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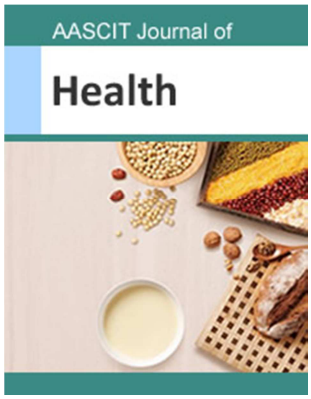

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Antiviral Activity of L-Arginine and Extended-release Vitamin C

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Abstract
About eight decades have passed since a serendipitous laboratory breakthrough by Dr. Fleming meant that the scourge of bacterial infections could be treated efficaciously and economically. Since then important advances have been made in treating selected viral infections (especially HIV and hepatitis C chronic infections) but the medical community is still researching a treatment for viral infections as wide-ranging and economical as penicillin was for bacterial infections. Here we describe our success in using a simple combination of two naturally-occurring substances with excellent clinical success in treating different types of viral infections. Currently we are making efforts in trying to detail the cellular pathways used by this treatment and testing its efficacy in different viral infections.

1. Introduction

At the beginning of 2010 a combination of arginine aspartate and vitamin C was administered to a patient with herpes labialis (type I) and it had very prompt effects in stopping the discomfort and swelling; it made the canker sore unnoticeable after 3 days of administration, while usually this affliction would take 2-3 weeks to heal. Shortly after this, same combination of L-arginine and vitamin C (LAVITAC) was given in a case of seasonal influenza and the results were again excellent, with resolution of symptoms and clinical cure after 48 hours of treatment. Those results were replicated shortly afterward in 3 other patients with herpes labialis and more than 3 other patients with influenza.

Given that herpes and influenza viruses have important differences between them (herpes virus is an enveloped, double stranded DNA virus/flu viruses are enveloped, single stranded RNA viruses classified as orthomyxoviridae), naturally the question has occurred of whether this combination would be effective in other viral infections, so a five-day course of LAVITAC was given to a patient with known chronic hepatitis C (non-enveloped, single stranded RNA virus) who was previously treated with interferon and ribavirin and who had clinical signs of relapse. Again clinical improvement has occurred within 48 hours and after the 5-day course there was no need for other antiviral therapy.

A similar therapeutic success was obtained in a case of zona zoster occurring in a patient taking chemotherapy, with the vesicles, itching and burning greatly subsiding after 5 days and complete remission occurring after 10 days of treatment.

Since then there were more than 12 patients with herpes and flu successfully treated including a patient with chronic hepatitis C and B who had excellent results with this treatment (clinical remission after 3 days).

At this stage we have applied for research grants to study the pathophysiology of this treatment, and while we wait for the necessary funds we feel that such a simple, effective

and economical treatment should be more known and used. Below we are discussing the two substances of the LAVITAC treatment and have summarized some known facts about them. Some of this information was made available in 2010 on the Bio-Forum Foundation site: www.bio-forum.net, and on June 1, 2013 a presentation was made at The Romanian Academy on this matter.

2. Established Facts and Research

Vitamin C or ascorbic acid, has molecular formula $C_6H_8O_6$, molecular mass M 176, and is water-soluble.

Almost all mammals manufacture their own vitamin C in amounts equivalent to human doses of thousands of milligrams per day. Vitamin C plays an important role in many cellular processes and biochemical reactions. It is essential for the synthesis of collagen (hydroxylation) as well as dopamine, noradrenaline and adrenaline in the nervous system and in the adrenal glands. It is needed to synthesize carnitine, important molecule in the transfer of energy to the cell mitochondria; it is also a cofactor for metaloenzyme hydroxylase and oxygenase (reactions given below).

