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REVIEW ARTICLE

Antiviral Mechanisms of Vitamin C: A Short Communication Consensus Report

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INTRODUCTION

Vitamin C is an essential micronutrient for humans, with an array of pleiotropic physiological functions related to its ability to donate electrons. It is a cofactor for numerous biosynthetic and gene regulatory enzymes (Carr & Maggini, 2017). Due to its strong reducing potential, Vitamin C is involved in numerous metabolic processes. Vitamin C contributes to the immune system by supporting various cellular functions of both the innate and adaptive immune system.

The immune system is a multifaceted and sophisticated network that protects the host from a range of pathogens, such as bacteria, fungi, parasites, cancer cells and viruses. The immune system can be characterized as innate and adaptive. The innate immune system is composed of physical and chemical barriers as well as cells such as phagocytic leukocytes, dendritic cells, natural killer cells, and plasma proteins. The adaptive immune system (also referred as the acquired immune system) has two types of adaptive responses: the cell-mediated immune response, which is carried out by T cells, and the humoral immune response, which is controlled by activated B cells and antibodies.

A major symptom of the Vitamin C deficiency disease scurvy is an enhanced susceptibility to infections, particularly of the respiratory tract, with pneumonia being one of the most frequent complications of scurvy and a major cause of death. Administration of vitamin C to patients with acute respiratory infections returns their plasma vitamin C levels to normal and ameliorates the severity of the respiratory symptoms (Hunt et al. 1994; Marik, 2018; Marik, 2018; Fowler et al. 2017).

Cases of acute lung infections have shown rapid clearance on chest X-rays following administration of intravenous Vitamin C (Bharara, 2016; Fowler et al. 2017). This vitamin C-dependent clearance of neutrophils from infected lungs could conceivably be due to enhanced apoptosis and subsequent phagocytosis and clearance of the spent neutrophils by macrophages (Vissers & Wilke, 2017).

Vitamin C has demonstrated potent antiviral activity when utilized in large doses either in strategically taken oral doses or by intravenous route (Colunga Biancatelli et al. 2020). Clinical evidence exists that shows vitamin C's potent antiviral effect. Studies in which very large amounts of vitamin C have been used to treat different viral infections have been published (Gonzalez et al. 2014; Marcial-Vega et al. 2017; Gonzalez et al. 2016; Gonzalez et al. 2018a; Gonzalez et al. 2018b). Frequent oral doses with vitamin C sufficient to reach a bowel tolerance limit will work as antiviral therapy for most people (Cathcart, 1981). Intravenous vitamin C is indicated for the most serious cases.

It is our experience, as well as others, that the sicker a person was, the more ascorbic acid they would tolerate orally without it causing diarrhea. A healthy person with a normal GI tract may tolerate 5 to 15 grams of ascorbic acid taken orally without diarrhea. A person with a mild cold may tolerate 30 to 60 grams; with a bad cold about 75 grams; with influenza close to 100 grams. With mononucleosis, viral pneumonia, etc. 150- 200 grams or more of ascorbic acid would be tolerated orally without diarrhea (Cathcart, 1981). The method to determine proper dose (the dose that will eliminate acute symptoms without causing diarreha), by titrating to bowel tolerence was first described by Cathcart. Symptoms are usually neutralized when a dose of about 90% or more of bowel tolerance is reached with oral ascorbic acid.

Another interesting concept is Hickey's dynamic flow model (Hickey et al. 2005). In the dynamic flow model, an excess of oral ascorbate provides a steady flow of electrons through the body. The dynamic flow model proposes restoring human physiology to approximate that of animals that synthesize their own vitamin C. This can be achieved by consuming excess ascorbate, over and above the amount normally absorbed. This intake is spread throughout the day, so a consistent supply is achieved. Vitamin C is transported across cellular membranes by the sodium-dependent vitamin C transporter (SVCT) and by glucose transporters (GLUT). Glucose transporters are a wide group of membrane proteins that facilitate the transport of glucose across the plasma membrane. The sicker you are the more active these transporters are.

