

The Free Radical Theory of Aging and Antioxidant Supplements: A Systematic Review

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Abstract

Free radical excess occurs when cells are exposed to reactive oxygen species greater than the amount that can be neutralized by cellular produced antioxidants such as superoxide dismutase. This is termed *oxidative stress*, which can be caused by excessive energy intake or external pollutants. Excess free radicals are proposed to increase the rate of cell aging, injury, and mutations leading to a shortened cell life span. Vitamins A, C, and E and flavoproteins are supplements that function as free radical scavengers. Antioxidants are present in natural foods but added amounts beyond the diet may detoxify excess free radicals during “oxidative stress.” Antioxidant supplements decrease cellular damage from excess reactive oxygen species but they have not been proven to prolong life span.

Keywords

oxidative stress, antioxidants, superoxide, dismutase, vitamin, flavoprotein

Introduction

The free radical theory of aging was proposed 55 years ago, but it still has not been proven statistically in humans. It has served as a stimulus for a large body of research, reviews, and controversy. The concept of free radical damage to cells was first noted in the presence of ionizing radiation, which created excess reactive oxygen species and cell senescence or death. The theory was expanded to include a concept termed *oxidative stress*, denoting increased free radicals in the cell that damaged DNA and mitochondria due to excess energy stores or use.

Over the past 20 years, the term *antioxidant* has been used for chemicals that covalently bond or scavenge the reactive oxygen molecule. Cellularly produced antioxidants have been identified as critical to cell homeostasis by removing the damaging free radicals. Superoxide dismutase is the best characterized of the natural scavengers. When the level of free radicals exceeds the capacity of cellular antioxidants to remove them, it is postulated that external antioxidant supplementation in the form of vitamins, colored fruits, and vegetables will prevent cellular damage from excess reactive oxygen species. The next proposal is that decreasing oxidant-induced cell damage will prolong cell life span.

Since 1943, the US Food and Drug Administration (FDA) has determined the amount of vitamins and minerals considered to be necessary in a diet to prevent deficiency diseases. These recommended daily allowances in humans are empirically determined by random assessment diet and absence of disease. They are not measurements of levels required to

remove excess free radicals or produce needed enzymes and proteins. This has recently been emphasized by studies of vitamin D using new criteria for deficiency that have required tripling the recommended daily allowance for vitamin D based on assessment of osteoporosis prevention research.

Methods

Initial literature search was done using search engines specific for peer-reviewed scientific publications beginning in 1956 when Dr Denham Harmon proposed the “free radical theory of aging.” The research publications were found using Google Scholar, PubMed, PubMed Central, and National Library of Medicine. Systematic review principles were obtained from The Cochrane Collaboration and using the PRISMA Statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). The author prioritized the articles without secondary reviewers.

Initial search was for “free radical theory AND vitamins.” A few research articles were found. Several reviews that were critical of the concept were included in the analyses. Refining

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the searches to free radical theory, physiologic mechanisms of aging, or antioxidants yielded more specific scientific studies for analyses. A new source of scientific research studies was *Physiological Reviews*.

Bias was assessed for each study and criteria for exclusion included a specific drug study, nonsystematic reviews, absence of peer review, and inadequate methods sections. When available, citation indices were used to rank the importance of each scientific publication. Abstracts were initially reviewed for relevance to the study. Relevant articles were then reviewed for methods, result, and conclusions. Those publications not excluded formed the basis for final summary and conclusions.

Results

The “free radical theory of aging” was proposed in 1956 by Harman.¹ There have been many articles, biochemical studies, and reviews that support the concept of free radical damage to cellular DNA and mitochondria. Finkel and Holbrook² summarized the concept of oxidative stress and the effects on aging. Low levels of oxygen in cell culture prolonged cell life span, whereas high oxygen concentration reduced life span and accelerated the rate of telomere shortening.

The shortening of telomeres (the ends of the chromosomes) is associated with aging. In 1998, Bodnar et al³ showed that adding telomerase in vitro to human cells increased telomere length and extended cell life span. The association of telomere shortening and oxidative stress has only been shown in vitro.

The current basis of the free radical theory is that reactive oxygen species (which are mutagens causing nuclear and mitochondrial DNA mutations) lead to cell aging or senescence. Mutations can also lead to overgrowth as in cancer. The dichotomy is difficult to resolve, but decreasing reactive oxygen species appears to reduce both cell damage and cancer development. The body has many natural antioxidants, which would indicate that removing excess oxidants is a normal bodily function. “Oxidative stress” is suggested as an excess of energy and oxygen that leads to production of reactive oxygen species in excess of those natural defenses. The next part of the free radical theory of aging is that introduction of external antioxidants during the periods of oxidative stress, which occur throughout the human life span, will slow aging. This concept of excess oxidants has been shown in vitro when cells are stressed by culture media changes. It is difficult to directly measure these reactive oxygen species because of their highly reactive nature, artificially lowering their levels, but metabolites are consistent with periods of excess oxidants in human studies.⁴

Bhatnagar⁵ showed that exposures to arsenic, lead, cadmium, pollutant gases, solvents, and pesticides increased peripheral thrombosis and atherosclerotic lesions in animal models. The mechanism was the increased production of nitric oxide from these pollutants. In a review by Fang et al,⁶ the ability of some vitamins to reduce reactive oxygen species has been well established. Vitamin E inhibits reactive oxygen species-induced generation of lipid peroxyl radicals that can damage very low-density lipoproteins, DNA, and cell membranes.⁷

Vitamin A inhibits the production of nitric oxide by the enzyme iNOS (inducible nitric oxide synthase), thus reducing cytotoxicity. Vitamin A directly inhibits the iNOS gene expression in smooth muscle cells, endothelial cells, and cardiac myocytes, thereby reducing damage to these tissues. Vitamin C reduces the amount of 8-hydroxydeoxyguanosine damage to DNA exposed to excess hydroxyl groups.

