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Relationship between Vitamin C, Mast Cells and Inflammation

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Abstract

Vitamin C deficiency causes scurvy and can compromise many bodily functions. Vitamin C is involved in mast cells and other immune cells, such as NK cells, and differentiation of Th0 subset into Th1 cells. In addition, vitamin C has an important effect on p38 MAPK pathway and NF-kappa activity. Vitamin C is an anti-oxidant which protects the immune cells against intracellular ROS generated in allergic inflammatory response. Administration of vitamin C opposes free radical production and decreases bronchial hypersensitivity, an effect mediated by mast cells. Here, in this paper, we studied the relationship between vitamin C, mast cells and inflammation.

Keywords: Vitamin C; Mast cells; Inflammation; Immunity

Introduction

Vitamin C was first isolated (1928) by C.G. King and W.A. Waugh at the University of Pittsburgh and Albert Szent-Gyorgyi in Hungary, from orange and cabbage juices, and adrenal glands. In 1933 Haworth determined its structure and in 1971 Linus Pauling published the beneficial effects of vitamin C in the common cold. Vitamin C occurs in two forms, namely reduced ascorbic (meaning "without scurvy") acid (AA), and oxidized dehydroascorbic acid where only the L isomer of AA has activity.

Vitamin C deficiency causes scurvy, a potentially fatal condition described before Christ, and with historical evidence of its existence in Rome, Greece, and Egypt, which is characterized by muscle and collagenous structure weakness, lethargy, bleeding gums, tooth loss, joint pains, bone and connective tissue disorders, poor wound healing, fatigue, and bleeding under the skin provoking tiny pinpoint bruises [1].

In the 1700s, British physician James Lind found that the men who ate citrus fruit were not affected by scurvy and those who were suffering from this disease rapidly improved.

Vitamin C is specifically for anti-scorbutic activity and is very susceptible to destruction through oxidation [2]. Low intake of vitamin C can compromise many body functions such as the ability to rid the body of cholesterol and fight off infections and other diseases such as cardiovascular and allergic diseases [3]. Ten mg of vitamin C is needed daily to prevent scurvy, a disease that rarely appears today, except in infants who do not get enough vitamin C. Supplements of AA are used to acidify the urine during certain bladder or kidney diseases, or are given to people who will be undergoing surgery to ensure a sufficient supply of vitamin C to promote healing [4]. Therefore this vitamin, a water-soluble antioxidant as well as a reducing agent, is absorbed in a manner similar to monosaccharide, and in its metabolism AA is first converted to dehydroascorbate by a number of enzyme or non-enzymatic processes and is then reduced in cell [5].

Discussion

Absorbed vitamin C is excreted in sweat, feces, and urine after concentration in blood plasma [6].

High levels of vitamin C are found in pituitary and adrenal gland, pancreas, liver, spleen and brain, and tend to localize around healing wounds [7]. Here we report the concentration of vitamin C in human tissues (Table 1).

Concentration (mg/100 g) of Vitamin C in Human Tissue	
Plasma	0.4-1
Muscle	3-4
Brain	3-15
Heart	5-15
Kidneys	5-15
Lungs	7
Thymus	10-15
Pancreas	10-15
Liver	10-16
Lens	25-31
Adrenals	30-40
Pituitary	40-50

Table 1: Concentration (mg/100 g) of vitamin C in human tissue.

It is widely accepted that vitamin C, which has also psychological effects, has been recommended for cold prevention and for the treatment of schizophrenia, senility, cancer, inflammation and other pathological conditions [8]. Administration of high doses of vitamin C in cancer patient have not been found to be toxic but show no effect on symptoms nor does it affect the survival [9]. However, in some

individuals, the administration of high doses of vitamin C can cause blood in the stool, and may lead to the development of calcium oxalate kidney stone. Moreover, it increases excretion of uric acid, decreases the amount of copper, breaks down red blood cells in individuals with an inherited disease (sickle cell anemia) and diarrhea, an effect mediated by intestinal mast cell [10]. It is well known that the immune system is involved in cancer, infection, and allergy, as well as autoimmune and neurodegenerative diseases. Dietary supplementation with vitamin C, enhances a number of aspects of lymphocyte, macrophages and mast cell functions, exerts anti-inflammatory effects in man and animals, and is an indicator of the degree of oxidative stress taking place in the plasma [11]. Moreover, high administration of vitamin C in experimental animals results in better outcome in sepsis, oxidative stress and inflammation [12].

