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Defense Mechanism of Natural Antioxidants Against Free Radicals

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Absract: Endogenous and exogenous antioxidants act as “free radical scavengers” by preventing and repairing damages caused by ROS and RNS, and therefore can enhance the immune defense and lower the risk of cancer and degenerative diseases. Free radicals reactive oxygen species and reactive nitrogen species are generated by our body by various endogenous systems, exposure to different physiochemical conditions or pathological states. A balance between free radicals and antioxidants is necessary for proper physiological function. If free radicals overwhelm the body's ability to regulate them, a condition known as oxidative stress ensues. Free radicals thus adversely alter lipids, proteins, and DNA and trigger a number of human diseases. Hence application of external source of antioxidants can assist in coping this oxidative stress. Synthetic antioxidants such as butylated hydroxytoluene and butylated hydroxyanisole have recently been reported to be dangerous for human health. Thus, the search for effective, nontoxic natural compounds with antioxidative activity has been intensified in recent years. The present review provides a brief overview on oxidative stress mediated cellular damages and role of dietary antioxidants as functional foods in the management of human diseases.

Keyword: defense, radicals, antioxidants, free, mechanism, natural, oxidation, exercise.

Introduction

Antioxidants are molecules that inhibit or quench free radical reactions and delay or inhibit cellular damage. Though the antioxidant defenses are different from species to species, the presence of the antioxidant defense is universal. Antioxidants exists both in enzymatic and non-enzymatic forms in the intracellular and extracellular environment.

Normal biochemical reactions, increased exposure to the environment, and higher levels of dietary xenobiotics result in the generation of reactive oxygen species (ROS) and reactive nitrogen species

(RNS). ROS and RNS are responsible for the oxidative stress in different pathophysiological conditions. Cellular constituents of our body are altered in oxidative stress conditions, resulting in various disease states. The oxidative stress can be effectively neutralized by enhancing cellular defenses in the form of antioxidants.[1,2] Certain compounds act as in vivo antioxidants by raising the levels of endogenous antioxidant defenses. Expression of genes encoding the enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSHPx) increases the level of endogenous antioxidants.

Antioxidants can be categorized in multiple ways. Based on their activity, they can be categorized as enzymatic and non-enzymatic antioxidants. Enzymatic antioxidants work by breaking down and removing free radicals. The antioxidant enzymes convert dangerous oxidative products to hydrogen peroxide (H_2O_2) and then to water, in a multi-step process in presence of cofactors such as copper, zinc, manganese, and iron. Non-enzymatic antioxidants work by interrupting free radical chain reactions. Few examples of the non-enzymatic antioxidants are vitamin C, vitamin E, plant polyphenol, carotenoids, and glutathione.

The other way of categorizing the antioxidants is based on their solubility in the water or lipids. The antioxidants can be categorized as water-soluble and lipid-soluble antioxidants. The water-soluble antioxidants (e.g. vitamin C) are present in the cellular fluids such as cytosol, or cytoplasmic matrix. The lipid-soluble antioxidants (e.g. vitamin E, carotenoids, and lipoic acid) are predominantly located in cell membranes.[3,4]

The antioxidants can also be categorized according to their size, the small-molecule antioxidants and large-molecule antioxidants. The small-molecule antioxidants neutralize the ROS in a process called radical scavenging and carry them away. The main antioxidants in this category are vitamin C, vitamin E, carotenoids, and glutathione (GSH). The large-molecule antioxidants are enzymes (SOD, CAT, and GSHPx) and sacrificial proteins (albumin) that absorb ROS and prevent them from attacking other essential proteins.

Free radicals play an essential role in several biological processes. Many of these are necessary for life, such as the intracellular destruction of bacteria by phagocytes, especially by granulocytes and macrophages. Researchers believe that free radicals are also involved in some cellular signaling processes, known as redox signaling. Because free radicals are necessary for life, the body has several enzymatic mechanisms to minimize radically induced damage and to protect against excessive production of free radicals. Antioxidants play a vital role in these defense mechanisms. In healthy organisms, protection against the harmful effects of reactive oxygen species is achieved by maintaining a delicate balance between oxidants and antioxidants. The continuous production of free radicals in aerobic organisms must therefore be equalized by a similar rate of antioxidant consumption. Enzymatic or non-enzymatic, antioxidants are substances that prevent the formation of free radicals, and seek and neutralize or repair the damage caused by them.[5,6] In cancers, alteration of purine or pyrimidine in the structure of cellular DNA, which is associated with a number of other reactions that produce oxides and free radicals, may be the cause of neoplasms. If the intracellular mechanisms of repair of oxidative defects are insufficient or disturbed in turn by the oxidative factors present, there are definitive consequences in some genes or products resulting from the expression of these genes, which causes mutagenesis and modification of the apoptotic mechanism of the cell, thus resulting in the tumor cell

