Importance of Vitamin C in Human Health and Disease

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Abstract Ascorbic acid (AsA or vitamin C) is an essential human micronutrient predominantly obtained from plants. Our primate ancestor lost its ability to synthesize AsA at a time when its diet was rich in AsA. Today, eating sufficient fruits and vegetables to obtain more than the minimum level of AsA consistently is a challenge for many people. Research is revealing the importance of AsA in human health well beyond merely preventing scurvy. AsA acts as a cofactor for enzymes involved in epigenetic programming. The link between AsA and epigenetics has profound implications on how dietary AsA might impact on human health. Epigenetic programming plays a crucial role in embryonic development, the progression of cancer, and age-related diseases and there is evidence AsA influences all of these processes. AsA also plays a key role in regulating iron uptake. Iron deficiency anaemia is the most common and widespread micronutrient deficiency, affecting around two billion people worldwide, especially women and children. While it has been long known that AsA enhances uptake of non-haem iron from food, recent studies have found that rather than simply acting in the gut to convert iron into a form that is more readily absorbed, AsA is likely a key regulator of cellular iron uptake. Increased understanding of the various cellular roles of AsA is revealing that regularly obtaining sufficient dietary AsA is important for long-term human health. Enhancing the AsA contents of crop plants has the potential to improve the uptake of dietary AsA and improve human health.

Keywords Vitamin C · Epigenetics · Iron absorption · Malnutrition

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1 Introduction

Unlike most animals, humans cannot synthesize ascorbic acid (AsA) due to mutations within the L-*gulono-γ-lactone oxidase* (*GLO*) gene, which in other animals encodes the enzyme catalysing the last step in the AsA biosynthetic pathway (Drouin et al. 2011). Humans must obtain AsA on a regular basis through their diet (Nishikimi et al. 1994) and the main source is fresh fruits and vegetables, which can vary greatly in their AsA contents.

Severe AsA deficiency results in scurvy, which was a major problem for sailors who lacked fresh fruits and vegetables in their diet. It has been estimated that two million sailors died of scurvy between 1500 and 1800 (Drymon 2008). In 1747, James Lind conducted the first clinical trial where he divided sailors into different trial groups and showed that citrus juice prevents scurvy (Lind 1757). However, Lind's discovery was largely ignored, and it took another 40 years before the British Navy began giving out lemon juice routinely. In 1907, Norwegian researchers Holst and Frölich were able to reproduce scurvy in guinea pigs (which fortuitously also have a non-functional *GLO* gene) by feeding them a diet of grain and flour (Holst and Frölich 1907) and 20 years later it was shown that scurvy is specifically caused by lack of AsA. Since then much research has been devoted to understanding AsA biosynthesis and catabolism, and its biological roles in plants and animals. We now appreciate that AsA is an essential molecule with diverse and critical biological functions.

2 Ascorbic Acid and Human Health

Why do we need dietary AsA? The physiological and biochemical functions of AsA are due to its ability to donate electrons (Du et al. 2012). AsA has two broad roles; it functions as a general antioxidant, and it is cofactor for mono- and di-oxygenase enzymes.

2.1 Ascorbic Acid as a General Antioxidant

Reactive oxygen species (ROS) are the by-products of normal metabolism, and the cell uses a range of antioxidants, including AsA, to avoid ROS damage. Cellular damage caused by ROS plays a role in ageing and many degenerative diseases, such as Alzheimer's disease (Hensley et al. 2000). Given the potent antioxidant properties of AsA, would increasing AsA consumption, e.g. by taking AsA supplements, be beneficial? While the supplement industry has promoted the health benefits of taking extra AsA and other antioxidants, there is no clear evidence that taking high doses of AsA in an attempt to increase the normal physiological levels of AsA