Vitamin C functions as an antioxidant that reacts with free radicals deactivating them before they cause damage to proteins or lipids, acts as a hydrogen donor involved in reversible oxidation and reduction, and it plays an important role in many biochemical reactions including incorporation of oxygen into the substrate [13]. In addition, vitamin C contributes towards synthesis, maturation, and secretion of collagen which can be degraded by MCs, along with various components of pericellular and extracellular matrices [14].

In 1878 a Nobel-Prize winner, immunologist Paul Ehrlich discovered small cells (6-12 mm in diameter) named mast cells (MCs). MCs derive from CD34+/CD117+ pluripotent progenitor cells, reside in the tissues, and they are mediators of allergic, inflammatory and autoimmune diseases [15,16]. They can be activated through IgE binding high-affinity surface receptor FceRI and other receptors such as TrkA, complement component receptors, Toll-like receptors, and cytokine receptors [17,18]. It is well known that MCs produce a plethora of mediators (such as arachidonic acid products, cytokines, phospholipases, tryptase, chymase, and cholinesterase) and participate in innate and adaptive immune systems [19,20]. They are distributed in virtually all organs and vascularized tissues, reside in the CNS where they are sensor and effectors, interacting with microglia and astrocytes through the release of neuroactive stored mediators and newly synthesized compounds such us arachidonic acid products [leukotrienes, prostaglandins and lipoxins] and cytokines/chemokines [21,22]. These compounds allow MCs to communicate with immune, vascular and nervous systems where they contribute to emotion and cognition [23].

It is well known that mast cells mostly reside on abluminal of the brain where there is a cross-talk between them and astrocytes, microglia, neurons and other resident cells [24]. Activated MCs generate numerous vasoactive, neuroactive, and immunoactive cellular and molecular response. Microglia and astrocytes respond to proinflammatory cytokines released by immune cells; on the other hand there are several biological compounds that enhance and regulate the interaction between mast cells and receptor brain cells [24]. MCs are also found in the hypothalamus, in connective tissues, as well as between the ganglion cells and nerve fibers. MCs are activated through cross-linking of their surface receptors for IgE, leading to degranulation, and release vasoactive, pro-inflammatory and nociceptive mediators that include histamine, serotonin, pro-inflammatory and anti-inflammatory cytokines/chemokines and proteolytic enzymes [25]. MCs are found preferentially in intraepithelial locations, and around blood vessels, and perform important beneficial roles in host defence [26].

Vitamin C is an important enzymatic cofactor involved in MCs, epithelial and endothelial barriers of the skin and plays an important function in maintaining tissue integrity [27]. It influences both cellular and humoral immune responses and orchestrates the function of innate and adaptive immune systems. Vitamin C has beneficial effects on systemic mast cell inflammation, therefore, since it is well known that its deficiency is associated with impaired cell-mediated immunity, it is possible that it may improve this interaction and be used as an adjuvant therapeutic compound in several inflammatory and allergic diseases [28]. Vitamin C deficiency provokes a decrease in appetite, growth, immunity, heart resistence, and skeletal muscle, and an increase in vascular capillary fragility, hemorrhage and nerve tenderness. In fact, it has been reported that deficiency of vitamin C suppresses T cytotoxic responses, natural killer (NK) cell activity, and antibacterial response and plays a role in delayed type hypersensitivity [29].

Vitamin C is involved in host resistance to tumor where it probably has a selective cytotoxic effect [30]. As an adjuvant this candidates it among the therapeutic compounds for the treatment of cancer. In addition to the classic therapies, vitamin C is involved in NK cell activation and differentiation of Th0 subset into Th1 characterized by interferon gamma generation and it is implicated with the synthesis of proinflammatory cytokines/chemokines, and the expression of adhesion molecules [31,32].

Because anti-tumor NK cells are activated by IL-2 and vitamin C may be an adjuvant in immunotherapy with IL-2, it may be pertinent to use vitamin C in immunotherapy in combination with IL-2 against certain cancers [33]. The addition of vitamin C in this immunotherapy, not only increases the effects of IL-2, but also reduces the production of TNF, a cytokine produced by several immune cells, including MCs, which has strong inflammatory properties, induces endothelial cell apoptosis and plays a relevant role in MC mediating asthma [34]. Moreover, vitamin C reduces endothelial cell expression of the adhesion molecule ICAM-1 in response to TNF-alpha in human umbilical vein endothelial and suppresses systemic neutrophil extravasation during bacterial infections; demonstrating its anti-inflammatory properties [35]. Therefore, vitamin C has significant impact on endothelial cells, including the inhibition of p38 MAPK pathway and endothelial NF-kappa B activity, and the suppression of endothelial permeability and vascular leakage; effects due to the inflammatory cytokines such as IL-1, TNF, IL-6 and IL-33 generated by MCs [36].

