

Dynamic Flow: A New Model for Ascorbate

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Abstract

This paper presents a new account of the action of ascorbate in humans: the dynamic flow model. The model is consistent with previous studies and with the known properties of vitamin C. Based on this model, we propose a mechanism by which human physiology can compensate for losing the ability to synthesize vitamin C. The dynamic flow approach links Linus Pauling's megadose suggestions with other reported effects of massive doses for the treatment of disease. The model also refutes the current low dose hypothesis and resulting recommendations for dietary intakes.

Introduction

This paper introduces the dynamic flow model, which describes the function and pharmacokinetics of vitamin C. In dynamic flow, an excess of oral ascorbate provides a steady flow of electrons through the body. Human physiology is restored to the condition before the evolutionary loss of the ability to synthesize ascorbate. The model supports and extends the ideas of Linus Pauling, Nobel Prize winner and founder of orthomolecular medicine. Back in the early 1970s, Pauling popularized the idea that high doses of vitamin C are essential to health.¹ The ensuing controversy about vitamin C requirements continues to this day. However, this situation is about to change, since the dynamic flow model brings together evidence from both sides of the argument, resolving the apparent contradictions.

Shortly after Pauling's death in 1994, the National Institutes of Health (NIH) published a highly acclaimed series of

papers, concerning the pharmacokinetics of ascorbate.^{2,3,4} These appeared to show that the claims of Pauling and others for megadose supplementation were incorrect. The NIH reported that doses of vitamin C as low as 200 mg per day saturate the body. This saturation claim was highly influential, becoming a cornerstone of the Recommended Dietary Allowance (RDA).⁵⁻¹¹ A purpose of this brief review is to establish definitively that the NIH papers, and hence the justification for the RDA, contain serious errors. Furthermore, when interpreted correctly, the NIH data supports the claims for high daily intakes.^{12,13}

Low-dose Hypothesis

The low-dose hypothesis, which forms the basis for the RDA, is that humans require only a few milligrams of ascorbate each day. This is in contrast to the majority of other animals, which manufacture their own vitamin C at substantially higher levels. In humans, an intake of less than 10 milligrams per day will prevent acute sickness and death from the deficiency disease scurvy. Researchers initially assumed that people do not need vitamin C above the scurvy-prevention level. However, objectors to this hypothesis pointed out that such a minimal intake may not be optimal; low doses could result in degenerative diseases, a compromised immune system and reduced ability to respond to stress.^{14,15}

The US Institutes of Medicine (IoM), who are responsible for setting the recommended allowances, used the NIH pharmacokinetic papers to justify their low dose RDA. Their argument was simple: if the body is saturated at an intake of 200 mg per day, there is no point considering a higher dose, as it will just be excreted. The NIH had themselves recommended

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an RDA, based on their studies of ascorbate pharmacokinetics in blood plasma and white blood cells. The IoM used these results, somewhat arbitrarily, to determine a recommended intake within the range 0-200 mg per day.

Megadose Hypothesis

The megadose hypothesis, popularized by Pauling and Stone, suggests that people need one or more grams of ascorbate per day. The proponents based their ideas largely on evolutionary arguments. Most animals synthesize large amounts of ascorbate internally or, less commonly, obtain equivalent gram-level intakes from their diets. Animals also increase their production of vitamin C when they are diseased. Therefore, researchers proposed that higher doses provide increased resistance to many, if not all, diseases. These suggestions are consistent with known biology and evolution.

Following Pauling's death, the NIH pharmacokinetic results led to a widespread assumption that the megadose hypothesis was wrong. If body saturation occurs at a daily intake level of 200 mg, the opponents argued, higher doses are unnecessary. They added that there is no point risking the possible side effects of higher doses, if such doses offer no benefit. Perhaps surprisingly, this second objection is logically inconsistent with the first. Saturation implies that higher doses are ineffective because the doses are not absorbed. However, if a high dose offers no benefits because the body does not absorb it, then similarly it should not lead to toxic effects, because it has not been absorbed.