Oxidative stress stimulates the immune response and causes allergic diseases, such as asthma, allergic rhinitis, atopic dermatitis, or food allergies. This means that the antioxidant protection system of patients with allergic diseases is outdated compared to that of healthy individuals Supplementation with antioxidants could therefore compensate for the increased inflammatory and oxidative stress processes in asthma patients. However, have shown that too much antioxidant supplementation can increase the susceptibility to allergic diseases and thus asthma, by decreasing the Th1-type immune response and increasing the Th2-type response with immunoglobulin synthesis.[7,8]

Discussion

Free radicals and other active derivatives of oxygen are inevitable by-products of biological redox reactions. Reduced oxygen species, such as hydrogen peroxide, the superoxide radical anion and hydroxyl radicals, inactivate enzymes and damage important cellular components. In addition, singlet oxygen, produced via formation of triplet state chlorophyll, is highly destructive. This oxygen species initiates lipid peroxidation, and produces lipid peroxy radicals and lipid hydroperoxides that are also very reactive. The increased production of toxic oxygen derivatives is considered to be a universal or common feature of stress conditions. Plants and other organisms have evolved a wide range of mechanisms to contend with this problem. The antioxidant defence system of the plant comprises a variety of antioxidant molecules and enzymes.[9,10]Considerable interest has been focused on the ascorbate-glutathione cycle because it has a central role in protecting the chloroplasts and other cellular compartments from oxidative damage. It is clear that the capacity and activity of the antioxidative defence systems are important in limiting photo-oxidative damage and in destroying active oxygen species that are produced in excess of those normally required for signal transduction or metabolism. In our studies on this system, we became aware that the answers to many unresolved questions concerning the nature and regulation of the antioxidative defence system could not be obtained easily by either a purely physiological or purely biochemical approach. Transgenic plants offered us a means by which to achieve a more complete understanding of the roles of the enzymes involved in protection against stress of many types: environmental and man-made. The ability to engineer plants which express introduced genes at high levels provides an opportunity to manipulate the levels of these enzymes, and hence metabolism in vivo. Studies on transformed plants expressing increased activities of single enzymes of the antioxidative defence system indicate that it is possible to confer a degree of tolerence to stress by this means. However, attempts to increase stress resistance by simply increasing the activity of one of the antioxidant enzymes have not always been successful presumably because of the need for a balanced interaction of protective enzymes. The study of these transformed plants has allowed a more complete understanding of the roles of individual enzymes in metabolism. Protection against oxidative stress has become a feasible objective through the application of molecular genetic techniques in conjunction with a biochemical and physiological approach.[11,12]

"Antioxidant" is a general term for any compound that can counteract unstable molecules called free radicals that damage DNA, cell membranes, and other parts of cells. Because free radicals lack a full complement of electrons, they steal electrons from other molecules and damage those molecules in the process. Antioxidants neutralize free radicals by giving up some of their own electrons. In making this sacrifice, they act as a natural "off" switch for the free radicals. This helps break a chain reaction that can affect other molecules in the cell and other cells in the body. But it is important to recognize that the term "antioxidant" reflects a chemical property rather than a specific nutritional property.

