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The Role of Antioxidants on Cellular Aging

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Abstract: Aging is the multidimensional process of changes in physical, physiological and behavioral condition of a cell over time. It is characterized by decline of multiple physiological functions that increase the probability of homeostatic imbalance and cellular death. Various free radicals are produced due to endogenous oxidative reactions. These highly reactive atoms cause oxidative damage and shorten lifespan of a cell. The antioxidants are the molecules, which neutralize free radicals and delay the cellular aging.

Keywords: Cellular aging, Free radical, Antioxidant.

1. Introduction

Cellular aging is the declining of physical, physiological and behavioral state of a cell in respect of time. The process by which cellular aging occurs is called cellular senescence (Hayflick, 1961). It is an avoidable property of a cell, that it is the result of genetic programming. The shortening of telomere, DNA damage and any lethal mutation induce aging. Besides these, the endogenous oxidative reactions, which are occurred mostly in mitochondria, produce free radicals, which alter biological structures and thus enhance the cellular aging. Antioxidants such as vitamin A, vitamin C, vitamin E, selenium, superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) act over and neutralize the free radicals such as reactive oxygen species (ROS), which alters or deletes a functional genomic sequence. Thus, antioxidants play antagonistic effects on free radicals. Hence, cellular aging is delayed.

2. Overview of the role of free radicals in cellular aging

The free radical theory of aging (FRTA) states that organisms age because cells accumulate free radical damage over time. A free radical is any atom or molecule that has a single unpaired electron in an outer shell. It has a short lifespan and highly reactive (Denham Harman, 1950). After producing from endogenous oxidative reactions, it causes oxidative damage.

Damage occurs when the free radical encounters another molecule and seeks to find another electron to pair its unpaired electron. The free radical often pulls an electron off a neighboring molecule, causing the affected molecule to become a free radical itself. The new free radical can then pull an electron off the next molecule and a chemical chain reaction of radical production occurs.

There are five main types of free radicals, all with varying degrees of toxicity. They are- Nitric oxide, Peroxynitrite, Hydrogen peroxide, Superoxide anion, Hydroxyl radical.

a. In humans and other animals, cellular aging has been attributed to the shortening of telomeres with each cell cycle; when telomeres become too short, the cells die. Thus, the telomeres are called "molecular clock" (Clark, 1998).

b. There is a consistent shortening of telomeres during cellular aging. Human telomeres shorten by about 100 bp per cell division. When several KB of telomeric DNA is lost, this triggers the cell to undergo senescence. The free radicals act over

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telomere and enhance cellular senescence (Ouellette, 2006).

c. The Sirtuin family of genes has been shown to have a significant effect on the lifespan of yeast and nematodes. Overexpression of the RAS2 gene increases lifespan in yeast substantially. It has been observed that the free radical regulates the expression of RAS2 gene in yeast (*Saccharomyces cerevisiae)*.

d. Nitric oxide is involved in smooth muscle relaxation, Neurotransmission, and immune regulation. It blocks cellular communication. The response feedback mechanism within the cells is also delayed (Robert, 1998).

e. Peroxynitrite attacks amino acids like cysteines, methionines, and tyrosines by adding a NO_2 to the ring of these amino acids. Thus, protein modifications occur which leads to apoptosis or cellular dysfunction (Orgel, 1995).

f. Hydroxyl radical (HO) reacts with nucleic acids, it modifies the bases. Examples of HO base attack products are 8-hydroxyguanosine, thymidine glycol and uric acid. This type of modification leads to mutation. If it appears as lethal, the cell may die.

g. When HO reacts with proteins, they are fragmented. This fragmentation is associated with reactions at specific amino acids such as proline and histidine. The fragmented protein seems to be nonfunctional.

h. Cysteines and methionines on intracellular proteins can be reversibly modified by free radicals (Orgel, 1995).

i. The breakage of the sugar phosphate backbone of nucleic acids is also done by reactive oxygen species (ROS). This is appeared as lethal to the cell. For example in some organisms such as yeast, *Caenorhabditis elegans* and *D. melanogaster*, when production of ROS was reduced to a certain level, the cellular lifespan was expanded.