In addition, through the enzyme cholesterol 7-alpha-monooxygenase, vitamin C is involved in the metabolism of cholesterol to bile acids and may be of benefit in cardiovascular disease and atherosclerosis, a disease where MCs are also involved [37]. Vitamin C is an antioxidant which protects the immune cells against intracellular reactive oxygen species (ROS) generated in the allergic inflammatory response and it is a reducing compound which enhances the hydroxylation of carcinogens due to the hepatic cytochrome P450 [38]. Supplementation of vitamin C and other vitamins opposes free radicals produced by antigen activated immune cells and in this way maintains efficient the immune functions. Therefore, when the immune system is not efficient, it would be good to recommend patients to take vitamin C [39].

Administration of vitamin C decreases bronchial hypersensitivity caused by the common cold [40], an effect also mediated by mast cells. In addition it shortens the duration of colds, prevents pneumonia, and

decreases the incidence of sneezing, runny nose, cough and other symptoms, all effects related to MC activation.

It has been reported that vitamin C inhibits excessive activation of the immune system and its administration seems beneficial to asthma patients, in fact, MC-mediated bronchial hypersensitivity, which is a characteristic feature of asthma is alleviated by vitamin C. Patients treated with AA administration express decreased bronchial hypersensitivity to histamine and bronchoconstriction in asthma, effects mediated by MCs.

Conclusion

In the light of these studies, we found that vitamin C relieves most of the symptoms of diseases that involve activation of MCs and we can conclude that further research on the role of vitamin C and MCs is needed.