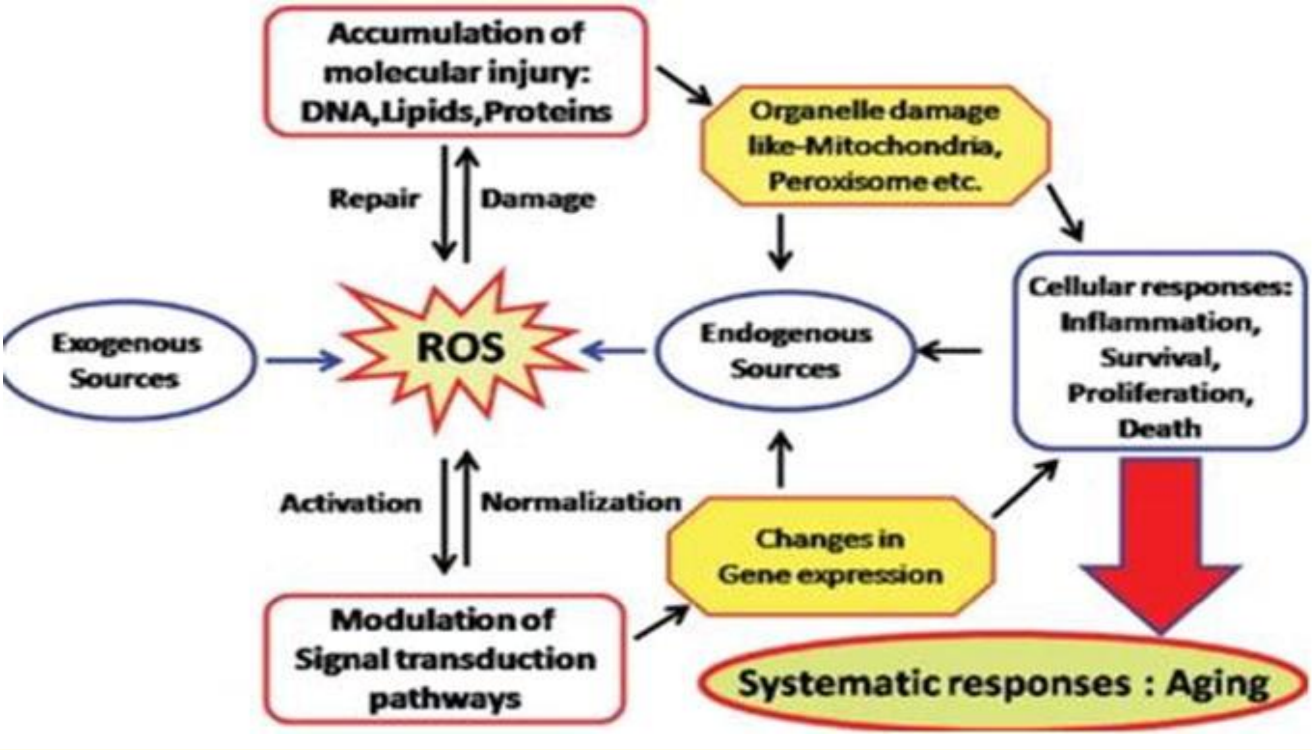
While free radicals are damaging by their very nature, they are an inescapable part of life. The body generates free radicals in response to environmental insults, such as tobacco smoke, ultraviolet rays, and air pollution, but they are also a natural byproduct of normal processes in cells. When the immune system musters to fight intruders, for example, the oxygen it uses spins off an army of free radicals that destroy viruses, bacteria, and damaged body cells in an oxidative burst. Some normal production of free radicals also occurs during exercise. This appears to be necessary in order to induce some of the beneficial effects of regular physical activity, such as sensitizing your muscle cells to insulin.[13]

Because free radicals are so pervasive, you need an adequate supply of antioxidants to disarm them. Your body's cells naturally produce some powerful antioxidants, such as alpha lipoic acid and glutathione. The foods you eat supply other antioxidants, such as vitamins C and E. Plants are full of compounds known as phytochemicals—literally, "plant chemicals"—many of which seem to have antioxidant properties as well. For example, after vitamin C has "quenched" a free radical by donating electrons to it, a phytochemical called hesperetin (found in oranges and other citrus fruits) restores the vitamin C to its active antioxidant form. Carotenoids (such as lycopene in tomatoes and lutein in kale) and flavonoids (such as flavanols in cocoa, anthocyanins in blueberries, quercetin in apples and onions, and catechins in green tea) are also antioxidants.