VITAMIN C AS A METABOLIC MODULATOR

Sepsis is characterized by systemic inflammation, increased oxidative stress, insulin resistance, and peripheral hypoxia. Sepsis is a life-threatening systemic inflammatory response that can result in multi-organ dysfunction. Sepsis represents a medical condition in which the presence of vitamin C and other antioxidants have been severely depleted. Immune effector cells depend on glycolysis as their source of energy, lung epithelial cells use mitochondrial oxidative phosphorylation to produce their energy. High-dose vitamin C treatment acts as both a pro-oxidant for immune cells, and an antioxidant for lung epithelial cells (Erol, 2020). The pro-oxidant role of vitamin C requires pharmacological (millimolar) rather than physiological (micromolar) concentrations. However, a concern that may arise with high-dose vitamin C treatment of pneumonia is that it produces an osmotic cell death of immune cells, rather than apoptosis, which could generate a local inflammation in the alveoli. Therefore, IV glucocorticoid treatment must be added to attenuate the possible inflammatory complications of high-dose vitamin C treatment. For the purpose of this article, we will define high-dose intravenous vitamin C treatment as infusion(s) of at least 5 g a day. It should be considered to add hydrocortisone 50 mg IV every 6 hours for 7 days to fight against vitamin C therapy-induced inflammation. Although we must mention that endogenous cortisol levels in sepsis are already very high, this activity occurs in an attempt to compensate for the oxidation of the cortisol receptors. vitamin C may reduce the oxidation of the receptors permitting endogenous cortisol to kick in. Vitamin C, when used as a parenteral agent in high doses, may act pleiotropically as a pro-oxidant to attenuate pro-inflammatory mediator expression (Lee et al. 2020; Mikirova & Scimeca, 2016), improve alveolar fluid clearance, and at the same time, may act as an antioxidant to improve epithelial lung cell functions (Rodrigues et al. 2018; Das et al. 2018). At high-dose, vitamin C acts as a pro-oxidant or antioxidant in a cell-type dependent (environmentally determined) manner (Erol, 2020; Lee et al. 2020; Mikirova & Scimeca, 2016; Rodrigues et al. 2018; Das et al. 2018; Yun et al. 2015; Ngo et al. 2019). This presents vitamin C as a multifunctional, multifaceted versatile metabolic modulator.

ANTIVIRAL MECHANISMS OF ASCORBIC ACID

Direct mechanisms:

1. **Damage of the viral capsid** due to ascorbic acid redox capacity when given in pharmacological doses. Ascorbic acid is a powerful reducing agent (Cheng et al. 2012; Furuya et al. 2008).

2. **Disruption of viral capsid sugar moiety** of its glycoprotein envelope when given in pharmacological doses (Asim et al. US20130004458A).

3. **Inhibition of viral replication** when provided in pharmacological doses by creating a hostile environment for this activity to occur, in addition to directly inhibiting viral replication enzymes (Colunga Biancatelli et al. 2020; Kim et al. 2013; Jariwalla & Harakeh, 1996). Ascorbic acid causes degradation of single and double-stranded genomes of RNA and DNA viruses (Murata & Kitagawa, 1973; Murata & Uike, 1976; Wong et al. 1974) so that replication becomes susceptible to ascorbate-mediated damage, resulting in reduced viral protein production.

Indirect mechanisms:

1. **Increases cellular immunity** through increasing the number, activity, and aggressiveness of immune cells such as leukocytes, lymphocytes, NK cells, macrophages. Lymphocyte function and production are influenced by vitamin C concentrations (Sorice et al. 2014). Vitamin C accumulates in the lysosomes of phagocytic cells and enhances chemotaxis, chemokinesis and phagocytosis. Vitamin C in the presence of oxygen favors the generation of reactive oxygen species such as H2O2 (Frei & Lawson, 2008). Vitamin C has been shown to increase mobility and chemotaxis of phagocytes (Murata & Uike, 1976). White blood cells accumulate vitamin C against a concentration gradient, resulting in values that are 50- to 100-fold higher than plasma concentrations (Goldschmidt, 1991; Bergsten et al. 1990; Evans et al. 1982).

