What Advanced Practice Nurses Need To Know About Free Radicals

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Abstract

The following manuscript defines free radicals and particularly one type of free radical called reactive oxygen species (ROS). For optimal health, a balance must be maintained between free radical formation and antioxidant production. This balance results in reduction and oxidation of free radicals which is called Redox. If there is an imbalance between free radicals and antioxidants, oxidative stress occurs that may lead to a number of diseases. Advanced practice nurses need to understand this relationship between free radicals and antioxidants to provide safe and effective patient care.

INTRODUCTION

Have you noticed the enormous media advertising campaigns for antioxidant products ranging from age-defying cosmetics to joint health? Understanding the basic concepts of free radicals and antioxidants is important so that advanced practice clinicians can make informed judgments concerning the latest information on vitamins, drugs or foods that may prevent free radical formation.

Free radicals are unpaired electrons that can damage cell proteins, DNA and lipids. Recall from basic chemistry that an atom consists of a positively charged nucleus surrounded by negatively charged electrons. The electrons are assigned to a theoretical location called an orbital or shell. Each shell can hold a specific number of electrons in the outer orbit. Most biological molecules contain paired electrons in the outer orbit. In the case of free radicals, an unpaired electron is alone in an orbit and is denoted as a superscript dot, e.g. $O_2^{\bullet-}$. This results in a highly reactive molecule eager to lose or gain an electron to achieve stability. Oxygen (O_2) is the quintessential greedy molecule, with two unpaired electrons. When O_2 is broken down electrons are lost; this is called oxidation. However, when electrons are added to O_2 it is referred to as reduction. This reduction/oxidation process is often called Redox. When radicals donate an electron to, or take an electron from a non-radical, that molecule then becomes a free radical. For example, adding one electron to the O_2 molecule yields the superoxide radical. This can initiate a self-perpetuating chain reaction that ultimately results in tissue damage. Only when two radicals meet do they stabilize.

The purposes of this manuscript are to review the concepts and terminology related to free radicals, and to highlight information relevant to clinical practice. An overview of endogenous and exogenous antioxidants is provided, in conjunction with a description of diseases associated with oxidative stress. This manuscript provides examples of how antioxidant supplements and pharmacological agents are currently being tested in practice to prevent or treat diseases.

FREE RADICALS

Free radical production in the body is a normal and essential component of cellular metabolism. Mitochondria are the major source of intracellular free radicals. Approximately 2-5% of oxygen used for aerobic metabolism in the mitochondria is converted to oxygen free radicals.[1] Some free radicals are formed as biological weapons against viruses, bacteria and cancer cells. They are also involved in the upregulation of certain genes, vasodilation and neurotransmission. Excessive free radical formation can be caused by environmental radiation, cigarette smoking, myocardial reperfusion, infection, hyperglycemia, hypoxia, chemical pollutants and certain drugs.

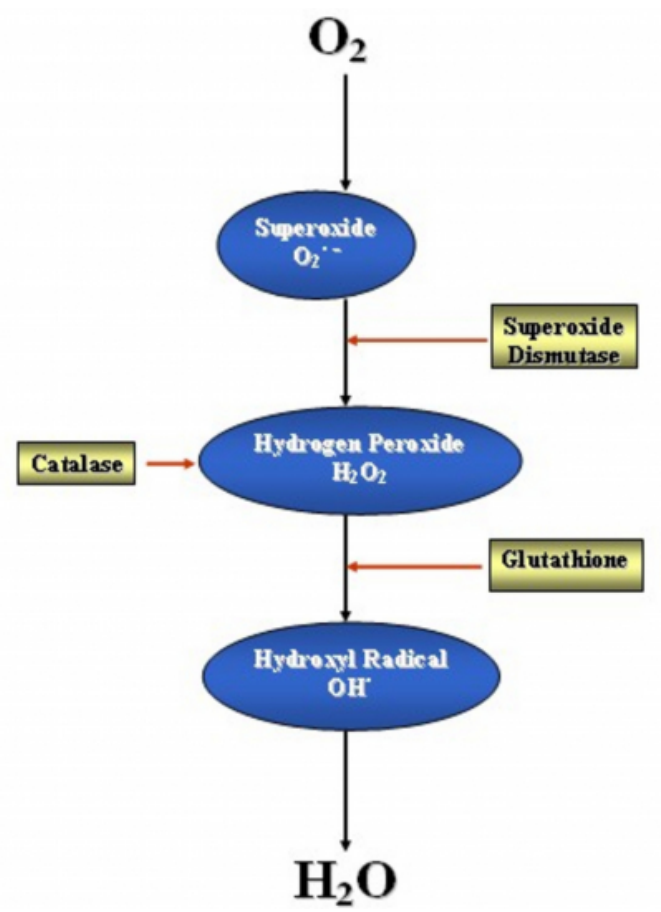
Two major forms of free radicals that are formed from oxygen and nitrogen: reactive oxygen species (ROS), and reactive nitrogen species (RNS). Superoxide ($O_2^{\bullet-}$) and hydroxyl ($OH^{\bullet}$) are examples of reactive oxygen radicals. However, the term reactive oxygen species can also refer to oxygen-derived non-radicals such as hydrogen peroxide

