

Ascorbic Acid and the Immune System

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Background

Our introduction to the benefit of vitamin C for preventing head colds was a study reported by Cowan, Diehl, and Baker in 1942 in which 200 mg/day reduced the incidence and severity of the common cold in a group of university students.¹ At that time, approximately 30 mg/day of vitamin C was considered to be all that was necessary to prevent scurvy, the only illness accepted by the nutrition establishment as being related to vitamin C deficiency. Thus, 200 mg was considered a megadose and looked upon with skepticism by many physicians. Such a radical notion was bound to stir a lot of interest in the medical community and stimulate further investigations.

Over the succeeding decades hundreds of studies of the effects of vitamin C (hereafter referred to as ascorbic acid), rather than settling the matter, only added fuel to a growing controversy; studies showing benefits were countered with studies that showed no benefit. The medical and nutrition communities endorsed the negative studies because they confirmed their professional opinion that ascorbic acid had no value, except for prevention of scurvy. Pauling surmised that perhaps the “lack of enthusiasm” for ascorbic acid on the part of physicians and nutritionists might be due to their mistaken idea that ascorbic acid was a drug and, like drugs, was toxic. Thus, it was to be administered only in small quantities.² As a result, these small quantities assured failure in studies of effects of ascorbic acid because they were too small to give positive results. Perhaps Pauling’s most intuitive surmise was a “lack of interest of the drug companies in a natural substance that is available at a low price and cannot be patented.”

Despite the naysayers, a few courageous and dedicated physicians explored the therapeutic use of large and frequent doses ascorbic acid, orally and intravenously, for a wide variety of infectious and noninfectious diseases, often with miraculous results.^{3,4,5} These valuable contributions to the fund of knowledge on the therapeutic benefits of ascorbic acid remained largely ignored until Pauling entered the field in the late 1960s.⁶ The positive experience he and his wife had had with an ascorbic acid regime, in the face of the prevailing medical opinion that ascorbic acid was of no value in treating the common cold, led him to examine the subject for himself.²

As the recipient of two Nobel Prizes (Chemistry, 1954; Peace 1962), Pauling was a well-known public figure; thus, his writings on any subject were widely read. Those on ascorbic acid spread the word among the general public and scientists outside of the medical community about the use of ascorbic acid for preventing and treating the common cold. Although his writings greatly increased public awareness and interest in ascorbic acid, they did little to stem the controversy, primarily because of opposition from the medical and nutrition establishments. The situation seems little changed today from the time that Pauling first brought ascorbic acid to public attention, except that sales of orange juice have experienced a great increase and vitamin C supplements are widely available in drug stores.

Ascorbic Acid Revisited

Despite the fact that the general public and the medical and nutrition communities still think of ascorbic acid as only a vitamin, a considerable amount of research, both theoretical and practical, has been conducted on ascorbic acid during the past several decades. The vast amount of infor-

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mation produced by this research, which demonstrates that ascorbic acid is not just a vitamin but an indispensable therapeutic agent, is well summarized by Levy.⁷

In 1959, Burns reported that the human requirement for ascorbic acid is the result of an inborn error of carbohydrate metabolism.⁸ In most animal species, glucose is converted through a series of four reactions to ascorbic acid. In a few mammalian species, most notably the human, the enzyme for the fourth step, L-gulonolactone oxidase, is inactive. As a result, the conversion of glucose to ascorbic acid cannot be completed. It has been calculated that if humans had intact glucose/ascorbic acid pathways, they would produce about two to four grams of ascorbic acid per day under normal conditions and at least 15 grams per day under stress.⁸

Studies of ascorbic acid at the molecular, cellular, and clinical levels conducted by a host of scientists from a variety of disciplines have revealed that ascorbic acid plays multiple biochemical roles. In addition to its participation in immunity, which is described below, ascorbic acid also serves important enzymatic, antioxidant, and regulatory functions. However, from the viewpoint of the clinician, perhaps the most important finding about ascorbic acid activity is its competition with glucose within the body. In 1975, Mann proposed that, because of their structural similarity, ascorbic acid and glucose might utilize the same membrane transport.⁹ This extremely important concept was eventually confirmed experimentally¹⁰⁻¹⁴ and ultimately led to an understanding of how glucose and ascorbic acid compete for transport by insulin and entry into cells.¹⁵

