancer. After his death, the Linus Pauling Institute of Science and Medicine moved to the campus of Oregon State University, his undergraduate alma mater

they were fed on a normal basis. At that time, most Europeans thought their deaths were a kind of sacrifice to the god of the sea. However, James Lind, a Scottish surgeon in the Royal Navy, did not agree with that idea and had kept thinking about the cause of their deaths. One day, when his ship had been sheltering from a hurricane on the coast of a northern African province during another voyage, he happened to find the cause of their deaths. He witnessed that many marine soldiers suffering from some kind of fatal illness had survived just after they ate some oranges or limes, which had been purchased from a merchant ship which was also sheltering from the hurricane. And since then, for the first time, that fatal disease was called scurvy, although vitamin C deficiency was proven to be the cause of that fatal disease much later on. He even did some human clinical trials using the marine soldiers on the voyage to prove his observations that he had made while sheltering at the African province. While at sea in May 1747, Lind fed some sailors citrus fruits (two oranges and one lemon) each day as well as their routine rations, while the others (actually five groups according to the different sorts of additional diets other than citrus fruits) continued on cider, vinegar, sulfuric acid, or seawater, along with their normal rations. The results conclusively showed that among them, the citrus fruit-fed group had the most remarkable recovery from scurvy; therefore, citrus fruits could prevent the disease. In the history of science, this should be considered the first recorded controlled clinical trial as well as a splendid achievement of science because his great scientific work reduced the number of victims that died from that fatal disease scurvy and even saved the lives of many people who should have died of scurvy otherwise. Lind published his work in 1753 in his *A Treatise on the Scurvy* (Lind J. *A Treatise of the Scurvy,* 1753). About 50 years later, at the beginning of the nineteenth century, the British government established a new marine regulation which permits the departure of any ship from a port only if that ship is loaded with limes or oranges based on the results of Lind's human trial. Thereafter, since the establishment of the law mandating every sailor eat citrus fruits while on board a ship, British sailors had to eat citrus fruits while on a ship to prevent scurvy. However, because they preferred limes among citrus fruits such as lemons, oranges, and limes, the British marine officers were nicknamed as "the limeys."

Why should there be such basic differences between scurvy and beriberi? The answer is because vitamin B is a real vitamin, while vitamin C is not a vitamin. By definition, a vitamin is a very small amount of a substance contained in food which humans or animals consume every day to maintain the health and functions of their body and to prevent death from starvation, in other words, to essentially keep on living. Hunger usually causes an increased appetite which makes the body eat whatever is available. Most of the food consumed to sustain life is composed of energy sources (carbohydrates and fats) because energy is essential for maintaining life because prolonged starvation will eventually lead to death. Therefore, many people, even children, say they are "starving to death" whenever they feel hunger. This relatively long explanation is the reason why any people cannot die of vitamin deficiency as long as they regularly consume some food which usually contains minerals in very small amounts including vitamins (A, D, E, F, and K), electrolytes (Na^+, Cl^-, K^+, Ca^{++}, and so on), and some metal ions (Fe, Zn, Mg, and Cu). Therefore, it is quite natural that minerals are commonly called "micronutrients." However, it is completely different in the case of vitamin C which is normally produced in the bodies of mammals except for primates which include humans. Specifically, vitamin C is produced in the liver. The raw material for vitamin C production is D-glucose which is converted into L-ascorbate through some enzymes, among which the last one is an oxidase for conversion of L-gulono-γ- lactone into L-ascorbate. The gene encoding the oxidase is mutated in primates, resulting in a failure of vitamin C production. The reason why these scientific facts about vitamin C are very important is that several conditions should be considered to determine the optimal dose of vitamin C to promote human health or to prevent disease which are different from those of other real vitamins. Nowadays, although many people take vitamin C worldwide and its market size is actually very large, there are still controversies surrounding Vitamin C. Although many specialists on vitamin C promote it widely, even laypeople know that vitamin C is very important in maintaining life and a healthy body. However, the biggest issue on vitamin C consumption has been always the daily recommended allowance.