Dual-phase Excretion

The ascorbate plasma levels corresponding to varying intakes of ascorbate exhibit dual-phase pharmacokinetics. The first phase occurs when blood levels are low: below 70 $\mu\text{M/L}$. In this phase, the

kidney's sodium dependent vitamin C transporters (SVCT) reabsorb ascorbate, but not its oxidized form, dehydroascorbate.^{16,17} When levels are relatively low, the transporters prevent ascorbate being lost in the urine. The second phase occurs when blood levels are high; during this phase, the body excretes ascorbate rapidly, as it does other small, water-soluble, organic molecules.¹⁸

The plasma half-life of ascorbate is widely reported to be between 8-40 days.^{11,19} However, this applies only to periods of deficient intake, when the kidney transporters are actively reabsorbing the vitamin to prevent acute scurvy. When intake levels are higher, rapid excretion occurs: during this phase, ascorbate has a half-life of about half an hour. The NIH pharmacokinetic data shows the rapid excretion phase clearly: we calculated this result from their initial plasma concentration decay slope for intravenous doses. This rate of decay follows the principles of pharmacology, as applied to a molecule with the characteristics of ascorbate.

Blood Plasma Levels

The NIH performed a series of pharmacokinetic experiments purporting to show that, with oral ascorbate, blood plasma is saturated at approximately 70 $\mu\text{M/L}$. This figure, however, is inconsistent with the researchers' own data in the same and later papers. The original papers show graphs in which the plasma level, following oral administration, is much higher than 70 $\mu\text{M/L}$. Subsequent papers suggest sustained plasma levels of at least 220 $\mu\text{M/L}$, following oral administration.²⁰ These higher plasma levels are consistent with other reports in the literature.^{49,21,22}

Bioavailability

In order to be used by the body, a dose of ascorbate must be absorbed. The NIH chose bioavailability as their measure

of the absorption of oral doses, claiming this was essential to establish an RDA for vitamin C.^{2,3} Bioavailability is a relative measure, which compares the oral absorption of a substance to an equal injected dose. If the oral dose results in the same plasma level as an equivalent intravenous dose, then the bioavailability is said to be complete. The NIH stated that the bioavailability of ascorbate is complete at an intake of 200 mg. This means that a dose of 200 mg or less is completely absorbed by the body, whereas a smaller proportion (although a higher absolute amount) of higher doses is absorbed. Unfortunately, the name is misleading; many people think bioavailability means the amount available to the tissues, which is wrong.

In considering bioavailability, the NIH ignore the short half-life of vitamin C during the rapid excretion phase. They indicate that bioavailability is complete for a single 200 mg dose then, implicitly, jump to an RDA (i.e. daily dose) of 200 mg. Since blood plasma levels above 70 $\mu\text{M/L}$ have a half-life of approximately half an hour, doses taken several hours apart are independent, as is their bioavailability. Two doses taken 12 hours apart have the same absorption characteristics as each other, which means that splitting a single large dose into several smaller ones, taken a few hours apart, increases the effective bioavailability of the large dose.

The NIH's assertion, that bioavailability is complete at 200 mg, implies that this is a fixed property of ascorbate. However, Cathcart's bowel tolerance method²³ indicates that individual bioavailability can vary by a factor of at least two orders of magnitude. This widely confirmed variation depends upon the current state of health of the subject. This means that bioavailability is not a static property of ascorbate, but is subject to individual differences and varies with the timing of the dose. If, as the NIH and IoM have sug-

gested, bioavailability is fundamental to determining the RDA, then it follows that the appropriate intake will vary widely, both between individuals and also over time for the same person, depending on factors such as state of health and intake patterns.

Ascorbate Transporters

Two families of biochemical pumps, SVCT and glucose transporters (GLUT), pump vitamin C into cells. The SVCT pumps are specific to ascorbate,²⁴ whereas GLUT transporters normally transport glucose but, since dehydroascorbate is structurally similar to glucose, can also transport oxidized ascorbate.^{25,26} Their transport rates for glucose and dehydroascorbate are similar, for equal plasma concentrations. However, glucose is normally several orders of magnitude more concentrated, so the role of GLUT transporters in pumping dehydroascorbate, as a mechanism for cellular accumulation of ascorbate, may have been overemphasized. The transporters' role may be to remove dehydroascorbate, which is relatively toxic, from the plasma, so the cells can reduce it back to ascorbate. The electrons used to reduce the dehydroascorbate come from normal metabolism.²⁷

An important feature of ascorbate transporters is often overlooked. Cell types in the body have different and characteristic forms of transporters on their surfaces. Even cells with identical transporter types may differ in the quantity and rate of ascorbate accumulation. The absorption and resulting intracellular concentration depend on the quantity, or concentration, of transporter molecules on the cell surface.^{13,28,29} This value can change between cells and even within a group of cells; for example, the number of GLUT4 transporters in the cell membrane increases rapidly in response to the hormone insulin.³⁰