(H_2O_2), ozone (O3), hypochlorus acid (HOCl) and singlet oxygen. Nitric oxide ($NO^{\bullet}$) and nitrogen dioxide ($NO_2^{\bullet}$) are nitrogen radicals, but the term ROS also encompasses certain non-radicals such as nitrous acid (HNO_2) and peroxynitrate ($ONOO^{\bullet}$).

Biological organisms have evolved defense mechanisms against free radicals that are known collectively as antioxidants. An antioxidant is a substance that prevents oxidation. In biological systems antioxidants can work in various ways, including catalytic removal of free radicals, as scavengers of free radicals or in the form of proteins that minimize the availability of pro-oxidants such as metal ions. However, there are circumstances in which certain antioxidants can actually behave as pro-oxidants.[2,3]

The major endogenous antioxidants are: 1) superoxide dismutase (SOD) which removes $O_2^{\bullet}$, 2) catalase which converts H_2O_2 to water (H_2O) and O_2, and 3) glutathione peroxidase which helps with H_2O_2 removal and prevents hydroxyl radical ($OH^{\bullet}$) formation (Figure 1). Many other substances such as uric acid, iron-binding proteins, selenium, ceruloplasmin, bilirubin and estrogen can also function as antioxidants in specific systems.[4] Lipoic acid and coenzyme Q10 are other antioxidants under investigation.[5] Although the body makes these, they are also available as supplements. Lipoic acid has the unique ability to regenerate several other antioxidants such as vitamin E, vitamin C, coenzyme Q10 and glutathione. Coenzyme Q10 can also regenerate vitamin E from its radical form and is capable of scavenging oxygen radicals and preventing disruption of lipid cell membranes.

Figure 1



Well known exogenous antioxidants include vitamin E (the tocopherols) and vitamin C (ascorbic acid). Vitamin C, the major plasma antioxidant, is a scavenger of many ROS and RNS, and is capable of regenerating -tocopherol from its radical. Vitamin E primarily scavenges peroxyl radicals and is a major `inhibitor of the free radical chain reaction of lipid peroxidation. [4,6] Beta- carotene, a plant derived precursor of vitamin A, is considered to be the most efficient scavenger of singlet oxygen, which is a non-radical ROS.[7] There are numerous other dietary sources of antioxidants.[8] Examples include lycopene from tomatoes, flavenoids from citrus, as well as tea and wine.

Production of antioxidants and free radicals in the body is theoretically balanced. When conditions favor free radical production, a state known as oxidative stress occurs. This can happen when either production of radicals is increased or antioxidant defenses are impaired. Cells can tolerate some degree of oxidative stress and typically respond by increasing the synthesis of antioxidants. Prolonged oxidative stress can result in oxidative damage to tissues.[9]

DAMAGE CAUSED BY FREE RADICALS

Free radicals such as hydroxyl radical ($OH^{\cdot}$) and nitric oxide ($NO^{\cdot}$) are directly cytotoxic. This can be beneficial in fighting microorganisms, but harmful if uncontrolled. Oxidative stress causes damage to three major structures: 1) DNA, 2) cellular proteins, and 3) lipids. It also affects cellular calcium metabolism. Uncontrolled rises in intracellular free calcium can result in cell injury or death.[4],[10] Damage to DNA strands can occur directly by free radicals in close proximity to the DNA or indirectly, for example, by impairing production of protein needed to repair DNA. Alteration in DNA is a major factor in the development of cancer.

Free radicals can attack fatty acid side chains of intracellular membranes and lipoproteins. A chain reaction known as lipid peroxidation ensues. The products of lipid peroxidation can further damage membrane proteins, making the cell membrane " leaky" and eventually leading to loss of membrane integrity. Lipid peroxidation is implicated in the development of atherosclerosis.[10],[11],[12]

The last structures damaged by oxidative stress are cellular proteins. Oxidized proteins may trigger antibody formation and autoimmune processes.[4]

HUMAN DISEASES ASSOCIATED WITH OXIDATIVE STRESS?