reduces oxidative stress or slows ageing or the progression of age-related diseases. All organisms already have sufficient antioxidants to keep ROS in balance, and there is no reason to believe taking large doses would be beneficial. However, it is important to ingest sufficient AsA to avoid deficiency. The balance between oxidation and antioxidation (redox balance) is critical in maintaining a health biological system (Bouayed and Bohn 2010). The antioxidant properties of AsA are needed throughout the body and play specific roles in some tissues. For example, AsA is found in eye tissue at high, millimolar levels, and this is proposed to protect the eyes from potential oxidative damage caused by solar radiation (Brubaker et al. 2000; Kern and Zolot 1987). AsA has an important role in the regeneration of other physiological antioxidants, in particular, vitamin E (Golumbic and Mattill 1941). Vitamin E functions to prevent lipid membrane oxidation and becomes oxidized in the process. AsA can reduce the oxidized vitamin E to maintain protection of membranes (Csallany et al. 1962). ROS also play important roles in the body and are involved in cellular signalling, regulation of immune responses, and fostering antioxidant defence responses (Bouayed and Bohn 2010). This balance means that high doses of antioxidants could be detrimental. For example, the immune system uses ROS to kill cancer cells before they metastasize and spread throughout the body and one study showed that mice given exogenous antioxidants had increased rates of metastasizing melanomas (Piskounova et al. 2015).

2.2 Ascorbic Acid as a Cofactor

Ascorbic acid serves as a cofactor for di-oxygenase (the Fe^{2+}/2-oxoglutarate-dependent di-oxygenases; 2-OGDO) and monooxygenase enzymes. The activity of the 2-OGDO enzymes require that core reactive iron atoms are reduced to Fe^{2+}, a step requiring AsA. Scurvy causes swollen, bleeding gums—sometimes teeth can fall out, severe joint or leg pain, skin that bruises easily. These symptoms arise from the reduced activity of the 2-OGDO enzyme, collagen prolyl 4-hydroxylase (CP4H), due to a lack of AsA. CP4H is required to hydroxylate the proline residues of collagen that form stable collagen fibres. Collagen is an essential component of connective tissue and as such has an essential role in wound healing. While scurvy is rare, poor vitamin C status is more common and is often undiagnosed since the early symptoms—fatigue, malaise, depression, and irritability are non-specific and unremarkable (Ben-Zvi and Tidman 2012). The fatigue and weakness of early scurvy is likely due to AsA role in the biosynthesis of L-carnitine (Du et al. 2012). L-Carnitine functions in energy metabolism, specifically the transport and oxidation of fatty acids and therefore is most important in tissues which derive their energy from fatty acids (Flanagan et al. 2010). The depression and mood swings characteristic of early scurvy are due to reduced neurotransmitters, as AsA is a cofactor for dopamine-β-monooxygenase, which converts dopamine to norepinephrine (Wimalasena and Wimalasena 1995).

Most people treated for scurvy feel better within 2 days and recover within 2 weeks. However, there may be more long-lasting effects of not consuming sufficient dietary AsA. Two classes of 2-OGDO enzymes are involved in epigenetic programming; the methylcytosine di-oxygenases (known as ten-eleven translocation (TET) di-oxygenases) that are responsible for DNA demethylation (Camarena and Wang 2016; Blaschke et al. 2013; Chen et al. 2013) and the Jumonji C domain-containing histone demethylases (Wang et al. 2011). The link between ascorbate and epigenetics has profound implications on how dietary ascorbate might impact on human health (Macknight et al. 2017). Epigenetic programming plays a key role in regulating development programmes and a link between AsA, epigenetics, and cancer has recently been established. Two recent high-profile papers have provided a link between AsA and leukaemia (Agathocleous et al. 2017; Cimmino et al. 2017). AsA was shown to play a role in the differentiation of blood-forming haematopoietic stem cells. A key step in this process of differentiation is the demethylation of DNA which alters gene expression. The enzyme TET2 carries out the first step in removing DNA methylation (the conversion of 5-methylcytosine to 5-hydroxy methylcytosine) and to achieve this the haematopoietic stem cells import 2–20 times more AsA via the upregulation of a specific ascorbate transporter (Agathocleous et al. 2017). AsA is thought to maintain TET activity by reducing Fe^{3+} to Fe^{2+} in the active site of the enzyme. Consistent with having an important role in stem cell differentiation, mutations in the TET2 gene are associated with various forms of leukaemia in humans. Experimentally reducing TET2 activity in mice also results in increased rates of leukaemia. In these mice, TET2 activity could be increased by administering AsA and this increased stem-cell differentiation and reduced cancer rates (Agathocleous et al. 2017). Similarly, when human acute myeloid leukaemia cancer cells were transplanted into mice, AsA supplementation induced differentiation and the death of the leukaemia cells (Cimmino et al. 2017). These experiments are consistent with epidemiological evidence indicating that a higher consumption of fruits and vegetables correlates with a lower risk of most types of cancer (Carr and Frei 1999; Li and Schellhorn 2007). However, randomized clinical trials have suggested that AsA supplementation does not reduce the risk of cancer (Galan et al. 2005; Gaziano et al. 2009; Hercberg et al. 2004; Lin et al. 2009; Qiao et al. 2009; Taylor et al. 1994). This apparent discrepancy is likely due to both, the AsA status of the patients in the clinical trials, and the longer term effects of low AsA consumption. People who are AsA deficient or had been AsA deficient for periods of their life might have higher rates of cancer. However, simply giving people who have had sufficient dietary AsA, extra AsA would likely have no effect on cancer rates.