j. The DNA damage and mutation both alters nucleotide sequences of nuclear and mitochondrial DNA. As a result, the synthesized protein of that exon which was altered becomes non-functional (Vilenchik & Knudson, 2000). Nuclear DNA damage can contribute to aging either indirectly (by increasing apoptosis or cellular senescence) or directly (by increasing cell dysfunction) (Brierley, 1998).

k. A protein named NF-ß, synthesized from the hypothalamus triggers inflammation in the brain and the activity of NF-ß in mice significantly accelerated the development of aging (CAI, 2013).

3. Action of antioxidants over free radicals for delaying cellular aging

Antioxidants are nutrients (vitamins and minerals) as well as enzymes (dismutase, catalase and glutathione peroxidase). They are believed to play a role in preventing the development of such chronic diseases as cancer, heart disease, stroke, Alzheimer's disease and Rheumatoid arthritis. Antioxidants also delay cellular aging by blocking the process of oxidation and neutralizing free radicals. The action of antioxidants over free radicals can be classified into two processes:

3.1 Chain-breaking

When a free radical release or steals an electron, a second radical is formed. This molecule then turns around and does the same thing to a third molecule, continuing to generate more products that are unstable. The process continues until termination occurs either the radical is stabilized with a chain-breaking antioxidant such as beta-carotene and vitamins C and E, or it simply decays into a harmless product. So, the amount of free radicals is decreased.

3.2 Prevention of oxidation

Antioxidant enzymes like superoxide dismutase, catalase and glutathione peroxidase prevent oxidation by reducing the rate of chain initiation. They can also prevent oxidation by stabilizing transition metal radicals such as copper and iron.

Antioxidants are helpful in reducing and preventing damage from free radical reactions because of their ability to donate electrons, which neutralize the radical without forming another. Ascorbic acid, for example, can lose an electron to a free radical and remain stable itself by passing its unstable electron around the antioxidant molecule. This has led to the hypothesis that large amounts of antioxidants, with their ability to decrease the numbers of free radicals, might lessen the radical damage causing chronic diseases, and even radical damage responsible for aging.

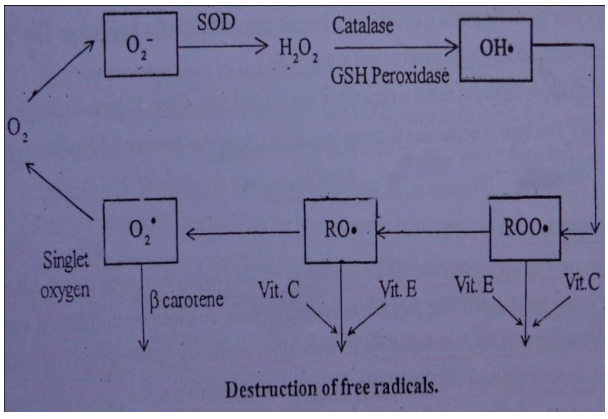

Fig. 1. Free radicals like superoxide radicals, hydrogen peroxide, OH radicals, peroxy radicals (ROO*), alkyl radical (RO*) and singlet oxygen (O_2*) which are responsible for DNA damage, mutation, cellular dysfunction and cellular aging. The free radicals are destructed by Vitamin A, Vitamin C, Vitamin E, Superoxide dismutase (SOD) and catalase. Thus aging is delayed.

The effectiveness of any given antioxidant in the body depends on which free radical is involved, how

and where it is generated, and where the target of damage is. Thus, while in one particular system an antioxidant may protect against free radicals, in other systems, it could have no effect at all.

4. Conclusion

The free radical theory of aging implies that antioxidants such as vitamin A, vitamin C, vitamin E (alpha-tocopherol), beta-carotene and Superoxide dismutase will slow the process of aging by preventing free radicals from oxidizing sensitive biological molecules or reducing the formation of free radicals. The antioxidant chemicals found in many foods are frequently cited as the basis of claims for the benefits of a high intake of vegetables and fruits in the diet.

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