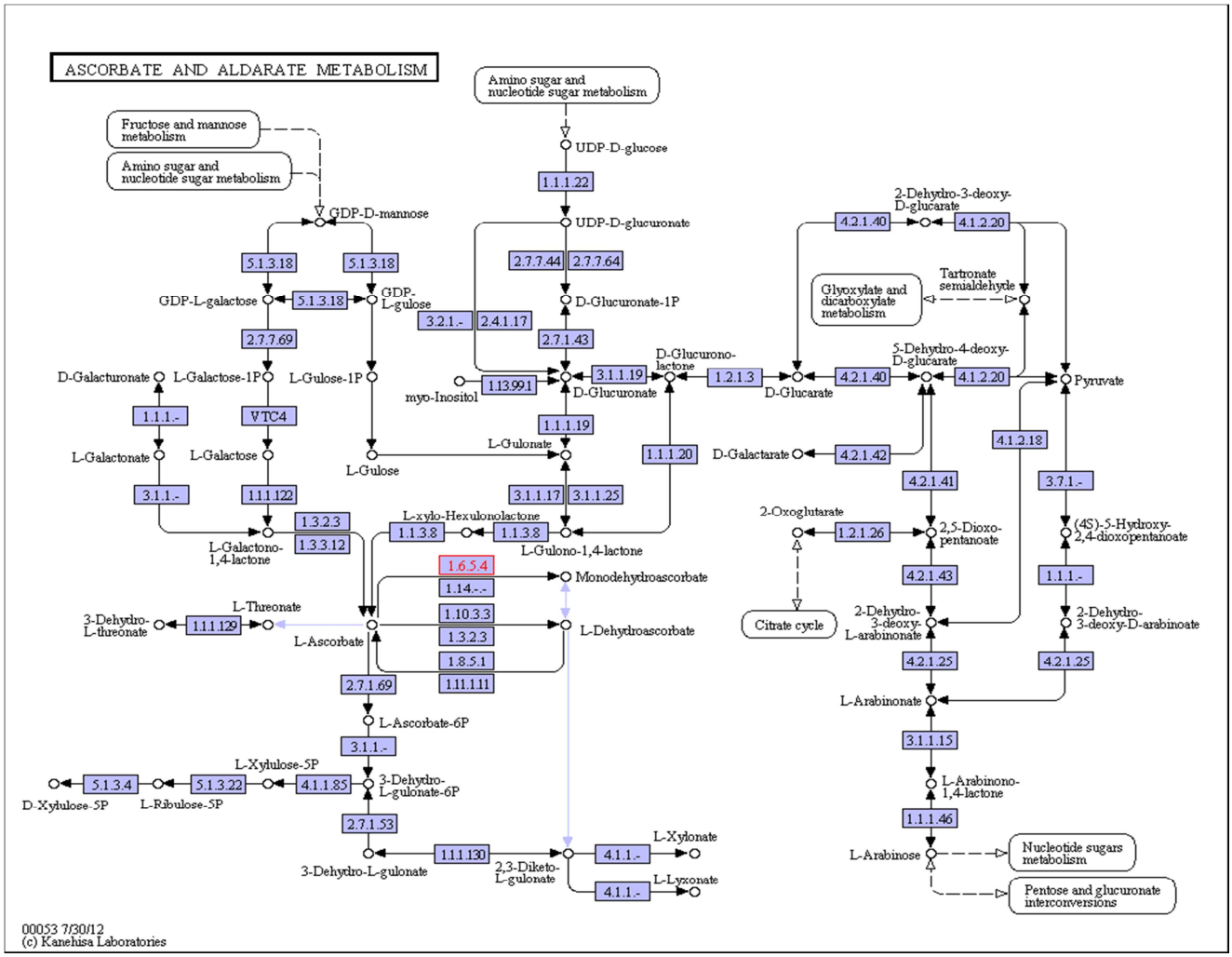

Figure 1. *Metabolic reactions involving vitamin C.*

An important characteristic of vitamin C is that it is easily oxidized; this is an essential aspect in vivo because it keeps enzymes in their reduced, active form. Also vitamin C is a strong antioxidant - it reduces free radicals (gives H^+) and (OH^-) reaction with organic compounds (cellular respiration -> O_2 -> O_2^- ->$H_2O_2^-$> OH^-).

L-arginine: acid 2-amino-5-guanidinovaleric; formula $C_6H_{14}N_4O_2$; Molecular mass 174; semi-essential; synthesized from citrulin argininosuccinat sintetase + argininosuccinase) or ornithine (arginase)

It needs specific transport for the cellular membrane and is a basic amino acid (like histidine and lysine)

pKa arginine: amino -9.0; R – 12,5

pKa lysine: amino -9.0; R - 10,5

pKa histidine: amino- 9,3; R - 6.0

The interest for L-arginine has boomed after its cardiovascular effects were shown in the 1990's (induces a natural, physiologic release of nitric oxide) and a 1999 metaanalysys showed that 25883 articles were written to the issue between January 1966 to July 1999 (1).