Independent of the mechanisms by which ascorbic acid performs its essential biochemical roles, the facts of this interrelationship between glucose and ascorbic acid should be widely disseminated throughout the medical and nutrition communities. For one, it explains why some

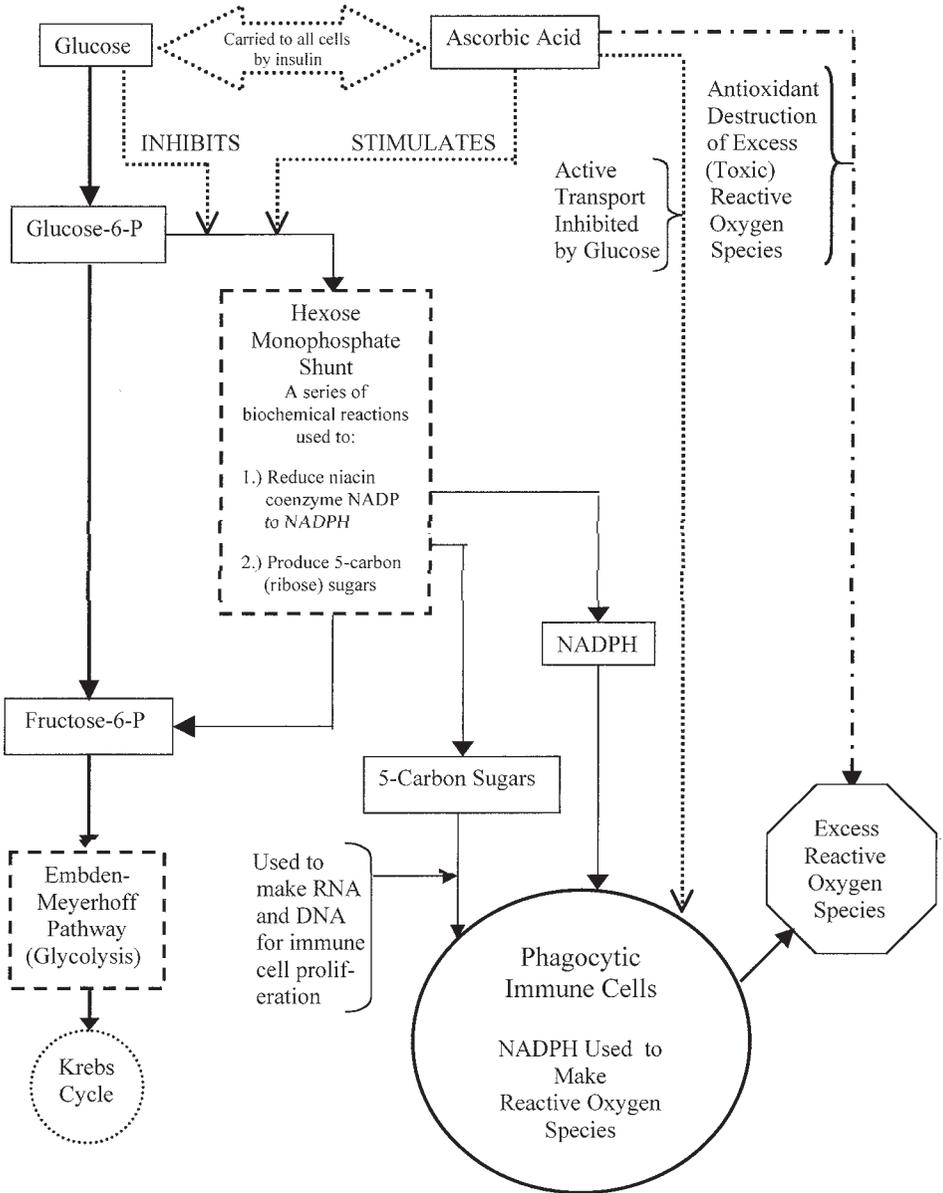
studies have shown little or no benefit from oral administration of ascorbic acid; they did not control for dietary provision of glucose, which would successfully compete with ascorbic acid and prevent its utilization. And two, it underscores the need for dietary carbohydrate restriction if ascorbic acid supplementation is to be of benefit in a healthful nutrition program.