Red Blood Cells

Red blood cells could provide a model for the uptake of ascorbate by many tissue cells. They are easily sampled cells that might be used to indicate the bodies' ascorbate requirements for the following reasons. The concentration of ascorbate in red blood cells is similar to that of the surrounding plasma.³¹⁻³³ Under physiological conditions, transport of ascorbate across the red blood cell membrane is relatively slow and internal concentrations (20-60 μM) correspond to plasma levels in unsupplemented individuals.³⁴⁻³⁶ Hence, raising the mean plasma concentration will lead to high levels of ascorbate in these cells, while transient changes will have little effect. Erythrocytes have a high capacity to import dehydroascorbate using GLUT1 and reduce it back to ascorbate.³⁷⁻³⁹ Uptake of dehydroascorbate by erythrocytes is a protective mechanism that can lower its concentration in healthy plasma to levels lower than 2 $\mu\text{M/L}$.^{40,41} Once inside the red blood cell, dehydroascorbate is reduced to ascorbate.^{36,39,42} Thus we can suggest uptake of dehydroascorbate by red blood cells is an antioxidant mechanism to prevent damage in many disease states.

White Blood Cells

White blood cells are highly specialized in terms of their redox metabolism,⁴³ ascorbate transport^{44,45} and biochemistry. Phagocytic white blood cells use oxidants to damage and absorb foreign bodies. Metabolism, ascorbate absorption and cycling increase greatly when white blood cells are activated.⁴⁶ Transporters and related mechanisms in white blood cell membranes allow them to accumulate ascorbate, even when levels are low in the surrounding medium.

White blood cells provide a model for a limited number of cells in the body, for which ascorbate deprivation is critical. Such cells contain transport mechanisms

that prevent loss when the rest of the body is deficient. Therefore, they do not provide a model for levels of ascorbate in the body as a whole. Most tissues do not accumulate ascorbate in the same way as white blood cells; if they did, such cells would contain millimolar levels, giving a total body pool at least 10 times greater than the observed value of one to two grams.

Redox Cycling and Tissue Health

Ascorbate and dehydroascorbate are involved in a redox cycle.⁴⁷ Ascorbate loses a single electron, forming the ascorbyl radical, which can lose a further electron, forming dehydroascorbate. Ascorbate can also be oxidized to dehydroascorbate in a single step by donating two electrons. Dehydroascorbate may be oxidized by the cellular metabolism, by way of NADPH, or it can be lost from the tissue and excreted in the urine. The ratio of ascorbate to dehydroascorbate, and by implication that of other related antioxidants, such as the reduced glutathione-oxidized glutathione couple, provides a measure of the redox environment of a tissue. Since oxidation appears to be a factor in many disease processes, this ratio is lower in damaged tissue. Restoring the ratio, by supplying additional ascorbate, reverses the oxidized state of the tissue and decreases free radical damage.⁴⁸

Ascorbate Synthesis

Ascorbate is abundant throughout the plant and animal kingdoms, where its main function appears to be as an electron donor. Humans and a few other animals do not synthesize ascorbate. This loss may be the largest, single, biochemical difference between these and other animal groups. It is generally stated that humans cannot manufacture ascorbate because they have lost the enzyme gulonolactone oxidase, which is used in the synthetic pathway from glucose to ascorbate. The

evidence for such a strong statement is inadequate.⁴⁹ It is possible that some humans can manufacture ascorbate, at a low level. Such low level manufacture, by specific individuals, could explain some of the variation in the incidence of scurvy under deprivation conditions.

Dynamic Flow

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. Some of the excess ascorbate is absorbed into the blood plasma, while the rest remains in the gut. As in animals that synthesize the molecule, some ascorbate is lost through the kidneys. However, there is a steady flow of antioxidant electrons through the body, with a reserve available to combat stress or free radical damage.

