

Vitamin C contributes to inflammation via radical generating mechanisms: a cautionary note

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Summary Reactive oxygen and nitrogen species (RONS) have been ascribed an important role in oxidative stress contributing to the progression of inflammatory diseases such as Crohn's disease and rheumatoid arthritis. Redox-active metal ions such as Fe(II) and Cu(I) further activate RONS and thus perpetuate their damaging effects. High intake of ascorbic acid exerts a pro-oxidant effect by its interaction with metal ions via a number of established RONS generating systems. Caution should be exerted regarding surplus ascorbic acid intake for patients with chronic inflammatory diseases.

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INTRODUCTION

Oxidative stress contributes to the pathogenesis of a number of inflammatory diseases including Crohn's disease, rheumatoid arthritis (RA), Alzheimer's disease, atherosclerosis and diabetes mellitus (1). It results from an imbalance between the generation of reactive oxygen and nitrogen species (RONS) and their suppression by anti-oxidant defence mechanisms (such as the antioxidant enzymes catalase and superoxide dismutase). In chronic inflammatory conditions, vascular compromise leads to red blood cell influx with concomitant iron deposition in inflamed tissues. In addition, activation of haem oxygenase results in further iron loading at sites of inflammation. Redox active metal ions can be mobilized from storage proteins via the action of superoxide generated from polymorphonuclear leukocytes.

Redox-active metal ions such as Fe(II) and Cu(I) have been shown to participate in several reactions that enhance oxidative stress (2). Although ascorbic acid has reported anti-oxidant properties, it plays a particular role in redox cycling metal ions and thus activates these ions to exacerbate oxidative stress. Current trends dictate vitamin C intake of the order of one gram or more per day, a level that is well above the recommended daily allowance (3). Elevated ascorbic acid intake, above the recommended allowance, may be deleterious in patients suffering from chronic inflammatory conditions.

HYPOTHESIS

Vitamin C exacerbates oxidative stress in chronic inflammatory conditions via the activation of redox-active metal ions which enhance the production of reactive oxygen and nitrogen species.

MECHANISMS OF REDOX-ACTIVE METAL ION MEDIATED RONS FORMATION

Ascorbic acid has a number of known interactions with metal ions. These interactions involve redox reactions

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including: (i) the reduction reactions of Fe(III) to Fe(II) and Cu(II) to Cu(I) facilitating their involvement in the activation of peroxides [the Fenton reaction] (4), (ii) metal ion catalysis of the oxidation of ascorbic acid with concomitant formation of hydrogen peroxide (H_2O_2) and potential hydroxyl radical ($\cdot\text{OH}$) generation [from (5–7)] and (iii) activation of molecular oxygen leading to oxidation of endogenous aromatic moieties [Udenfriend's system] (8,9).

Fenton chemistry

The Fenton reaction involves the transition metal catalyzed reduction of H_2O_2 to generate a powerful oxidizing species. Transition metals have varying oxidation states, and therefore they are able to catalyze oxidation and reduction reactions. In the blood, circulating iron is tightly bound to the protein transferrin, which reduces its reduction potential, and subsequently its reactivity with H_2O_2 . In chronic inflammatory diseases low molecular mass metal ion deposits can result from: (i) compromised vasculature, (ii) the activation of haem oxygenase and (iii) release from storage proteins via superoxide (1). In addition to circulating iron and other body stores, there is a pool of iron within cells referred to as the 'low molecular weight iron'. This iron is loosely bound to 'low molecular weight' compounds such as ATP, phosphate and citrate. The Fenton system can generate hydroxyl radicals from the metal ion activation of H_2O_2 (Eq. [1]) (10). Ascorbic acid can then recycle Fe(III) to Fe(II) facilitating further generation of $\cdot\text{OH}$ by subsequent Fenton cycles.

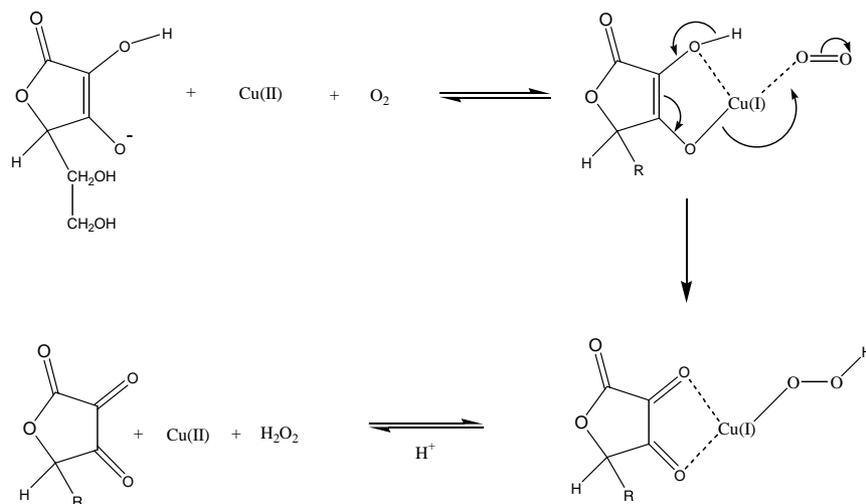
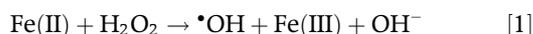


Fig. 1 Proposed mechanism for the generation of H_2O_2 via the oxidation of ascorbic acid.