According to Halliwell,[4] oxidative stress occurs in most human diseases. This is not to say that oxidative stress is the cause of most diseases. The increase in free radicals may be secondary to the disease process. Free radicals are very short lived and difficult to study in-vivo. Direct detection of free radicals is possible with electron spin resonance, but it is very expensive and complex.[7],[13] Therefore, a variety of surrogate markers to ascertain free radical activity must be used. Developing accurate methods to measure biomarkers for DNA damage and lipid peroxidation is challenging. A few methods in the current literature include urine levels of F2-isoprostanes as a biomarker for lipid peroxidation, measurement of oxidized low density protein (LDL), use of a chemical mutogenic product of fat oxidation, and 8-oxo-deoxyguansine, which is associated with a decline in mitochondrial function.[13],[14],[15] There have also been efforts to detect changes in the levels of antioxidants such as SOD, glutathione or vitamin E in the body in response to oxidative stress, but results have not been consistent.[16]

Table 1 identifies many conditions associated with free radical formation. The implications of the presence of free radicals in cardiovascular, pulmonary and neurological disease as well as the inflammatory process are currently under intense investigation.

Figure 2

Table 1

Clinical Conditions Associated With Free Radical Damage

• Alzheimer's	• Coronary Artery Disease
• Amyotropic Lateral Sclerosis	• Heart Failure
• Arthritis	• Hypertension
• Atherosclerosis	• Inflammatory Bowel Disease
• Cancer	• Macular Degeneration
• Cataracts	• Multiple Sclerosis
• Chronic Gout	• Parkinson's
• Chronic Obstructive Pulmonary Disease	• Raynaud's Phenomenon
• Diabetes	• Reperfusion Injuries

Free radicals affect the cardiovascular system in several ways. In the development of atherosclerosis, oxidative modification and degradation of lipoproteins results in foam cells, which are major components of fatty streaks. Modified lipoproteins also initiate an inflammatory response. As the current literature indicates, inflammation is a key component in the atherosclerotic process from plaque generation through rupture.

Reperfusion injury, the paradoxical myocardial dysfunction that results after reopening a stenosed coronary artery, has been well studied in animal models. A few human studies have also measured indirect markers of oxidative stress.[1],[17],[18] ROS have the ability to directly damage cardiac myocytes and exert an inhibitory effect. Superoxide radical in particular has been detected in the post-ischemic myocardium.[18] Endothelial cells are thought to be the source of the free radicals. It is speculated that the combined action of lipid peroxidation and protein oxidation alters cellular function via the effects on intracellular membranes of the mitochondria, sarcoplasmic reticulum and the sarcolemma. Adenosine triphosphate (ATP) depletion and calcium ion imbalance could result in decreased contractility and arrhythmogenicity.[10],[18]

Damage from free radicals is also seen in patients with essential hypertension. Levels of $O_2^{-\cdot}$ and H_2O_2 have been elevated while those of free radical scavengers have been depressed.[10] The role of NO in endothelial dysfunction and resultant hypertension is currently being studied. Oxidative stress may contribute to hypertension by inactivating NO which is a potent vasodilator.[19] Antioxidant vitamins E and C

have been shown to restore NO mediated vasodilation in both human and animal studies.[10,19] Oxidative stress has been proposed as a contributory mechanism in chronic left ventricular dysfunction.[16,17,20] Calcium ion imbalance, oxidative byproduct toxicity, mitochondrial DNA mutations and impaired cellular energy production are suspected of contributing to the pathogenesis of heart failure. Although the deleterious effects of free radicals on myocytes have been shown with in-vitro studies and animal models, studies in humans are few. Lack of reliable means to measure free radical activity is a major obstacle in study design.

It is easy to appreciate that the lungs are vulnerable to inhaled agents that stimulate ROS/RNS production. These include ozone, nitrogen dioxide, sulfur dioxide and other toxins present in polluted air. Cigarette smoke contains numerous toxins that are either free radicals themselves or impair antioxidant defenses. ROS/ RNS can stimulate lipid peroxidation and oxidation of DNA bases in the lungs. The irritant effect of smoke also activates lung macrophages and neutrophils with resultant production of additional ROS.[4] Furthermore, cigarette smoke may supply free iron, which can initiate free radical chain reactions.