Brief Explanation of the Biochemical Properties of Vitamin C

Many people have known that vitamin C is just one of many antioxidants, and some people even think that vitamin C is the strongest antioxidant. Those facts are not true. Actually, vitamin C has unique functions beyond just its function as an antioxidant. Here, three points should be stressed with regard to the real biochemical characteristics and biological importance of vitamin C. First, vitamin C is water-soluble. Water-soluble substances usually have a very easy accessibility to any cells or organs as well as have rapid reaction potentials. Therefore, vitamin C is superior in preventing oxidative damage to the body compared to other antioxidant vitamins such as vitamin A, vitamin E, or β–carotene, which are lipid soluble. Second, vitamin C has a very unique pattern of antioxidant action. Chemically, an antioxidant is a kind of electron donor so that it is usually converted into a radical which is very toxic to cells or tissues. Therefore, actually, in the body, radicals are usually removed within an ultrashort time period after their generation. If not, tissues and cells will be severely damaged by the radicals, which in some cases result in death. Vitamin C, L-ascorbate (reducing form of vitamin C), is converted into the L-ascorbyl radical after the first donation of one electron and then finally converted into dehydroascorbate (DHA, oxidizing form of vitamin C) after the second donation of one electron, so that vitamin C has a two-step action pattern for the antioxidant unlike other antioxidants. Furthermore, the potential of one-electron transfer is very low, implying that vitamin C can easily act as an antioxidant, but its antioxidant strength is weak. And in some cases, vitamin C has a prooxidant property. Especially, vitamin C must act as prooxidant in cancer cells. That is to say, even though vitamin C is known to be one of the many antioxidants, it has a unique redox potential. This is also the reason why vitamin C is known to be chemically very unstable. In the living body, there should be a key substance which can easily and harmlessly eradicate radicals within an ultrashort time period which are inevitably produced while preventing oxidative damage to tissues or cells by the antioxidant actions of so many antioxidants present in their own form. Very interestingly, vitamin C also generates radicals after its antioxidant action like other antioxidants, but the ascorbyl radical is the least toxic. The chemical instability of vitamin C is also the third biochemical characteristic of vitamin C. Actually, vitamin C has an important role in regenerating toxic radicals derived from many antioxidants after their action into the safe original form. For example, vitamin E is a well-known antioxidant vitamin, which is called α-tocopherol, and is known to have a role in preventing lipid peroxidation, which is a prerequisite condition for atheroma formation. α-Tocopherol is converted to the α-tocopheroxyl radical, which is very toxic to the body, after its antioxidant action, and then, the radical is regenerated into the original form, α-tocopherol by vitamin C within a very short time. Conclusively, there are clear reasons why vitamin C is water-soluble and has the least toxic radical after its action. There are many antioxidants that have their own roles in preventing oxidative damage to the body, especially in the deepest part of the body, and as such, many kinds of radicals are generated. Those radicals should be regenerated to the safe original form very quickly and without any damage to the body by the water-soluble and least toxic radical generating antioxidant, otherwise known as vitamin C. Therefore, these characteristics of vitamin C should be considered before people take other antioxidant vitamins. Namely, they should take an excessive amount of vitamin C so that their body is fully saturated with vitamin C before they take other antioxidant vitamins, such as vitamin A, vitamin E, and β-carotene. Full knowledge of these characteristics of vitamin C should help to understand the Copenhagen report (called "Copenhagen shock" because the report was shocking to general people) published in JAMA (Dr. Chritian Gluud, 2007.) (Refer to the next session, *Copenhagen Report*).

Copenhagen Report

This report has been also called "Copenhagen shock" because the facts included in this report were shocking to many people in the world. This report has been published in JAMA (February 28, 2007) with the title of the article "Mortality in Randomized Trials of Antioxidant Supplements for Primary and Secondary

Prevention: Systematic Review and Meta-analysis," performed by European scientists (the principal investigator is Dr. Goran Bjelakovic) affiliated with several institutes such as the Cochrane Hepato-Biliary Group, Cochrane University Hospital, Department of Internal Medicine at the University of Nis, and Divisione di Medicina in Palermo, Italy. They analyzed the data statistically through systemic review of many reports and then meta-analysis for 3 years and 3 months in 68 independent scientific articles from 232,606 participants (male, 55.5%; female 44.5%), who have taken antioxidant supplements daily or once in a while for 2 years and 7 months (average); their physical changes have been checked. The results were contrary to the concepts conventionally accepted as a health dogma, in which antioxidants can give the beneficial effects on human health. According to the summarized results, the combination treatment with beta-carotene, vitamin A, and vitamin E increases mortality by 5%, and independent treatment with vitamin A increases mortality by 16%, with vitamin E by 4%, and with beta-carotene by 7%, respectively. And the potential roles of vitamin C and selenium need further study (Bjelakovic et al. 2007). One year later (April 2008), a very similar report, entitled "Antioxidant Supplements for Prevention of Mortality in Healthy Participants and Patients with Various Disease (Review)," has been published in the latest issue of *The Cochrane Library* by Dr. Christian Gluud, director of medical science, associate professor and department head of the Copenhagen Trial Unit at the Centre for Clinical Intervention Research and Copenhagen University Hospital in Denmark, and his colleagues. After reviewing nearly 70 randomized studies on the effects of vitamin or antioxidant supplements, they concluded there is no evidence that they prolong life and even found evidence that some of them, such as beta-carotene, vitamin A, and vitamin E, may actually shorten it (Bjelakovic et al. 2008).