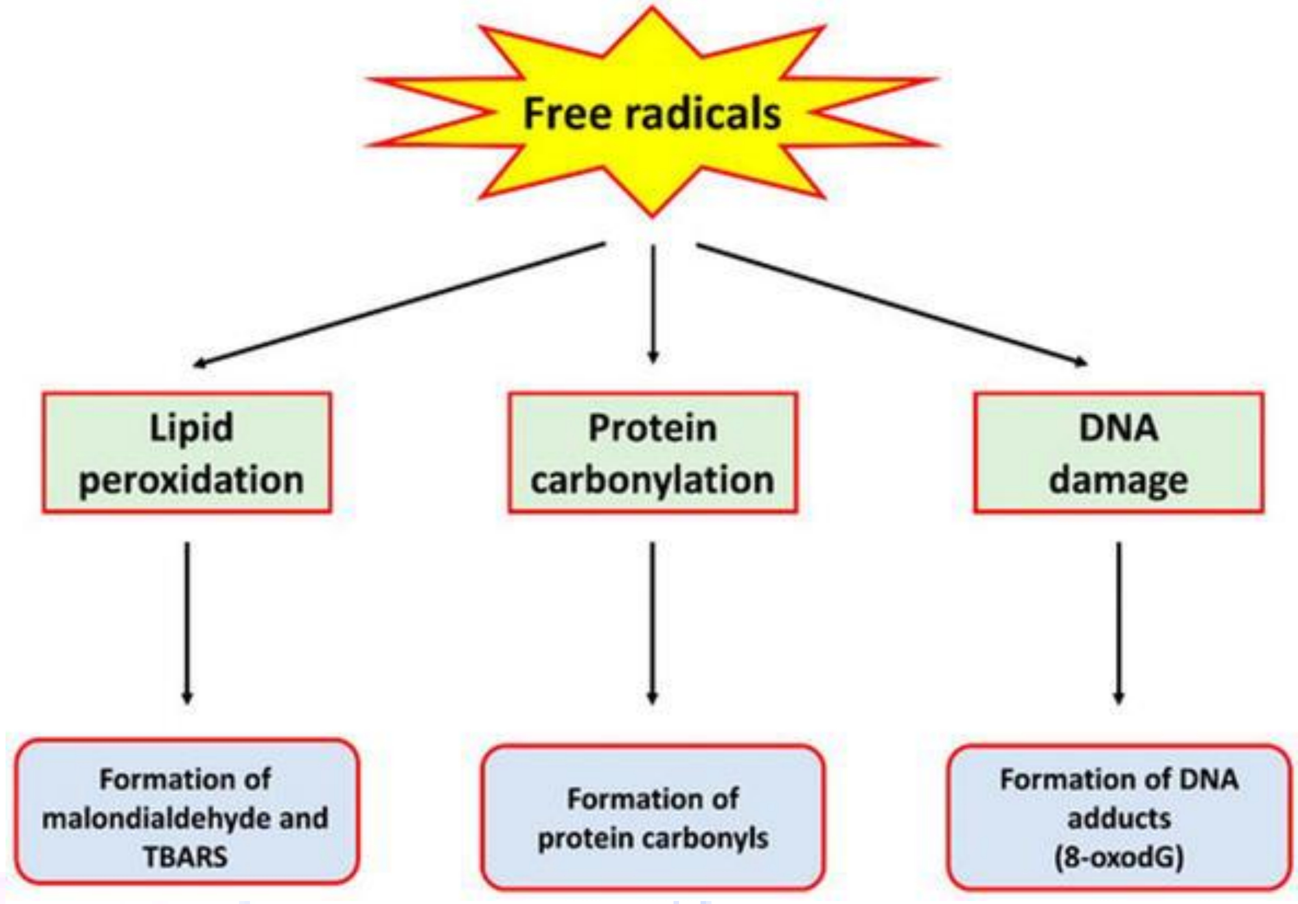
News articles, advertisements, and food labels often tout antioxidant benefits such as slowing aging, fending off heart disease, improving flagging vision, and curbing cancer. And laboratory studies and many large-scale observational studies (those that query people about their eating habits and supplement use and then track their disease patterns) have noted antioxidant benefits from diets rich in them, particularly those coming from a broad range of colorful vegetables and fruits.[14,15]

Results

Reactive oxygen species (ROS) generation by endogenous and exogenous sources can lead to oxidative damage and accumulation of proteins, lipids and DNA, when defensive (repair) mechanisms of the body become weak. These ROS also modulate the signal transduction pathways, which result in organelle damage, and changes in gene expression followed by altered responses of the cells, which finally results into aging.