There is a large body of evidence that maintaining normal AsA levels provides protection against other human diseases, such as cardiovascular and neurodegenerative disease (Chambial et al. 2013; Harrison 2012). Given the fundamental roles epigenetics has in controlling gene expression throughout our life, any alteration in this process could result in disease, especially those that might involve slow cumulative changes typical of age-related diseases (Camarena and Wang 2016). Again, there is no evidence that taking AsA supplements on top of a normal, healthy diet provides any protective effects (Chambial et al. 2013; Harrison 2012).

3 Role of AsA in Iron Absorption

AsA also plays an important role in the uptake of dietary iron. Iron deficiency is the most common and widespread nutritional disorder in the world, predominantly affecting developing countries but is also the only nutrient deficiency significantly prevalent in industrialized countries (World Health Organization 2015). The predominant dietary source of iron is from non-haem iron, sourced from fruits and vegetables. Absorption of iron from non-haem sources is lower than that of haem iron from animal sources and several factors influence this (Lynch and Cook 1980). AsA was initially thought to have roles in non-haem iron absorption as a reductant and a chelator (Conrad and Schade 1968). When iron is consumed, it is oxidized to the Fe^{3+} state, and for absorption to occur, iron must be reduced to the Fe^{2+} state. AsA was proposed to be a reducing agent responsible for the reduction of iron (Gunshin et al. 1997), but this has now been shown to be performed by the action of ferrireductase (McKie et al. 2001). However, this does not exclude AsA from being involved in the reducing process. The main role for AsA in iron absorption is therefore proposed to be promoting iron stability (Teucher et al. 2004). AsA could act to improve iron stability through its action as a chelator, forming an AsA-iron complex (Conrad and Umbreit 1993). This complex would maintain the solubility of iron with the increasing pH of the small intestine (duodenum) allowing for its absorption via the intestinal mucosal lining cells (Teucher et al. 2004). AsA also influences iron absorption by acting to negate the effect of inhibitors such as phytates and polyphenols (Hurrell and Egli 2010).

In addition to enhancing the iron absorption in the gut, AsA aids cellular iron uptake. Iron is a cofactor for a number of enzymes and is also needed for the haemoglobin and myoglobin to bind oxygen. Iron is highly toxic to cells and virtually all iron transported in the plasma is bound to the iron-binding protein, transferrin. Recent work indicates that AsA enhances transferrin-dependent iron uptake and also stimulates the synthesis of the cellular iron-binding protein, ferritin (Lane et al. 2013; Lane and Richardson 2014). Thus, AsA appears to play a central role in controlling iron levels and this might explain why vitamin C deficiency can result in anaemia.

Early feeding studies involving a single meal eaten with and without orange juice showed significant differences in iron absorption; iron absorption increased from 3.7 to 10.4% in one study (Callender et al. 1970) and 2.5-fold in a second study (Rossander et al. 1979). Direct supplementation of AsA in a single meal has resulted in a 2.9-fold increase in non-haem iron absorption (Fidler et al. 2004). Variation in single meal studies has been attributed to differences in meal compositions, in particular, the levels of iron absorption inhibitors and enhancers other than AsA. The molar ratios of AsA to non-haem iron and inhibitors has been shown to affect iron absorption (Gillooly et al. 1983, 1984; Hallberg et al. 1986, 1989; Siegenberg et al. 1991).

Studies which have looked at the effect of AsA on non-haem iron in a complete diet have shown either no or only a small effect compared to single meal studies

(Cook and Reddy 2001). A significant increase in iron absorption was observed in Mexican women, with a two-fold increase in dietary AsA resulting in a 3.3-fold increase in iron absorption (Diaz et al. 2003). The women in this study were iron deficient and normally had a diet low AsA (Diaz et al. 2003). It is likely that if individuals with normal levels of iron and AsA, consume more AsA it will have little effect on iron uptake. However, for individuals deficient in iron and AsA, increasing dietary AsA will have the added benefit of increasing iron uptake. Thus, increasing AsA levels in food crops might be an effective strategy to reduce iron deficiency.