The absorption from the gut of a single oral dose is not instantaneous, but occurs over a period of several hours. As the ascorbate is absorbed, it is transported to other body compartments, such as lymph, and into cells. However, this transportation is limited by the short plasma half-life. A single, oral dose increases plasma levels for a maximum of two to three hours following intake, and then decays back towards baseline levels. The average plasma level, and thus the intake into erythrocytes and typical cells, remains low after single daily doses. However, repeated doses, at an interval of less than 5 half-lives, produce a high, steady-state value in blood plasma. This also leads to a large increase in erythrocyte and other typical cell ascorbate levels. Ascorbate levels in white blood cells and other redox sensitive tissues is not greatly increased, because these cell types accumulate ascorbate preferentially,

at low external concentrations. When dynamic flow has been achieved, the mean and minimum plasma levels are relatively high: consistent levels of 220 μM can be attained. The body pool is also increased, because of increased absorption by tissues whose levels are related to those in the surrounding micro-environment. More ascorbate is available when required and the ratio of ascorbate to dehydroascorbate is high. Hence, the tissues are maintained in a reduced state, through ascorbate's interaction with other antioxidants, such as the tocopherols, tocotrienols and glutathione. If the person encounters a viral infection, or other free radical stress, high levels of ascorbate are immediately available, providing electrons to neutralize the free radicals and quench the disease process. Additional ascorbate for this process is recruited by absorption from the intestines, while dehydroascorbate is excreted preferentially by the kidney.

During Illness

Under normal conditions, such as mild stress, dynamic flow is predicted to maintain a reducing state in the body, reducing the incidence of disease. However, diseased tissues may generate large numbers of free radicals, in which case the maximum absorption from the gut may increase greatly. Under such conditions, dynamic flow cannot be maintained by normal intakes. The intake required to sustain plasma levels during illness may increase to 200 grams, or more. During illness, achieving dynamic flow corresponds to the bowel tolerance technique, described by Cathcart. For severe illnesses, intravenous doses may be required, to maintain a reducing state in the damaged tissue.

Cancer

Cancer is an exception to the role of ascorbate as an antioxidant. Depending on the conditions, ascorbate can act as

a pro-oxidant or reducing agent; this feature is common to many organic antioxidants. In normal tissues, ascorbate acts as an antioxidant. However, in the presence of free iron, ascorbate can participate in a Fenton reaction and become an oxidant, generating free radicals which lead to cellular damage. Cancer cells can absorb high levels of ascorbate, and their disturbed metabolism produces redox cycling and free radical production.⁵⁰ High levels of ascorbate kill cancer cells by apoptosis, while leaving normal cells undamaged. In cancer, and other infected or damaged cells, ascorbate's beneficial effects may involve oxidation.

Research Implications

The research implications of the dynamic flow model are profound. Many studies have used low doses of ascorbate, assuming wrongly that, because of the low-dose hypothesis or tissue saturation, the results could be extrapolated to higher intakes. Since doses many times higher than 200 mg can be absorbed and utilized by the body, such extrapolation is unjustified. Clearly, an intake of five grams per day could have quite different effects to an intake of 100 mg. To take a specific example, it is not valid to conclude that vitamin C has no effect on heart disease, based on inconclusive or even negative results with low doses.

The short half-life presents immediate and wide-ranging implications for research into this vitamin. Most studies have used single, daily doses of vitamin C or, occasionally, twice daily doses. Occasional studies have used low-dose, slow release formulations. These studies all require urgent re-evaluation. A single dose will produce a transient increase in blood plasma levels, leaving the mean, modal and minimum concentrations largely unchanged. Such doses will not load tissues, such as red blood cells, or

increase the body pool substantially. A large, single, daily dose of ascorbate will therefore produce a minimal biological effect.

To be explicit, consider Linus Pauling's suggestion for prevention of the common cold. It is occasionally reported that this suggestion has been refuted.^{51,52} However, these once or twice daily megadose supplementation studies would not be expected to show more than a minimal biological effect, when compared with dynamic flow. In the light of the dynamic flow model, the available results are consistent with Pauling's proposal. Similar statements can be made for a multitude of other conditions, such as atherosclerosis and arthritis.

Discussion

The dynamic flow model provides a new paradigm, that is consistent with the known pharmacokinetics of ascorbate. It is also consistent with claims for the health benefits of high doses.

Current knowledge of ascorbate pharmacokinetics and tissue biology challenges the low dose hypothesis. In particular, it is not valid to model human intakes on the specialized properties of white blood cells. Red blood cells are also specialized, but have characteristics closer to those of typical body tissues. Such body tissues gain their supply of ascorbate through the blood supply: mean and minimum blood plasma values are thus of central importance to the availability of ascorbate. Previously, the NIH data on ascorbate pharmacokinetics have been misinterpreted, resulting in inappropriate recommended intakes. Considering that the scientific data is consistent with claims for large health benefits with higher doses, the result of adhering to the low-dose hypothesis may be unnecessarily high rates of illness and premature death.

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