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ASCORBIC ACID: ITS ROLE IN IMMUNE SYSTEM, CHRONIC INFLAMMATION DISEASES AND ON THE ANTIOXIDANT EFFECTS

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Annotation: Vitamin C (ascorbic acid (AA)) is very popular for its antioxidant properties. Consequently, many other important aspects of this multifaceted molecule are often underestimated or even ignored. In the present paper, we have tried to bring to the foreground some of these aspects, including the peculiarities of the AA biosynthetic pathway in different organisms, the remarkable function of AA as a co-substrate of many important dioxygenases, the role of AA-regenerating enzymes and the known pathways of AA catabolism, as well as the intriguing function of AA in gene expression.

Key words: vitamin C, mannose, L-galactose, oxidative stress, antioxidants, brain, antinflammatory role; antiviral role; ascorbic acid; chronic diseases; immune system; inflammation

Introduction

Since its discovery in the late 1920s [1], probably no other chemical has ever been as celebrated as ascorbic acid (AA). The beneficial effect of vitamin C is almost universally recognised. The reason for this unprecedented popularity is probably linked on one hand to common sense (AA is present in relatively high amounts in fruit and vegetables, which are known to be healthy), and on the other hand – especially today – to expensive advertising campaigns for vitamin C-based products.

Until a few decades ago, the most common answer to the question ‘what is the function of vitamin C?’ would have been the same given by Albert Von Szent Györgyi in 1937, when he was awarded the Nobel Prize for the discovery of AA: it is the factor able to cure the variety of clinical symptoms known as scurvy, a syndrome occurring in humans whose diet is deficient in fresh fruit and vegetables. At that time, however, little molecular explanation for this effect was available. Nowadays, the same question would receive a different answer. Not many would mention scurvy, as this pathological state is no longer very common. Some specialists in the field would explain that the inability of humans to synthesise AA is due to the lack of L-gulono-lactone oxidase (GulL-ox), the last enzyme in its biosynthetic pathway. A large majority of people asked (irrespective of their scientific education) would promptly answer that AA is an antioxidant which efficiently scavenges toxic free radicals and other reactive oxygen species (ROS) formed in cell metabolism. Actually, ROS are associated with several forms of tissue damage and disease and also with the process of ageing [2]. Aerobic organisms have evolved intricate and interrelated processes for protection against the effects of free radicals and derived toxic species, including both enzymatic and non-enzymatic defences. Enzymatic mechanisms include superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-px) and, in plants, ascorbate peroxidase (AA-px).

According to the generally assumed model of enzyme-mediated removal of ROS [3], SOD catalyses the disproportionation of superoxide anion to H_2O_2 and oxygen; in turn H_2O_2 is converted by CAT into water and molecular oxygen. CAT turnover number is very high, but its affinity for H_2O_2 is relatively low, and consequently a certain amount of H_2O_2 remains in the cell. This is potentially troublesome, since H_2O_2 can react with superoxide anion formed in oxidative metabolism and generate the highly reactive hydroxyl radical. GSH-px and AA-px are capable of removing low amounts of H_2O_2 due to their high affinity for H_2O_2. Thus, the co-operativity of SOD, CAT and peroxidases ensures low levels of superoxide anion and H_2O_2 and therefore limits the risk of hydroxyl radical formation (Fig. 1). In addition to enzymatic mechanisms, some compounds, known as antioxidants, are present in the cell that, on entering into redox reactions, contribute an electron to neutralise free radicals to non-reactive species. Many chemicals could serve this purpose because the high reactivity of free radicals results in extracting an electron from almost any available molecule. However, an efficient biological antioxidant is supposed to do more than simply react with free radicals: (a) it must be present in an adequate amount in the cell, (b) it must react with a variety of free radicals, and (c) it must be suitable for regeneration [4]. This combination of properties is typical of AA; therefore this compound is considered the perfect antioxidant for the cells of nearly all aerobic organisms. However, it should be considered that under several circumstances ROS and free radicals in general also play a pivotal role in signal transduction and the mechanism of enzyme action [5], [6], thus indicating that the function of antioxidants is the fine regulation, rather than total extinction of free radicals. Moreover, in some cell compartments (i.e. plant cell walls) AA regeneration is impaired due to the absence of NAD(P)H and GSH. Eventually, if AA can be considered an efficient antioxidant and consequently an efficient free radical scavenger, it cannot be ignored that under some circumstances (such as the presence of metal ions and adequate pH conditions) AA has a pro-oxidant and even mutagenic effect [7], [8], [9].

All the above-mentioned observations lead us to conclude that deciphering the details of the antioxidant action which is attributed to vitamin C it is still very difficult for at least two reasons: (a) we lack reliable analytical methods to accurately measure AA distribution in different cell compartments, and (b) AA antioxidant action takes place by means of non-enzymatic (and therefore more difficult to predict) reactions, excepting AA-px. In addition, considering the key role of AA in cell metabolism to be limited to its antioxidant action could be misleading. In fact, this approach does not take into consideration many AA-dependent metabolic reactions that influence essential physiological processes, ranging from cell division to gene expression and the activation of biological defence mechanisms [10].

The aim of the present article is to summarise our present knowledge on the AA system in both animals and plants, in order to demonstrate that the pleiotropic action of vitamin C is, in all organisms, largely due to its function as a co-substrate of dioxygenases, a versatile family of enzymes. Moreover, we have also tried to suggest new directions for research, in order to give a three-dimensional portrait of this very well known, but still poorly understood compound.