2. **Increases humoral immunity** through the production of antibodies (Carr & Maggini, 2017; Tanaka et al. 1994; Feigen et al. 1982).

3. **Increases anti-viral proteins** such as α/β interferons while downregulating the production of pro-inflammatory cytokines TNF-α and IL-6 (Colunga Biancatelli et al. 2020; Wintergerst et al. 2006; Dahl & Degre, 1976).

4. **Increases energy** by providing necessary electrons and electron movement that increases mitochondrial electron flux for ATP generation (Gonzalez et al. 2005, Gonzalez et al. 2010).

5. **Limits glucose utilization** as the main source of energy pathogenic organisms, when provided in pharmacological doses (Dakhale et al. 2011, Sanchez 2015; Ripoli et al. 2010). DNA and RNA viruses are able to induce glycolysis. Viruses are able decrease host cell oxidative phosphorylation and increases dependence on extracellular glucose.

6. **Antioxidant action** is elicited when vitamin C is provided in proper doses to prevent the dangerous and severe pathological cascade of the cytokine storm (Carr & Maggini, 2017; Marik 2018a; Marik 2018b; Hickey et al. 2005; Marik, 2016). Mitigates the cytokine storm – cytokines can elicit pro-inflammatory or anti-inflammatory responses, and Vitamin C appears to modulate systemic and leukocyte-derived cytokines. Vitamin C protects the host cells against the oxidants released by phagocytes. Vitamin C decreases the generation of the pro-inflammatory cytokines TNF-α and IL-6 (Chen et al. 2014).

The lethal pathology underlying COVID-19 is acute lung injury (ALI)/acute respiratory syndrome (ARDS) induced by cytokine storm or significantly elevated oxidative stress. These pathologies were also found in SARS and MERS and other respiratory viral infections, as well as viruses affecting other parts of the body causing multi-organ failure. The clinical observations of vitamin C in ameliorating pneumonia, ARDS and sepsis support vitamin C's antioxidant, anti-viral, and immune-boosting effects.

7. **Maintains structural integrity of cells** via the promotion of collagen formation (Englard & Seifter, 1986; Murad et al. 1981). Vitamin C protects endothelial barrier function against the insult of sepsis (Han et al. 2010).

8. **Modulates gene expression**. Vitamin C administration decreases expression of susceptibility genes, including mitochondrial antiviral signaling (MAVS) and interferon regulatory factor 3 (IRF3), and increased expression of NF-κB. These in conjunction induce type I interferons (IFNs) and elicit innate antiviral response (Cai et al. 2015).

Vitamin C is capable of combating all types of viruses when given in high doses, but even at a low supplemental amount, it is helpful. This is very important for those with low incomes and few treatment options. For example, in one well-controlled, randomized study, just 200 mg/day of vitamin C given to the elderly resulted in improvement in respiratory symptoms in the most severely ill, hospitalized patients; in addition, there were 80% fewer deaths in the vitamin C group (Hunt et al. 1994).

The SARS-coV-2 (coronavirus), as an acute infection, should be expected to be just as susceptible to vitamin C as all of the other viruses against which it has been proven to be very effective. There has never been a documented situation in which sufficient high dosages of vitamin C have been unable to neutralize any virus against which it has been tested (Klenner, 1951).

Many physicians consider high doses of Vitamin C to be so powerful an anti-viral agent that it may be ranked as a functional immunization for a variety influenza strains (Saul, 2005).

CONCLUSION

Vitamin C can be used as a stand-alone therapeutic agent to eradicate a viral/bacterial infection if given in high doses as constant infusions (Zabet et al. 2016). Based on this mechanistic rationale explaining the therapeutic use of vitamin C to prevent inflammatory hyperactivation in myeloid and lymphoid cells we conclude that supplementation with high dose vitamin C appears to be able to both prevent and help treat respiratory and systemic infections. Ascorbate at sufficiently high doses can prevent viral disease and greatly speed recovery from an acute viral infection.

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