These reports have made many average people get in deep confusion and panic because they have known and believed that antioxidant supplements can scavenge oxygen free radicals so that body damages by them could be reduced, resulting in successful maintenance of their health. Even there have been so many debates on these shocking reports. Although these reports do not seem to be absolutely correct, definitely they look like proving a part of truth about the role of antioxidant supplements in keeping sound human health.

In this chapter, a couple of critiques on these reports will be given. First of all, it should be noted that there are no evidences in these reports that vitamin C might have the harmful effects on human health when they take vitamin C for a long time. Rather, among the reports, the fact that vitamin C could reduce mortality rate by 12% has not been known well to the public. It is more important to understand the reason why there have been few reports that vitamin C could prolong life. Because in every trial using vitamin C, people take too small amount of vitamin C (maximum 500 mg daily). Even worse, they do not abide by the correct method of administration, which is to take vitamin C every 6 h, considering the pharmacokinetics of vitamin C in the blood. Secondly, in the case of beta-carotene, it is quite natural that beta-carotene could increase mortality by 7% because the participants took six times of beta-carotene (30 mg) as much as recommended optimal daily dose (5 mg). Lastly, most scientists, who performed the experiments for the data included in the

Copenhagen report, do not look like they have an exact knowledge of biochemical properties of antioxidants. Generally, every antioxidant has become toxic radicals except vitamin C after functioning as antioxidant. For example, vitamin E, also called chemically alpha-tocopherol, which is a stronger antioxidant than vitamin C, becomes alpha-tocopheroxyl radical, which is very toxic to the body and can give chronic damages to cells and tissues within a very short period, on functioning as potent antioxidant, thereby known to prevent lipid peroxidation, resulting in prevention of vascular atherosclerosis. Therefore, regeneration of toxic tocopheroxyl radical to nontoxic tocopherol should be needed urgently in the body. In this regeneration process, vitamin C has been known to play a very important role as regenerator. Interestingly, only ascorbyl radical, which is a by-product formed after first step of antioxidant action (one-electron donation), does not have toxicity enough to give the damage to cells and tissues. In addition, because vitamin C is water-soluble, it is quite natural to have very quick and broad antioxidant function and have no potent adverse effects. It is surely understandable that the phenomenon of Copenhagen shock could never happen in the animals, which can synthesize substantial amount of vitamin C daily in their body. This is a reason why people should benchmark the animals when they want to keep their health by administration of antioxidant supplements. Conclusively, people should take adequate amount of vitamin C three times daily (i.e., every 6 h) and then even better to take other antioxidant supplements because fully saturated vitamin C in the body can prevent potential toxic effects caused by antioxidant radicals .

Other Biological Activities of Vitamin C Besides Its Roles as an Antioxidant

Vitamin C has very important functions beyond the biological roles as a key antioxidant. Those roles are as important cofactors of several enzymes involved in key processes of life. Classically, a representative symptom of vitamin C deficiency is delayed wound healing, which requires synthesis of an adequate amount of procollagen, which needs the maximum activity of two enzymes, (1) prolyl and (2) lysyl hydroxylases (Levine 1986).

Vitamin C has a very important role in the biosynthesis of carnitine, which has a critical role in energy metabolism by transporting long fatty acids into the mitochondria for β-oxidation, in which the maximum activities of (3 and 4) two dioxygenases are essential (Burri and Jacob 1997). Actually considering that the early symptoms of vitamin C deficiency are fatigue and lethargy (Levine et al. 1996b), it is not surprising that some people usually confess the termination of these early vitamin C deficiency symptoms after taking a substantial amount of vitamin C regularly.