Ascorbic acid (vitamin C) is an abundant component of plants. It reaches a concentration of over 20 m*M* in chloroplasts and occurs in all cell compartments, including the cell wall. It has proposed functions in photosynthesis as an enzyme cofactor (including synthesis of ethylene, gibberellins and anthocyanins) and in control of cell growth. A biosynthetic pathway via GDP-mannose, GDP-L-galactose, L-galactose, and L-galactono-1,4-lactone has been proposed only recently and is supported by molecular genetic evidence from the ascorbate

deficient vtc1 mutant of *Arabidopsis thaliana*. Other pathways via uronic acids could provide minor sources of ascorbate. Ascorbate, at least in some species, is a precursor of tartrate and oxalate. It has a major role in photosynthesis, acting in the Mehler peroxidase reaction with ascorbate peroxidase to regulate the redox state of photosynthetic electron carriers and as a cofactor for violaxanthin de-epoxidase, an enzyme involved in xanthophyll cyclemediated photoprotection. The hypersensitivity of some of the vtc mutants to ozone and UV-B radiation, the rapid response of ascorbate peroxidase expression to (photo)oxidative stress, and the properties of transgenic plants with altered ascorbate peroxidase activity all support an important antioxidative role for ascorbate. In relation to cell growth, ascorbate is a cofactor for prolyl hydroxylase that posttranslationally hydroxylates pro line residues in cell wall hydroxyproline-rich glycoproteins required for cell division and expansion. Additionally, high ascorbate oxidase activity in the cell wall is correlated with areas of rapid cell expansion. It remains to be determined if this is a causal relationship and, if so, what is the mechanism. Identification of the biosynthetic pathway now opens the way to manipulating ascorbate biosynthesis in plants, and, along with the vtc mutants, this should contribute to a deeper understanding of the proposed functions of this multifacetted molecule.

Ascorbic acid (vitamin C) is required in the diets of humans, certain other primates, guinea pigs and several other species [l-5]. These animals, in contrast to most others, do not have the ability to synthesize ascorbic acid from glucose because they lack the enzyme L-gulonolactone oxidase, which is required for the formation of 2-keto-L-gulonolactone; this compound is spontaneously converted to ascorbic acid. Ascorbic acid deficiency leads to scurvy, which can be prevented in humans by administration of as little as 10mg of ascorbic acid per day [6]. Many have thought that larger doses of ascorbic acid might be beneficial for health [3,7]. Szent-Gybrgyi, soon after his pioneering research on ascorbic acid, considered the idea that it might have a useful role in the therapy of infections. Ascorbic acid has been claimed to be effective in the prevention and treatment of cancer [7-lo], the common cold [11,121, atherosclerosis [3,13,14], cataracts [15] and AIDS [16]. It has been claimed that increased intake of ascorbic acid has favorable effects on the immune system, healing of wounds, various types of stress including those due to physical exertion, cigarette smoking, and extremes of temperature, allergic responses, and mental health problems. These subjects have been reviewed [3,7,15,17,18]. In general, each of these claims has been contradicted, at least to some degree, by subsequent studies and the literature continues to reflect controversy apparently because it has not yet been possible to obtain reproducible objective evidence. A claim that a particular drug or treatment can cure a wide variety of conditions, perhaps everything from housemaid's knee to tuberculosis, is typically viewed with skepticism. So too might one be justifiably dubious about a theory according to which a wide variety of diseases are produced by oxidative phenomena and free radicals. Nevertheless, if such a theory is even partially valid, beneficial effects might be expected after administration of compounds such as ascorbic acid which has potent reducing properties and which is highly reactive.

Ascorbic acid in the brain

Ascorbic acid is highly concentrated in the central nervous system. Measurement of the extracellular concentration of ascorbate in animals, mainly by the technique of voltammetry in vivo, has demonstrated fluctuation in release from neuropil, both spontaneously and in response to physical stimulation of the animal and to certain drugs. Although in the adrenal medulla ascorbate is co-released with catecholamines, release of ascorbate from brain cells is associated principally with the activity of glutamatergic neurones, mainly by glutamate-ascorbate heteroexchange across cell membranes of neurones or glia. This phenomenon is discussed in relation to a possible role of ascorbate as a neuromodulator or neuroprotective agent in the brain.

Ascorbic Acid: Its Role in Immune System and Chronic Inflammation Diseases

Ascorbic acid (AA), also known as vitamin C, was initially identified as the factor preventing the scurvy disease, and became very popular for its antioxidant properties. It is an important co-substrate of a large class of enzymes, and regulates gene expression by interacting with important transcription factors. AA is important in all stressful conditions that are linked to inflammatory processes and involve immunity. It has been known for decades that the persistence of an inflammatory stimulus is responsible for the onset of many diseases. AA is essential to stimulate the immune system by increasing the strength and protection of the organism. Therefore, its immunostimulant, antinflammatory, antiviral and antibacterial roles are well known, we have summarized its main functions in different types of diseases related to the immune system and chronic inflammation. We can conclude that AA, due to its effects and diversity of regulated pathways, is suitable for use in various fields of medicine including immunology, toxicology, radiobiology and others. AA is not preferable to be used as an isolated mode of treatment, but it can be co-applied as an adjuvant to regulate immunity, gene expression and other important physiological processes. However, we propose that future studies will take into consideration the research of new combinations of antioxidant natural substances and drugs.

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