Understanding Oxidative Aging

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It is amazing to think that aging begins at birth with the very first breath of oxygen. Oxygen is necessary for human life and human aging. We are young individuals who are growing old, with each inhalation creating oxygen radicals that damage our carbon-based structure. How exactly does oxidative aging happen? This article will examine our current understanding of oxidative aging and how it affects everyone and everything on the planet.

What Are Reactive Oxygen Species?

Oxygen is a relatively new element to our planet, originating approximately 2 billion years ago when water-splitting microorganisms first released oxygen to create the earth's atmosphere. The development of plants engaged in photosynthesis further increased the atmospheric oxygen levels, some ending up as UV-protective ozone. Oxygen molecules possess 2 unpaired electrons, which make them diradicals. When a molecule accepts an electron, it undergoes a reduction reaction; when it loses an electron, it undergoes an oxidation reaction. The univalent reduction of oxygen, or the addition of 1 electron at a time, produces reactive oxygen species (ROS). These reactions are diagrammed as follows:

Oxygen + 1 electron = superoxide (O_2–)

Superoxide + 1 more electron = hydrogen peroxide (H_2O_2)

Hydrogen peroxide + 1 more electron = hydroxyl radical (·OH)

Hydroxyl radical + 1 more electron + hydrogen = water (H_2O)

Only superoxide and hydroxyl radicals are considered free radicals. Although hydrogen peroxide is an ROS, it is not a free radical, and water of course is completely stable. There also is a fourth type of ROS known as singlet oxygen. These basic interactions of hydrogen and oxygen are involved in human respiration.

What Other Elements Does Oxygen React With in the Body?

Oxygen can react with other elements 1 electron at a time, besides hydrogen, including transition metals. The most physiologically relevant transition metal is iron, which is found in red blood cells bound to hemoglobin for carrying oxygen. Iron is able to accept and transfer oxygen molecules; when oxygen reacts with iron in the environment, the result is known as rust. Certain materials such as gold, however, do not rust because they cannot interact with oxygen.

What Are the Oxidative Effects of Superoxide?

Superoxide is the result of adding 1 electron to molecular oxygen, creating a highly reactive molecule with 1 or more unpaired electrons. Superoxide forms when UV radiation strikes oxygen and can be created by certain enzymatic reactions as part of metabolism. Superoxide can irreversibly react with itself to produce hydrogen peroxide in the following reaction:

$O_2^- + O_2^- + 4H \rightarrow H_2O_2$

Hydrogen peroxide can be destroyed by peroxidases, which convert hydrogen peroxide to oxygen and water. Although hydrogen peroxide is not a powerful oxidant, it is damaging to body tissues because it can diffuse rapidly across cell and nuclear membranes. Hydrogen peroxide also can be converted to the hydroxyl radical in the presence of iron, which can react with and damage DNA as illustrated below:

$H_2O_2 + Fe^{II} \rightarrow \cdot OH + -OH + Fe^{III}$

The resulting reaction explains why exogenous hydrogen peroxide is used as a skin surface disinfectant and is manufactured by the body as part of the innate immune system to topically kill foreign organisms. Hydrogen peroxide also is produced by superoxide dismutase and cross-links or denatures proteins.

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What Are the Effects of the Hydroxyl Radical?

The hydroxyl radical produces most of the cellular oxidative damage to nuclear DNA. Hydroxyl radicals are able to interact with the purine and pyrimidine bases, damaging the DNA code, but repair mechanisms are in place to remove the damaged bases.

What Is the Physiologic Effect of Singlet Oxygen?

When oxygen is irradiated with UV light, it absorbs the energy, which changes its molecular configuration. Singlet oxygen is created when 1 of the unpaired electrons is elevated to a higher energy level and, most importantly, its spin number is inverted, allowing the singlet oxygen to damage proteins and the double bonds in fatty tissue and cell walls. This damage is known as oxidative stress.

What Are the Effects of Oxidative Stress on the Human Body?

Oxidative stress occurs when body structures are damaged over time with repeated insults, which are cumulatively labeled as aging. For example, superoxide attacks unsaturated fatty acids in the cell membrane, damaging its integrity. When unsaturated fatty acids are oxidatively damaged in food, the food is said to be rancid. Aging is basically the rancidity of the human body. When fatty acids in the body are damaged, an amorphous yellow material known as lipofuscin is produced. Lipofuscin can accumulate in the skin and accounts for the dusky yellow hue of facial skin that is characteristic in heavy tobacco smokers. This lipid peroxidation requires 1 or more double bonds to occur. Peroxidation commonly occurs in essential fatty acids found in the body, such as linolenic acid, because they possess 3 double bonds. The reaction is outlined below:

Polyunsaturated fatty acid (PUFA) + superoxide → lipid free radical (LFR)

LFR + oxygen → peroxy lipid radical

Peroxy lipid radical (new) + PUFA → lipid hydroperoxide (new) + LFR

The reaction of superoxide with a PUFA produces an LFR that reacts in turn with molecular oxygen to form a peroxy lipid radical. The peroxy lipid radical in turn reacts with an adjacent PUFA to steal a hydrogen atom and form a lipid hydroperoxide. The lipid hydroperoxide is then decomposed either by catalase or another enzyme into more reactive components that can cross-link or denature proteins. One of the reactive by-products is malonyldialdehyde (MDA), which is a marker of lipid peroxidation. Systemic levels of MDA can be used to determine the amount of oxidative stress the body has endured. Vitamin E is an important antioxidant to prevent the formation of MDA.

How Does the Body Protect Itself From Oxidative Stress?

The body must protect itself from oxidative stress for survival. As a matter of fact, individuals who age more slowly may have better oxidative stress protection than those who age rapidly. The endogenous mechanisms for oxidative stress protection are summarized in the Table. Of these mechanisms, intracellular vitamin E is important in preventing the hydroxyl radical reaction by stopping the chain reaction of lipid peroxidation. Vitamin C functions as a secondary antioxidant by regenerating active vitamin E. This process represents an oxidation reduction whereby vitamin E loses a hydrogen molecule to the hydroxyl radical and is oxidized. Vitamin C reduces the

Endogenous Oxidative Stress Protection

Antioxidant Enzymes

- Superoxide dismutase: converts superoxide to peroxide and oxygen
- Catalase: converts hydrogen peroxide to water and oxygen
- Glutathione peroxidase: converts hydrogen peroxide to water and oxygen

Lipid-Soluble Antioxidants

- Tocopherol (vitamin E): quenches hydroxyl radicals
- Beta-carotene (vitamin A): quenches singlet oxygen
- Ubiquinol/ubiquinone: quenches hydroxyl radicals and singlet oxygen

Water-Soluble Antioxidants

- Ascorbic acid (vitamin C): regenerates vitamin E; may react directly with other reactive oxygen species
- Glutathione: reacts with hydroxyl radicals; part of the glutathione peroxidase system
- Uric acid: quenches singlet oxygen; hydroxyl radicals inhibit xanthine oxidase, which forms superoxide

vitamin E back to an active form by donating a hydrogen molecule. The reaction is summarized below:

Vitamin E−OH (natural vitamin E) + ·OH → vitamin E (oxidized vitamin E, a quinone) + O + H_2O

Vitamin E + O + vitamin C → vitamin E−OH + oxidized vitamin C (dehydroascorbate)

This reaction can occur with vitamin C, uric acid, and glutathione. Without this type of oxidative protection, the body would rapidly age and die. Aging basically is oxidation of the human body. It may be that the secret to youth is the development of a human preservative! ■