

Vitamin C: More than Just an Antioxidant and Preventing Scurvy

Michael Eskin*

Department of Human Nutritional Sciences, University of Manitoba, Canada

*Corresponding author: Michael Eskin, Department of Human Nutritional Sciences, University of Manitoba, 406 Human Ecology Building Winnipeg, MB R3T 2N2 Canada, Tel no: 204-474-8078; E-mail: Michael.Eskin@umanitoba.ca

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Editorial

The anti-scurvy properties of oranges and lemons were first reported in 1747 by Dr. John Lind, a ship's surgeon in the British Royal Navy, in his Treatise on the Scurvy. It took almost two hundred years before ascorbic acid or vitamin C was chemically identified and synthesized in 1933. For this work Szent-Gyorgyi and Walter Norman Haworth shared the Nobel Prize in Chemistry in 1937. This vitamin has since been shown to be essential for a number of enzymatic reactions including collagen formation, wound-healing as well as for its antioxidant properties [1].

During the 1970's Linus Pauling promoted the beneficial health effects of megadoses of vitamin C against such diseases as cancer [2]. Clinical trials by Cameron and Pauling [3] concluded that intravenous megadoses of vitamin C (10 g/d) delayed the death of 100 terminal cancer patients. A follow up study by Cameron and Pauling [2] reported a survival time of almost a year for cancer patients compared to controls which represented a fourfold increase in the survival period. Researchers at the Mayo Clinic, however, were unable to confirm these findings when the same mega doses of vitamin C (10 g/d) were given orally [4,5]. A possible discrepancy between these studies, however, was likely the much higher plasma levels of vitamin C in cancer patients given the vitamin intravenously compared to those taking it orally. The anti-cancer properties of vitamin C were subsequently confirmed by Chen and co-workers [6] who recorded decreases in the growth and weight of human, rat, and murine tumor xenografts in athymic, nude mice following i.p. injection of pharmacologic doses of vitamin C. Further *in vitro* studies also demonstrated the cytotoxic effects of megadoses of Vitamin C on a variety of cancer cells with little or no effect on normal cells [7,8]. Tian and co-workers [9] recently described a mechanism in which the Warburg effect, triggered by activation of the hypoxia-inducible factor (HIF) pathway, rendered multiple cancer lines far more susceptible to vitamin C induced toxicity. The Warburg effect is a phenomenon in which most cancer cells rely on aerobic glycolysis for energy as distinct from normal differentiated cells which use mitochondrial oxidative phosphorylation as their source of energy [10].

Several *in vitro* studies pointed to a possible role for vitamin C in peripheral nerve myelination [11,12]. This was recently confirmed *in vivo* by Gess et al. [13] who reported collagen gene transcription was reduced in sodium-dependent vitamin C transporter 2 (SVCT2) deficient mice but hydroxyproline was not. This suggested that collagen was regulated at the transcriptional and not at the post translation level. The reduction in ascorbic acid and hypomyelination and defects in collagen formation in periphery nerve of SVCT2+/- mice resulted in sensory impairment. It was clear from this study that a better understanding of the transport mechanisms of ascorbic acid and pharmacological manipulation of SVCT2, could lead to new therapies for peripheral neuropathies.

In addition to its presence in the central nervous system, ascorbic acid is highly concentrated in the retina with levels rising over 100 times higher than that found in blood plasma [14,15]. A deficiency renders the photoreceptors more susceptible to light damage by decreasing retinal ascorbate [16]. Using goldfish retinal slices, Calero and co-workers [17] reported that ascorbic acid may act as an endogenous agent potentiating GABAergic neurotransmission in the central nervous system. GABAergic plays a critical role by acting on both GABA_A and GABA_B receptors generating wakefulness and controlling the state of active sleep [18].

Besides its anticancer properties [19], vitamin C exerts many other important roles in the human body. Even the oxidized form of vitamin C, dehydroascorbic acid (DHA) has some unique properties. Unlike vitamin C, DHA can penetrate the blood-brain barrier. As a result, Huang et al. [20] proposed that DHA would improve outcome after a stroke by augmenting brain antioxidant levels. Based on its effect on cerebral ischemia in mice, DHA was considered to be a promising pharmacological therapy for strokes.

A novel role for ascorbate in epigenetic regulation was recently discovered by Minor et al. [21]. Ascorbate was shown to hydroxylate 5-methylcytosine (5-mC) to 5-hydroxymethylcytosine (5-hmC) in the DNA catalyzed by ten-eleven translocation (Tet) methyl cytosine dioxygenase. This modification of the epigenetic control of genome activity by vitamin C opens up whole new areas of study that could have a profound effect on many cellular processes with significant consequences for health and disease [22].

From the range of activities described, it is clear that vitamin C is definitely not just limited to being an antioxidant or preventing scurvy.

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