Discussion

Reactive oxygen species or free radicals are molecules with unpaired electrons in the outer ring. Such molecules with unpaired electrons are very unstable and reactive. The oxygen free radicals include superoxide anion, hydroxyl radical, and hydrogen peroxide. The common nitrogen and oxygen free radicals include nitric oxide and nitrogen dioxide. Under normal conditions free radicals are required for critical cellular reactions such as signal transduction, gene transcription, leukocyte adhesion, platelet aggregation, smooth muscle relaxation, and hemodynamics. Oxidative stress occurs when aerobic metabolism of protein, fats, and glucose increases in response to exercise, strenuous work, or overeating, creating excess energy. The increased production of aerobic energy enhances mitochondrial production of unused free radicals. In normal physiologic conditions, 1% to 3% of oxygen consumed by the body is converted into free radicals, but when oxidative stress occurs, the production of free radicals increases rapidly beyond metabolically required amounts. The excess of free radicals can damage critical molecules, can increase DNA mutations, and can cause cell death or mitochondrial depletion. An additional cause of excess free radical production is cellular injury to mitochondria created by unused free radicals under normal physiologic conditions, not just during oxidative stress.⁶

Excess free radicals are detoxified by many naturally produced enzymes such as superoxide dismutase, peroxidases, reductases, catalases, and antioxidant nutrients. The damage caused by free radicals occurs when production exceeds reduction or physiologic need. External free radicals are also inhaled or consumed in the form of nitric oxide, nitrogen dioxide, and hydroxyl radicals. Common sources of these pollutants are radiation, cigarettes, combustion, and alcohols.⁵

A systematic review of the literature supports the concept that oxidative stress and free radical cellular damage occur in a variety of species, including humans, both in vitro and in vivo. What is not clear is whether this damage leads to a decrease in life span. Studies suggesting free radicals induce precancerous conditions, induce mitochondrial mutations, and compromise the immune system in vitro are more suggestive of cause and effect.⁴ Another well-established fact is that moderate starvation prolongs life in animals, whereas excess food intake decreases life span. Free radical reduction by starvation has been shown, but cause and effect are not proven.

Specific vitamins directly reduce free radicals and upregulate physiologic antioxidant enzymes. Vitamins A, C, and E and folate have been shown to be the most effective supplemental antioxidants in decreasing free radicals in vivo and in

vitro. Excesses of extracellular and intracellular free iron by increased iron intake or decreased protein intake generate increased free radicals. Copper, zinc, and manganese are critical cofactors for superoxide dismutase, the most prevalent cellular produced antioxidant. Phytochemicals, such as flavonoids and tea polyphenols, are strong antioxidants in animals. In opposition to the benefit of reducing free radicals, Howes in his article in the *Journal of Evidence-Based Complementary & Alternative Medicine* titled "Mythology of Antioxidant Vitamins?" stated, "I believe that they can be inherently harmful but they can also function usefully as pro-oxidant precursors."^{8(p156)} Presumably, he is suggesting excess intake not physiologic doses.

Fifty years after Harman's proposal in 1956 of the free radical theory concerning cellular damage,¹ the idea of free radicals causing aging has been accepted by many researchers. Our present environment contains many inhaled and consumed free radicals. The present recommended daily allowances of many antioxidant nutrients might not be sufficient in this environment. Therefore, it is possible that supplemental antioxidants could lower free radicals in humans and thereby improve cellular function and decrease cancer. However, this does not prove that antioxidant supplements increase life span; nor does it prove that they shorten it.

Conclusions

Free radicals (eg, reactive oxygen species) are critical electron donors for normal metabolism. Excess free radicals are routinely scavenged by enzymes such as superoxide dismutase preventing cellular damage. When free radicals exceed the capacity for detoxification the proposed reaction is termed *oxidative stress*, leading to nuclear and mitochondrial DNA damage. Research studies in vitro strongly support this concept and suggest that supplemental antioxidants can lower the level of excess free radicals in the cell and extracellular matrix. The "free radical theory of aging" proposes that decreasing excess free radicals will slow aging by preventing cell damage and nuclear and mitochondrial DNA mutations.

Research on aging has been equated with prolonged life span, which is almost impossible to prove in humans. Decreasing cell damage can slow skin wrinkling, can improve heart muscle contractions, can slow tumor growth, or can retard macular degeneration, as suggested in individual research studies. This does not prove that reducing "oxidative stress" will prolong life.

A recent study by Park et al⁹ on multivitamin use in 182,099 participants in the Multiethnic Cohort Study showed neither adverse effects from daily use of supplements nor any decrease or increase in mortality over 11 years.

The use of a daily multivitamin with minerals and antioxidants appears to present no harm. The present recommended daily allowance is possibly too low for removal of excess free radicals and free radical excess does cause cellular aging and injury. Antioxidant supplements do remove excess free radicals and have shown promise in preventing cancer and certain organ aging. Therefore, taking a single daily antioxidant supplement appears to be a safe way to potentially slow cellular damage and cellular aging by decreasing any deficiencies induced by the present environment.

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Ethical Approval

Since this was a systematic review of the literature, no institutional review board approval was necessary. This was an unbiased assessment.

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