Vitamin C has also a critical function in the biosynthesis of norepinephrine, which is a representative stress hormone. Vitamin C has a role as a co-substrate for

(5) dopamine β-monooxygenase for dopamine hydroxylation by converting dopamine to norepinephrine (Levine 1986; Burri and Jacob 1997; May et al. 2013). Not surprisingly, the concentration of vitamin C in the adrenal glands, where the most important stress hormones epinephrine (adrenaline) and norepinephrine (noradrenaline) are normally produced in the medullary zone, is 100–200 times higher as that in the peripheral blood. In addition, it is quite natural that vitamin C is usually depleted in the peripheral blood after prolonged exposure to mental or physical stress, which requires more stress hormone production.

Vitamin C is also known to be involved in cholesterol metabolism. Cholesterol is indispensable for the production of steroid hormones including sex hormones, which have critical functions in energy metabolism, the maintenance of blood pressure, the inflammatory process, and so on. In addition, bile acids, which are synthesized in the liver and help lipid digestion by emulsifying lipids in the small intestine, are formed from cholesterol. During these two metabolic processes, vitamin C has a critical role as a co-substrate of (6) the enzyme 7α-monooxygenase (Burri and Jacob 1997).

Vitamin C is also well known to be involved in downregulating high blood pressure by increased endothelial nitric oxide (Duffy et al. 1999), mediated by the enhanced activity of (7) endothelial nitric oxide synthase by keeping its cofactor tetrahydrobiopterin in the active, reduced form (Huang et al. 2000; Gewaltig and Kojda 2002).

Vitamin C is also known to increase the activity of a family of (8) oxygen-dependent prolyl hydroxylase enzymes only in vitro, which plays an important role in the ability of cells to recognize and respond to hypoxia (Bruick and McKnight 2001; Jaakkola et al. 2001; Vissers and Wilkie 2007; Page et al. 2008; Kuiper et al. 2014), but my research team reported that vitamin C also had the same function in vivo (Li et al. 2010).

Sodium-Dependent Vitamin C Transporters (SVCTs)

Understanding how vitamin C can be transported into and out of the cells should be discussed first before a review of the functions and biological significance of vitamin C. Up to the twentieth century, it has been known that vitamin C can be transported only through several glucose transporter proteins (GLUTs), which can mediate transportation of only the oxidized form of vitamin C (dehydroascorbate, DHA), which is immediately converted into the reducing form (L-ascorbate) chemically by the action of glutathione (GSH) or enzymatically by several catalases within the cell. In the peripheral blood, almost 98% of vitamin C is present in the reducing form (L-ascorbate), while a very small proportion (less than 2%) is present in the oxidizing form (DHA). How is the reducing form of vitamin C transported into the cells? In 1999, Dr. Hediger's group has first cloned the SVCT genes and reported the full sequence of the genes (Tsukaguchi et al. 2007), which made it possible to know that the trans-plasma membrane gradient of ascorbate is generated by specific ascorbate transporter proteins, two isoforms of which are known, SVCT1 and SVCT2. While SVCT2 is distributed widely in several organs such as the placenta, liver, retina, spleen, endocrine organs (adrenal glands, prostate, testis, and ovary), and brain (neurons), where the tissue concentration of vitamin C is exceptionally high, reaching up to 10 mM, SVCT1 is distributed in only some limited organs, such as the epithelial surfaces of the intestine and the proximal tubules of the kidney, where vitamin C is actively absorbed or reabsorbed, suggesting that SVCT1 is involved in the bulk transport of vitamin C, whereas SVCT2 is involved in organ- or tissue-specific uptake of vitamin C (Hediger 2002). The distribution pattern of SVCT2 in several organs or tissues reflects the specific role of vitamin C in each organ. For example, the concentration of vitamin C in the adrenal gland, with one of the highest expressions of SVCT2, where several steroid hormones such as glucocorticoid, mineralocorticoid, and even sex hormones (estrogen progesterone and testosterone) are produced via biochemical pathways, in which vitamin C has a key role as a cofactor for some enzymes, is 10 mM. Another good example is the brain, which is composed of neurons and supporting cells such as astrocytes and glia. The brain consumes 20% of the total oxygen inhaled despite its low proportion (2%) of total body weight. The amount of oxygen consumption by neurons is five times higher as those of the supporting cells. The intracellular concentration of vitamin C in neurons is 10 mM, whereas those in the supporting cells are 2 mM, indicating that the vitamin C concentration is proportional to the amount of oxygen consumption in each organ. Therefore, it is not surprising that the expression of SVCT2 in neurons, which use a greater amount of oxygen than other organs or cells, is at the highest level in the body.