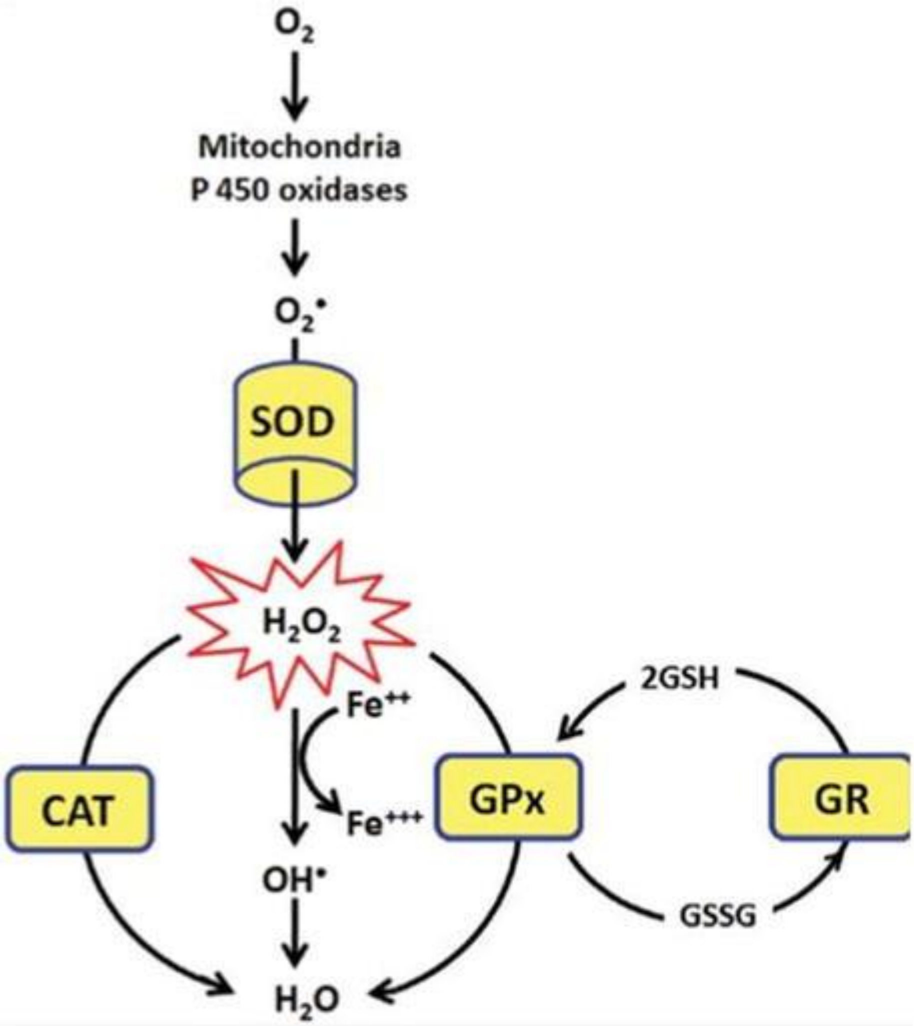
Protein oxidation can lead to amino acid modification, fragmentation of the peptide chain, aggregation of cross-linked reaction products, and increased electrical charges. Oxidized proteins are more susceptible to proteolysis, and a raise in oxidized proteins may be responsible for the loss of selected physiological and biochemical roles. Free radical damage to proteins may play a role in the causation of cataracts and aging[16]



Lipids have an important structural and functional role in cell membranes. After cell death, membrane lipids are susceptible to peroxidation and this process can cause misinterpretation of some lipid peroxidation assays. In particular, polyunsaturated fatty acids are susceptible targets for ROS attack. The important reactive moiety and initiator for ROS chain reaction and lipoperoxidation of polyunsaturated is $OH^{\bullet}$. Because of lipid peroxidation, several compounds are produced, such as alkanes, malondialdehyde, and isoprostanes. These compounds are utilized as indicators in lipid peroxidation assay, and have been confirmed in diseases including neurogenerative diseases, heart disease, and diabetes.[17]

Activated oxygen and agents that produce oxygen-free radicals, for example, ionizing radiations, promote damage in DNA that leads to deletion, mutations, and other fatal genetic effects. Through this DNA damage, both sugar and base moieties are susceptible to oxidation, leading to base degradation, single-strand breakage, and cross links to proteins. Free radical damage to DNA is associated in the causation of cancer and accelerated aging