4 Ascorbic Acid and the Common Cold

AsA supplementation is commonly marketed for the maintenance of good health and the prevention of the common cold. However, there has been significant controversy in the scientific literature for at least 70 years about whether AsA prevents or treats the common cold. Reviews of the literature have shown that AsA does not reduce the incidence of colds in the general population, showing AsA supplementation for this purpose to be unjustified (Hemilä and Chalker 2013). However, individuals exposed to brief periods of severe physical exercise, cold environments, or those with marginal AsA status could benefit from AsA supplementation to reduce the incidence of colds (Douglas et al. 2007; Wintergerst et al. 2006). While there is some evidence that AsA reduces duration and severity of colds when AsA is taken on regular basis, supplementation once a cold has been contracted was ineffective (Hemilä and Chalker 2013). As with AsA other roles, it is likely that the major benefit is when individuals who are not getting sufficient dietary AsA are provided with supplementary AsA (Johnston et al. 2014).

5 Recommended Daily Intake of AsA

How much dietary AsA do we need? AsA is water soluble and must be regularly ingested, as excess cannot be stored. The recommended daily intake (RDI) or recommended daily allowance (RDA) for nutrients is the amount needed to meet the requirements of 97–98% of healthy individuals and are set by representative agencies for each country. The intake of a particular nutrient required each day is dependent on the body's needs, and the efficiency of uptake and excretion. RDA for AsA varies between countries (Table 1), and it has been suggested a higher recommended intake might be required for optimum health (Carr and Frei 1999; Levine et al. 1996). The amount of dietary AsA needed also depends on an individual's lifestyle. The USA RDA states a requirement for smokers to have an AsA intake 35 mg/day higher than their non-smoking counterparts (Institute of Medicine 2000), due to smoking significantly reducing AsA levels (Schectman et al. 1989). Associated with RDI and RDA is the upper level of intake or maximum daily allowance. This is the

Table 1 AsA recommended daily amounts in mg

Individuals	Australia/NZ[a]	USA[b]
0–6 months	35	40
7–12 months	35	50
1–3 years	35	15
4–8 years	35	25
9–13	40	45
14–18	40	75(M), 65(F)
19+	45	90(M), 75(F)
Pregnancy 18 and under	55	80
Pregnancy 19 and older	60	85
Breastfeeding 18 and under	80	115
Breastfeeding 19 and over	85	120

[a]Capra (2006)
[b]Institute of Medicine (2000)

intake at which a mineral or nutrient becomes toxic due to excess. The selective uptake of AsA by humans means there is a very low risk of toxicity from AsA. The Australian and New Zealand guidelines have set a prudent limit of 1000 mg/day (Capra 2006).

AsA deficiency is prevalent in developing nations and is also present in developed nations. Older studies revealed 20–30% of adults in the USA consume less than 60 mg AsA daily and about 15% were deficient (Hampl et al. 2004). More recent studies have revealed insufficient levels in Canadians with 14% AsA deficient and 33% consuming suboptimal amounts (Cahill et al. 2009) and 40% of Mexican women AsA deficient (Garcia et al. 2003). Given our new understanding of the importance of consuming sufficient AsA, this could be a significant factor in reduced life-long good health.

6 Conclusion and Future Perspectives

When our primate ancestors lost the ability to synthesize AsA, their diet of vegetation and fruits would have provided 25–100 times more AsA than the current RDA (Macknight et al. 2017). In this situation, there would have been no evolutionary disadvantage in not being able to make AsA. However, today consuming sufficient fruits and vegetables to provide the optimal intake of dietary AsA is a challenge for many people, with the majority of staple crops having very low levels of AsA.

As we begin to understand the fundamental importance of AsA in health and disease, it is clear that consuming sufficient AsA is not just important to avoid scurvy. AsA plays a crucial role in many essential cellular processes and while consuming excess AsA is likely to be of little benefit, consuming insufficient AsA will likely contribute to poor health. As our knowledge of how plants regulate the

synthesis of AsA increases, there will be opportunities to increase the AsA content of crops to help alleviate AsA deficiency (Macknight et al. 2017). Since AsA also regulates iron uptake, increasing dietary AsA should also help reduce iron deficiency.

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