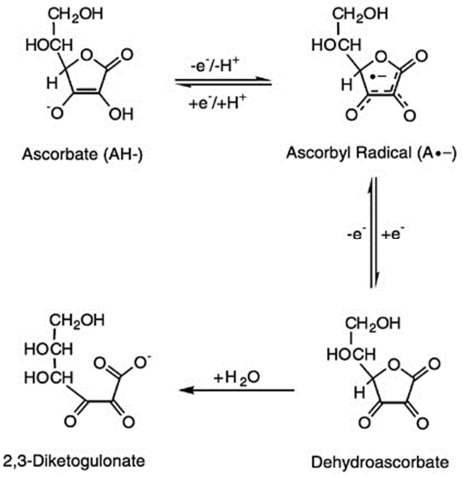

Figure 2. *Redox reactions involving vitamin C.*

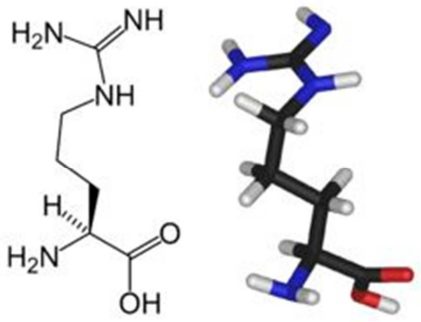

Figure 3. *L-Arginine molecule has small size and basic moieties.*

The immunological actions of arginine were highlighted in the 1980's by Dr Barbul, surgeon from Baltimore, while trying to improve wound healing and recovery after surgery using a substance with no serious risks or side effects. His team has conducted experiments in rats on wound healing with arginine treatment and showed arginine's effects on the thymus: increases its weight in the healthy animal; minimizes the involution of the thymus linked to the wound healing process; significant increase in lymphocyte content of thymus, especially the total number of lymphocyte and lymphoid blastogenesis in response to mitogens. A 1981 study (2) on healthy volunteers (n=21) has shown an increase in the activity of lymphocytes in peripheral blood and blastogenesis in response to nonspecific mitogens (concanavalin A, phytohemaglutinin) – while the total number of lymphocytes and the T/B ratio remained unmodified. A 1990 study (3) with 36 healthy volunteers – has shown the effect of arginine supplementation on wound healing and T lymphocyte function. 3 groups of 12 patients each: administration for 2 weeks with 30 g arginine HCl (24,8 g free arginine); 30 g arginine aspartate (17 g L-arginine); and placebo. It involved measuring mitogenesis in peripheral lymphocytes in response to phytohemaglutinin and concanavalin A initially, and after 1 and 2 weeks. Arginine has stimulated lymphocyte mitogenesis in a dose-dependent manner, confirming its effect on healing and improving immune response. A review of those studies and newer information on arginine's actions was published in 2004 (4).

Even though by 2000 the knowledge of arginine action on immune cells included its promotion of T-cell proliferation and generation of lymphokine-activated killer cells (5), a much greater understanding of its actions was gathered by further studying arginine's actions from the level of tissue and cell to its biochemical functions and molecular interactions. It was thus shown that it is involved in many pathways and linked to important molecules such as nitric oxide, creatine phosphate, agmatine, polyamines, ornithine, and citrulline, while it serves as substrate for two enzyme systems: arginase (part of the urea cycle) and nitric oxide synthase.

A comprehensive review on the immune functions of arginine (6) shows that arginine acts physiologically involving both nitric oxide independent and dependent pathways. Via nitric oxide it modulates vascular tone, expression of adhesion molecules, leukocyte adhesion, and platelet aggregation. It is postulated that nitric oxide synthase and arginase competes for L-arginine as a substrate and this event appears to play a key role in the regulation of the inflammatory process.

Another review (7) shows that the switch of arginine as a substrate for the cytostatic iNOS/NO axis to the pro-growth arginase/ ornithine/polyamine and proline axis is subject to regulation by inflammatory cytokines as well as inter-regulation by the arginine metabolites themselves; arginine is the precursor of another important biogenic amine – agmatine.

The interplay between inflammation and cancer and its role in immunity has even prompted using arginine in some types of neoplasia (8); in this 2013 study, 37 patients with head & neck cancer given supplements with arginine and omega-3 fatty acids (8,4 or 12.6 g arginine/day) showed improved lymphocyte levels.

3. Increasing pH Hinders Some Viruses

A different aspect altogether on arginine's actions during the immune response involves its physiologic ability to modify the pH of its environment. A very important finding on this direction was presented in a 2006 study (9) which showed that hepatitis C infection is mediated by a pH-dependent membrane fusion process, a pH lower than 6.3 being needed for infection. Those results were replicated in a 2009 study (10) which showed that the fusion of hepatitis C virus to cellular membrane is pH-dependent, but receptor-independent. Modifying the pH of the cellular membrane units was shown to be the main effect of arbidol (11), an antiviral successfully used to treat influenza by blocking the fusion of viral hemagglutinin with the cellular membrane.

It is thus very likely that arginine – with pKa 9.0 and 12,5- (and possibly other basic amino-acids - lysine, histidine, ornithine) defeats some viral activities by simply raising the pH of the membranes above a threshold pH where fusion of viral particles with the cellular membrane stops, thus limiting and preventing viral replication. The interplay between

arginine and vitamin C is yet to be elucidated, but it is probable that vitamin C helps destroy the viral nucleic acids (both DNA and RNA) while they are freely circulating outside the cells and while their fusion with the cell membrane is being hindered by arginine's actions.

4. Dosage Considerations and Conclusion

The doses we used for antiviral treatment were 3-5 g of arginine and 3-4 g of vitamin C divided in 3-4 daily administrations. The safety of such doses is very good, especially given the short treatment duration (up to 14 days of continuous administration). It is known from studies and clinical practice that arginine doses between 4-20 g are safely used in adults for cardiovascular conditions (angina pectoris, intermittent claudication, etc.) and even in premature infants up to 1 g/day was safely administered to prevent inflammation of the digestive tract.

Finally, while the separate roles of arginine and vitamin C in improving immunity are well studied, there is not much information on the concomitant action of the two substances, which clearly act in synergistic ways and greatly improve the functioning of the immune system against viral infections. We are making efforts to obtain research support in this direction (12). This is one of the rare situations where clinical success precedes laboratory research, and the promise of an efficacious and very affordable antiviral treatment which acts in ways yet to be detailed is too great to go unheeded.

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