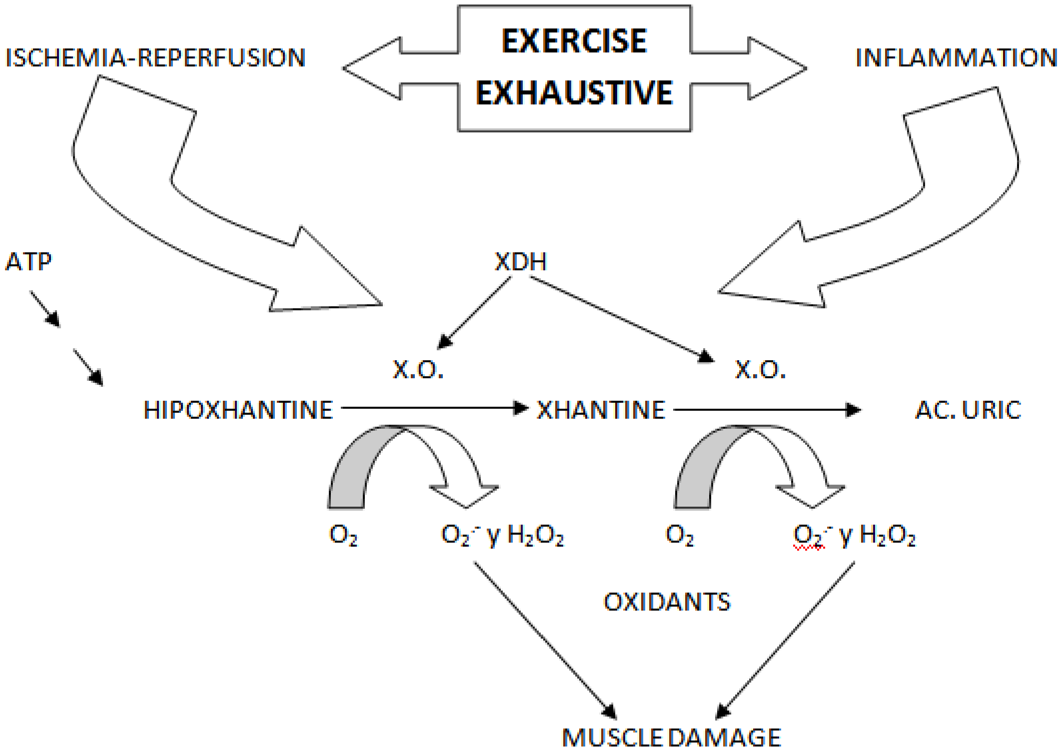
ROS such as H_2O_2, $O_2^{\bullet}$, and $OH^{\bullet}$ are produced irreversibly during metabolism. Therefore, methods have been extensively studied to reduce the damage enhanced by oxidative stress. Intracellular antioxidant enzymes produced in the cell are an essential protective mechanism against free radicals formation. SOD, CAT, GPx, GR, GST, thioredoxin reductase, and hemeoxygenase are the most important antioxidants enzymes. SODs convert $O_2^{\bullet}$ into H_2O_2, which is then converted into water by CAT, GPx, and Fenton reaction. Thus, two toxic species are converted into a harmless product [18]



Conclusions

Chronic exercise also leads to the upregulation of the body's antioxidant defence mechanism, which helps minimize the oxidative stress that may occur after an acute bout of exercise. Recent studies show a beneficial role of the reactive species, produced during a bout of exercise, that lead to important training adaptations: angiogenesis, mitochondria biogenesis, and muscle hypertrophy. The adaptations occur depending on the mechanic, and consequently biochemical, stimulus within the muscle. This is a new area of study that promises important findings in the sphere of molecular and cellular mechanisms involved in the relationship between oxidative stress and exercise.[19]

Healthy exercise is being done on a regular basis (several days a week) at a moderate intensity so that the human body in its capacity for homeostatic adaptation (with this type of exercise) increases the physiological antioxidant defenses (enzyme systems such as glutathione peroxidase, catalase, superoxide dismutase), and will offset the appearance of oxidizing species upon exercise (radical and non-radical) with this increased enzyme activity; however, the exercise leads to an increase in the oxidative body state. When more oxidizing species are generated, the body can counteract the so-called oxidative stress, which appears to be unhealthy. If the body does not sufficiently increase the physiological antioxidant defense, it is necessary to provide these through dietary antioxidants such as those included in fruits and vegetables.[20]



Scheme of the relationship between exhaustive exercise and muscle damage.

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