Weissberger system

Metal ion catalysis of the oxidation of ascorbic acid has long been an established process for the formation of H_2O_2 . The reaction was studied in detail initially by Weissberger et al. (Fig. 1) (5) and subsequently by Martell et al. (6). Although the reaction between ascorbic acid and oxygen proceeds slowly in the absence of metal ions, the introduction of redox active metal ions [Fe(III) and Cu(II)] in catalytic amounts greatly enhances the rate of reaction. The very low rate constant for the ascorbic acid auto-oxidation is reported as $5.87 \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$ (6). Catalytic rates in the presence of Fe(III) and Cu(II) are greatly enhanced to $6.4 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$ and $2.5 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$. Importantly, in the presence of metal ion chelators other than ascorbic acid the reaction proceeds to give a Cu(I) complex which would react rapidly with H_2O_2 to generate $\cdot\text{OH}$ (11). This generation of toxic $\cdot\text{OH}$ from a simple system containing metal ions, ascorbic acid and oxygen has potentially deleterious consequences owing to the ubiquitous nature of these components in diseased tissues. Under these conditions it is imperative to restrict ascorbic acid intake to recommended daily intake levels.

Udenfriend's system

The Udenfriend system has been demonstrated to hydroxylate aromatic compounds, saturate hydrocarbons to alcohols and olefins to epoxides (12). It has been distinguished from the Weissberger system in both the mechanism and type of oxidation products produced (12). Udenfriend's system involves ascorbic acid as a two-electron donor complexed to a transition metal such as Fe(II) (8). It is speculated that in the presence of O_2 ,

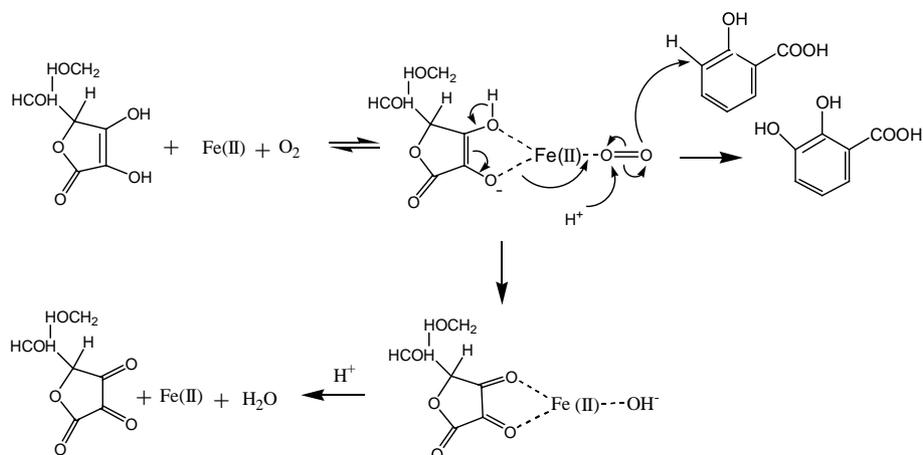


Fig. 2 Proposed mechanism for the hydroxylation of aromatic moieties.

complexation between Fe(II) and ascorbic acid results in the formation of an active oxygen species speculated to be $\cdot\text{OH}$ (13). The proposed mechanism (Fig. 2) shows the oxidation of ascorbic acid to dehydroascorbic acid, by electron transfer through Fe(II), and subsequent hydroxylation of an aromatic compound (14). This reaction has been shown to be enhanced when iron is coupled with a chelator for example in iron-citrate complexes found within biofluids (15).

IMPLICATIONS FOR INFLAMMATION

Iron and ascorbic acid form a potentially toxic cocktail. The chemical mechanisms given above have been established demonstrating the potential for these compounds to interact and oxidatively damage surrounding tissues. In patients suffering from chronic inflammatory diseases where tissue iron deposition occurs, high levels of ascorbic acid can thus exacerbate the condition. Ascorbic acid has been shown to exhibit both anti-oxidant and pro-oxidant effects in a dose related fashion. Even in healthy subjects a positive or negative deviation from the optimal plasma ascorbic acid level results in oxidative damage (16). The detrimental effects of intake of large quantities of ascorbic acid in patients with chronic inflammatory diseases warrants further investigation. In addition dietary supplements containing iron and ascorbic acid may be deleterious as these components do not naturally come in concentrated form (as in supplementation tablets).

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