Chronic lung inflammation such as asbestosis, asthma and cystic fibrosis is also associated with elevated markers of oxidative stress. While free radicals do not cause these diseases, they may contribute to the ongoing pathology.[4]

The brain may be especially sensitive to oxidative damage. One postulation concerns the high calcium traffic across neural membranes and the high ratio of oxygen consumption in the brain per unit mass of tissue.[4] Neurotransmitters are susceptible to oxidative modification. Also, brain metabolism produces H_2O_2, which is a non-radical ROS. Catalase, which reduces H_2O_2, is only present in low levels in the brain. Oxidative stress can damage neurons and glial cells in a manner similar to other tissues: via products of lipid peroxidation that are neurotoxic, DNA damage, cellular protein damage and the induction of cell death.[4,21,22]

Reperfusion injury also occurs in the brain after a stroke. Superoxide produced during reperfusion results in abnormalities of cerebral vascular responses and blood-brain barrier permeability.[22] Extracellular glutamate levels in the brain increase rapidly during ischemia, leading to increased production of $OH^{\bullet}$ radicals, calcium ion imbalance and increased neurotoxicity.[4] If bleeding occurs with the stroke, normally sequestered iron molecules are released and may initiate harmful free radical chain reactions. Cerebral vasospasm is one potential consequence.[2,5]

Neurodegenerative diseases associated with ROS/RNS include Parkinson's. Alzheimer's, amyotrophic lateral sclerosis, and Huntington's.[4,13,23] Sorting out causative versus contributory roles is the subject of ongoing research. It is possible that although the initiators of the disease state vary, free radicals are involved in a common pathway that leads to neural cell death.

The acute inflammatory response is typically beneficial to the organism. It is a major defense against microorganisms and is usually self-limited. However, the superoxide-producing neutrophil itself is destroyed in the process and healthy surrounding cells may also be damaged.[24] When inflammation becomes chronic, the overall impact of the continued generation of free radicals is deleterious. One example is rheumatoid arthritis (RA). Degradation of hyaluronic acid (synovial fluid) is driven by the presence of $OH^{\bullet}$. These radicals may be produced by phagocytic cells in the joint, by changes in tissue oxygenation due to swelling, followed by reperfusion, or by some of the drugs used to treat RA.2

Finally, the free radical theory of aging postulates that it is the cumulative effect of free radical damage, particularly on mitochondrial DNA, which contributes to the aging process. One visible example of this cumulative effect is excessive wrinkling associated with exposure to sunlight.

IMPLICATIONS FOR PRACTICE

When considering primary prevention, the goal is to minimize overproduction of free radicals and maximize availability of antioxidants. Lifestyle modifications such as smoking cessation, minimizing sun exposure, avoidance of air pollution and inhalation of toxic chemicals such as gasoline fumes, and moderating alcohol intake are all prudent measures to recommend.

Cardiovascular disease and cancer risk reduction are associated with diets rich in fruits and vegetables.8 The antioxidants present in these foods may be responsible for this protective effect. However, it has been difficult to isolate the antioxidant properties as the sole mechanism.[14]

Antioxidant supplementation is controversial.[6,7,12,25,26] There are numerous opinions, but no definitive answers in the literature. There is a bewildering array of products on the market, including vitamins C and E, and minerals such as selenium, manganese, zinc and copper which are all

involved in the free radical scavenging process. Coenzyme Q10, alpha lipoic acid, n-acetylcysteine, and even glutathione are available at a variety of stores. Numerous skin care products claim to reduce the appearance of aging with their antioxidant ingredients. Patients may be seeking a professional opinion about these products, and some may even request laboratory testing of biological markers of oxidative stress. A good source of information for consumers and health care professionals is the IBIDS Database available from the National Institutes of Health Office of Dietary Supplements at http://ods.od.nih.gov/databases/ibid.html.

Cardiovascular, neurodegenerative and chronic inflammatory diseases are specific areas of intense pharmacological research. The development of drugs designed to counteract specific free radicals or boost antioxidants may be on the horizon. Having a basic understanding of free radicals and antioxidants will help advanced practice nurses better appreciate the theoretic basis for how these drugs work.

CONCLUSION

While free radicals may not come up in daily conversation among advanced practice clinicians, questions from patients about antioxidants, and vitamins in particular, are on the rise. In addition, the next time you adjust the medications of your heart failure patient, discuss smoking cessation, or research current approaches for your patient with rheumatoid arthritis, you may find knowledge of free radical formation and antioxidants quite helpful. Free radicals may be viewed as a "foe" because the damage to cellular structures can lead to different diseases. However, free radicals are the body's "friend" in protecting against foreign substances. Thus, the balance of the reduction and oxidation (Redox) of free radicals in the body is important in maintaining health.

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