Pharmacokinetics of Vitamin C

There are three active forms of vitamin C in the biological system: ascorbate (reduced form), ascorbyl radical (intermediate oxidized form), and dehydroascorbate (DHA, oxidized form) (Fig. 1.1).

Ascorbate is mainly absorbed in the small intestine actively through SVCT1 expressed on the apical side of enterocytes. However, the transportation mechanism from enterocytes to the blood vessels (the so-called basolateral efflux) is not known yet. The physiological characteristics of the intestinal absorption of DHA in humans, which is known to be mediated via GLUTs, especially GLUT1, GLUT3, and, to some extent, GLUT4, are not well known yet (Levine et al. 1996a, b; Rumsey and Levine 1998). Intestinal absorption of ascorbate and DHA is known to be inhibited by glucose in a competitive inhibition manner caused by the structural similarity between both substances (Malo and Wilson 2000).

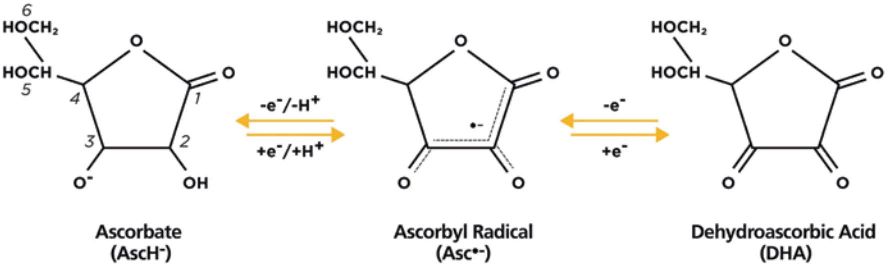

Fig. 1.1 Three forms of active vitamin C. Oxidation of ascorbate (AscH-) by two serial one-electron donation steps to give the ascorbyl radical (Asc・ -) and dehydroascorbic acid (DHA), respectively. Due to low one-electron transfer potential, the two-way reactions among three forms occur very easily, which is the reason why vitamin C has been known to be chemically unstable (Higdon and Frei 2002)

Before comments about the absorption, distribution, and excretion of vitamin C, it is necessary to understand actually how the bioavailability of vitamin C works in living organisms. In pharmacokinetic terms, bioavailability means the difference between the blood levels of vitamin C administered orally and intravenously. In other words, it reflects the absorption rate of vitamin C administered orally. As the only study showing the true bioavailability of vitamin C in humans, the bioavailability was very diverse according to the amounts of vitamin C given orally: when a liquid solution of ascorbate was given to fasting men at a steady state, the bioavailability was more than 80% for a dose less than 100 mg, 78% for a 200-mg dose, 75% for a 500-mg dose, and 62% for a 1250-mg dose (Graumlich et al. 1997). Two pharmacokinetic studies using healthy young men and women showed that doses of vitamin C ranging from 30 to 100 mg/day increased the blood concentration of vitamin C rapidly, whereas doses more than 400 mg/day of vitamin C showed a decreased rate in its increased blood concentration (Levine et al. 1996a, 2001). These reports have usually provided scientific rationale for the determination of the optimal daily allowance of vitamin C. When considering several characteristics of vitamin C, the blood level of vitamin C can not only be a guideline for determining the optimal daily allowance. About this issue, further discussion will be reviewed in the next step, “Scientific Background on the Optimal Dose of Vitamin C.”

Details on the urinary excretion of vitamin C should be scrutinized because the excretion pattern is one of the several important factors to consider when determining the optimal daily allowance of vitamin C. Actually, urinary excretion of vitamin C will be discussed thoroughly in the next step, “Scientific Background on the Optimal Dose of Vitamin C.”

The usual vitamin C concentration in human peripheral blood ranges from 11 to 90 μM. People whose plasma concentration is less than 11 μM are called scurvy patients. Those people whose plasma concentration range is from 11 to 28 μM are in a sub-scurvy status (Jacob 1999).