Ascorbic Acid's Role in Immunity

Numerous reports in the older scientific literature describing the antibacterial activity of ascorbic acid *in vivo* and *in vitro*^{16,17} suggested a role for ascorbic acid in immunity. Other studies demonstrated that the ascorbic acid content of leukocytes, which are responsible for host defence, was up to 80 times greater than that in the plasma.^{18,19} Such a large difference between intra- and extracellular concentrations could only be effected by an active transport system. The fact that ascorbic acid is actively transported into leukocytes against a plasma concentration gradient is testimony to the importance of ascorbic acid for immune function. Studies such as these were accompanied by many others and eventually led to elucidation of the role of ascorbic acid in immune function.^{20,21}

Figure 1 (p.181) presents a simplified overview of the relationship of ascorbic acid to the immune system. Starting at the upper left-hand corner of the diagram, it shows that insulin carries both glucose and ascorbic acid to all cells of the body, including the phagocytic cells that seek, attack, and remove bacteria, viruses, tumor cells, and assorted microscopic cellular debris from the blood. This common transport system describes the competition between glucose and ascorbic acid and explains why, in order to exert a beneficial effect, large doses of ascorbic acid are necessary to overcome inhibition by glucose. Glucose not only inhibits the transport of ascorbic acid to all cells of the body but also inhibits stimulation of the hexose monophosphate (HMP) shunt by ascorbic acid.²²

Figure 1. The relationship of ascorbic acid to the immune system.



The HMP shunt is a detour between the first and second steps of the Embden-Meyerhoff glycolytic pathway. As shown in Figure 1, the first step in glycolysis, in preparation for conversion of glucose to CO₂, H₂O, and energy in the Krebs cycle, is phosphorylation to glucose-6-P. The second step in glycolysis is rearrangement of glucose-6-P to fructose-6-P. Again in Figure 1, ascorbic acid stimulates the diversion of glucose-6-P from glycolysis to the HMP shunt.

Two of the functions of the HMP shunt are important for the immune system. One is conversion of glucose (six carbons) to the five-carbon sugars, ribose and deoxyribose, which are essential for synthesis of the genetic components RNA and DNA, respectively. The second is reduction of the niacin coenzyme NADP to NADPH, which is needed for participation in a variety of oxidation reactions. The components of the shunt that are leftover after the needs for five-carbon sugars and NADPH are met are returned to glycolysis at the fructose-6-P step.

The five-carbon sugars are needed by the immune system to support elevated mitotic activity for proliferation of immune system cells. The first line in host defence against pathogens is rapid deployment of large numbers of phagocytic leukocytes. As shown in Figure 1, the five-carbon sugars permit synthesis of the DNA and RNA required for this proliferation of phagocytic cells. The NADPH generated by the HMP shunt is used by phagocytes to produce superoxide and a series of highly reactive oxygen species, which are used, in turn, to kill the invading pathogens.^{23,24}

Finally, phagocyte-derived highly reactive oxidants that are in excess of what are used by phagocytes for their killer activity leak out of their cells into extracellular space. These oxidant biochemicals are toxic to host cells and must be destroyed before they do damage to the host. Ascorbic acid comes into play here and, serving as an antioxidant, destroys these excess toxins.²³

Conclusion

There exists in the scientific literature a wealth of data that explains the role of ascorbic acid in immune system function and documents its requirement for greater than micronutrient quantities to fight infections. The inhibitory effect by glucose of the actions of ascorbic acid could well explain the lack of beneficial effect of ascorbic administration in many studies reported in the literature because few, if any, such studies controlled for dietary carbohydrates. In light of the current dietary sugar excesses and concomitant obesity epidemic, clinicians should be reminded of the great importance of the long recognized but largely unappreciated inhibitory action of glucose against ascorbic acid. In summary, ascorbic acid is essential for effective immune system function and, further, it can be a potent immune system stimulator when high glycemic dietary carbohydrates are restricted.

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