References

1. Kelley DS, Bendich A (1996) Essential nutrients and immunologic functions. Am J Clin Nutr 63: 994S-996S.
2. Riccioni G, Bucciarelli T, Mancini B (2007) Antioxidant vitamin supplementation in cardiovascular diseases. Ann Clin Lab Sci Winter 37: 89-95.
3. Arnson Y, Itzhaky D, Mosseri M (2013) Vitamin D inflammatory cytokines and coronary events: A Comprehensive Review. Clin Rev Allergy Immunol 45: 236-247.
4. Pignot G, Lebret T, Chekulaev D (2011) Healing and targeted therapies: Management in perioperative period? Prog Urol 21: 166-172.
5. Ullah MF, Bhat SH, Hussain E (2012) Ascorbic acid in cancer chemoprevention: translational perspectives and efficacy. Curr Drug Targets 13: 1757-1771.
6. Van der Beek EJ (1991) Vitamin supplementation and physical exercise performance. J Sports Sci 9: 77-90.
7. Snodgrass SR (1992) Vitamin neurotoxicity. Mol Neurobiol 6: 41-73.
8. Feio M, Sapeta P (2005) Xerostomia in palliative care. Acta Med Port 18: 459-465.
9. Head KA (1998) Ascorbic acid in the prevention and treatment of cancer. Altern Med Rev 3: 174-186.
10. Bahr RL, Wilson DC (2015) The impact of high-dose vitamin C on blood glucose testing in ^{18}F-FDG PET imaging. J Nucl Med Technol 43: 70-71.
11. McMurray DN (1984) Cell-mediated immunity in nutritional deficiency. Prog Food Nutr Sci 8: 193-228.
12. Macdonald J, Galley HF, Webster NR (2003) Oxidative stress and gene expression in sepsis. Br J Anaesth 90: 221-232.
13. Delmastro-Greenwood M, Freeman BA, Wendell SG (2014) Redox-dependent anti-inflammatory signaling actions of unsaturated fatty acids. Annu Rev Physiol 76: 79-105.
14. Abe M, Yokoyama Y, Amano H (2002) Effect of activated human mast cells and mast cell-derived mediators on proliferation, type I collagen production and glycosaminoglycans synthesis by human dermal fibroblasts. Eur J Dermatol 12: 340-346.
15. Kritas SK, Saggini A, Cerulli G (2014) Impact of mast cells on multiple sclerosis: inhibitory effect of natalizumab. Int J Immunopathol Pharmacol 27: 331-335.
16. Kritas SK, Saggini A, Cerulli G (2014) Relationship between serotonin and mast cells: inhibitory effect of anti-serotonin. J Biol Regul Homeost Agents 28: 377-380.
17. Dawicki W, Marshall JS (2007) New and emerging roles for mast cells in host defence. Curr Opin Immunol 19: 31-38.
18. Kritas SK, Caraffa A, Antinolfi P (2014) IgE generation and mast cell activation. Eur J Inflamm 12: 21-25.
19. Spinas E, Kritas SK, Saggini A (2014) Role of mast cells in atherosclerosis: a classical inflammatory disease. Int J Immunopathol Pharmacol 27: 517-521.
20. Shaik-Dasthagirisaheb YB, Varvara G, Murmura G (2013) Role of vitamins D, E and C in immunity and inflammation. J Biol Regul Homeost Agents 27: 291-295.
21. Saluja R, Hawro T, Eberle J (2014) Interleukin-33 promotes the proliferation of mouse mast cells through ST2/MyD88 and p38 MAPK-dependent and Kit-independent pathways. J Biol Regul Homeost Agents 28: 575-585.
22. Kritas SK, Saggini A, Cerulli G (2014) Corticotropin-releasing hormone, microglia and mental disorders. Int J Immunopathol Pharmacol 27: 163-167.
23. Dong H, Zhang X, Qian Y (2014) Mast cells and neuroinflammation. Med Sci Monit Basic Res 20: 2002-2006.
24. Khalil M, Ronda J, Weintraub M (2007) Brain mast cell relationship to neurovasculature during development. Brain Res 1171: 18-29.
25. Spinas E, Saggini A, Kritas SK (2014) Obesity, inflammation and neurological alterations. Eur J Inflamm 12: 415-418.
26. Kritas SK, Saggini A, Cerulli G (2014) Neuropeptide NGF mediates neuro-immune response and inflammation through mast cell activation. J Biol Regul Homeost Agents 28: 177-181.
27. Ormerod AD, Copeland P, Hay I (1999) The inflammatory and cytotoxic effects of a nitric oxide releasing cream on normal skin. J Invest Dermatol 113: 392-397.
28. Secor VH, Secor WE, Gutekunst CA, Brown MA (2000) Mast cells are essential for early onset and severe disease in a murine model of multiple sclerosis. J Exp Med 191: 813-822.
29. Cameron E (1982) Vitamin C and cancer: an overview. Int J Vitam Nutr Res Suppl 23: 115-127.
30. Baker DH, Wood RJ (1992) Cellular antioxidant status and human immunodeficiency virus replication. Nutr Rev 50: 15-18.
31. Holmannová D, Koláčková M, Krejsek J (2012) Vitamin C and its physiological role with respect to the components of the immune system. Vnitr Lek 58: 743-749.
32. Wagner SC, Markosian B, Ajili N (2014) Intravenous ascorbic acid as an adjuvant to interleukin-2 immunotherapy. J Transl Med 13: 127.
33. Romay Ch, González R, Ledón N (2003) C-phycocyanin: a biliprotein with antioxidant, anti-inflammatory and neuroprotective effects. Curr Protein Pept Sci 4: 207-216.
34. Bevilacqua MP, Nelson RM, Mannori G, Cecconi O (1994) Endothelial-leukocyte adhesion molecules in human disease. Ann Rev Med 45: 361-378.
35. Cindrova-Davies T, Spasic-Boskovic O, Jauniaux E (2007) Nuclear factor-kappa B, p38, and stress-activated protein kinase mitogen-activated protein kinase signaling pathways regulate proinflammatory cytokines and apoptosis in human placental explants in response to oxidative stress: effects of antioxidant vitamins. Am J Pathol 170: 1511-1520.
36. Gey KF (1998) Vitamins E plus C and interacting conutrients required for optimal health. A critical and constructive review of epidemiology and supplementation data regarding cardiovascular disease and cancer. Biofactors 7: 113-174.
37. Delafuente JC (1985) Immunosenescence. Clinical and pharmacologic considerations. Med Clin North Am 69: 475-486.
38. Bucca C, Rolla G, Arossa W, Caria E, Elia C et al. (1989) Effect of ascorbic acid on increased bronchial responsiveness during upper airway infection. Respiration 55: 214-219.
39. Empey DW, Laitinen LA, Jacobs L, Gold WM, Nadel JA (1976) Mechanisms of bronchial hyperreactivity in normal subjects after upper respiratory tract infection. Am Rev Respir Dis 113: 131-139.
40. Hemilä H (2013) Vitamin C and common cold-induced asthma: a systematic review and statistical analysis. Allergy Asthma Clin Immunol 9: 46.