Oxidative Stress and Damage Recovery

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Abstract

Oxidative stress is a form of stress that produces free radicals. Free radicals, in an over-abundance, are known to cause damage to proteins, DNA, cellular membranes, lipids, and genes. When left unchecked, these free radicals contribute to a number of chronic diseases and have a role in the speed at which we age. Oxidative stress is a state where oxidative forces exceed antioxidant systems due to loss of the balance between the two. Antioxidants are internal and external defense systems with some antioxidants occurring naturally within the body while other antioxidants are obtained through consuming functional foods, supplements, and a variety of variety of fruits and vegetables. Antioxidants are found in enzyme and non-enzyme form and as micronutrients such as vitamins and minerals. This projects looks at what free radicals and reactive oxygen species are, how they are both beneficial and deleterious to the human body and how antioxidants help restore the balance in the body caused by an overabundance of oxidative stress. *Keywords: oxidative stress, antioxidants, free radicals, reactive oxygen species*

Introduction

Humans are exposed to varying degrees of stress every day, all day. Stress is a physiological response by the body viewed in terms of wear and tear; it is also a psychological response, a level of anxiety caused by events and responsibilities that exceed a person's coping abilities (Seaward, 2012). The definition of physics says stress is an amount of force or tension placed on an object to bend or break it, stress on the human body is seen as the amount of tension placed on the mind, body, and/or soul of a person (Seaward, 2012). A number of definitions have evolved over the years to define just what stress is to the human body, and one of the most encompassing definitions is found in *Managing Stress*, Seaward (2012): "Stress is the experience of a perceived threat (real or imagined) to one's mental, physical, or spiritual well-being, resulting from a series of physiological responses and adaptations (p. 3)."

Stress can also be defined as altered biochemical homeostasis brought on as a result of psychological, physiological or environmental stressors. These stressors place a demand on the body challenging or threatening the safety of the body (Rahal, A., Dumar, A., Singh, V., Yadav, B., Tiwari, R., Chakraborty, S., & Dhama, K., 2014).

Oxidative stress is a form of physiological stress. Rahal, et al (2014) reports that oxidative stress produces free radicals that may damage proteins, membranes, and genes, and once they start causing damage may start a chain reaction. Oxidative stress puts harmful tension on our cellular functions, tension that is linked to damage to our DNA and leading to a number of human degenerative and autoimmune diseases (Ahsan, H., Ali, A., Ali, R., 2003). This type of stress is gaining a significant place in the study of disease and chronic illness. Researchers are finding that oxidative stress is linked to some of our most deleterious diseases: arthritis, vasculitis, systemic lupus erythematosus, adult respiratory distress syndrome, ischemic diseases, stroke, intestinal ischemia, hemochromatosis, AIDS, emphysema, organ, transplantation, gastric ulcers, hypertension and preeclampsia, neurologic diseases (Multiple Sclerosis, Alzheimer's, Parkinson's, Amyotrophic lateral sclerosis, muscular dystrophy), alcoholism, and smoking related diseases (McCord, 2000). Research suggests that oxidative stress is brought about by a chain reaction of free radicals, that when left unchecked, cause the rapid destruction of the cellular walls in our cells, leading to inflammation and the inability of our immune system to protect us from bacteria, viruses and other damage to the human body.

The human body undergoes countless biochemical activities and biological functions within a twenty-four hour period. In the study of pathophysiology, we learn that the body strives to achieve two very important states. The first is *homeostasis*, which is defined as "remaining stable by remaining the same (Copstead & Banasik, 2013, p. 12). Homeostasis comes from the Greek words *homeo*, meaning "same" and *stasis*, or "stable" (Copstead, & Banasik, 2013). The second state the body tries to maintain is called *allostasis*, from the Greek words *allo*, or "variable", and *stasis*, meaning, "stable" (Copstead & Banasik).

Homeostasis had been the gold standard since at least the nineteenth century, the idea being, "the body attempts to achieve balance around a single optimal level or set point for a given physiologic variable (Copstead & Banasik, 2013, p. 13)." However, since 1988, science has developed a more complex and definitive definition and that is, the body is a complex organism with "variable levels of activity, necessary to reestablish or maintain homeostasis (Copstead, p. 13)." The body has a natural response to variable levels of activity with set points that have to be adjusted for various circumstances (Copstead & Banasik, 2013). The definition of allostasis is, "the ability to successfully adapt to challenges. The organic organism has to vary all parameters of its internal milieu and match them appropriately to the demands placed on the organism; additionally, allostasis is a dynamic process that supports and helps the body achieve homeostasis (Copstead, p. 13).” This concept is extremely important because much of the activity the body goes through to adjust for the various demands placed on the human body can often result in oxidative stress (also known as *redox imbalance*).

What is oxidative stress? There are countless definitions available defining oxidative stresses. The one I found most easy to understand comes from Yoshikawa & Naito, (2002) where they initially describe oxidative stress as a harmful event because oxygen free radicals attack lipids, proteins, and DNA which are believed to have a role in the production of tissue damage in a number of chronic illnesses and aging. Looking a bit deeper at the role of oxidative stress, they further define oxidative stress as “a state where oxidative forces exceed antioxidant systems due to loss of the balance between them (Yoshikawa & Naito, 2002).”

There are reactions that occur are called reduction-oxidation (redox) reactions, which result in varying degrees of oxidative stress. What is significant about these reactions is that electrons or hydrogen atoms are transferred from one reactant to another (McCord, 2000). When electrons are removed the molecules this is called oxidation and when a substance receives electrons it is being reduced (McCord, 2000).

Reactive oxygen species (ROS), also known as free radicals, are a normal part of human biochemistry, however, when there are an excess of free radicals, there are breakdowns in the immune system and reactive oxygen species are known to have a role in many chronic illnesses (Hanson, 2005). Oxidative stress is a result of various reactions such as the redox reactions and reactive oxygen species are a product of oxidative stress. Free radicals are formed in the body through enzyme reactions and non-enzyme reactions as well as exposure to sources outside the body (Lobo, V., Patil, A., Phatak, A., & Chandra, N., 2010).

The following are a variety of ways in which free radicals are generated in the human body: our mitochondria (cellular energy powerhouses), peroxisomes (linked to utilization of oxygen), inflammation, phagocytosis, exercise, ischemia/reperfusion injury, cigarette smoke, environmental pollutants, radiation, some drugs and pesticides, industrial solvents, and the ozone (Lobo, V., Patil, A., Phatak, A., & Chandra, N., 2010). Figure 1 below shows the classification internal and external stressors.

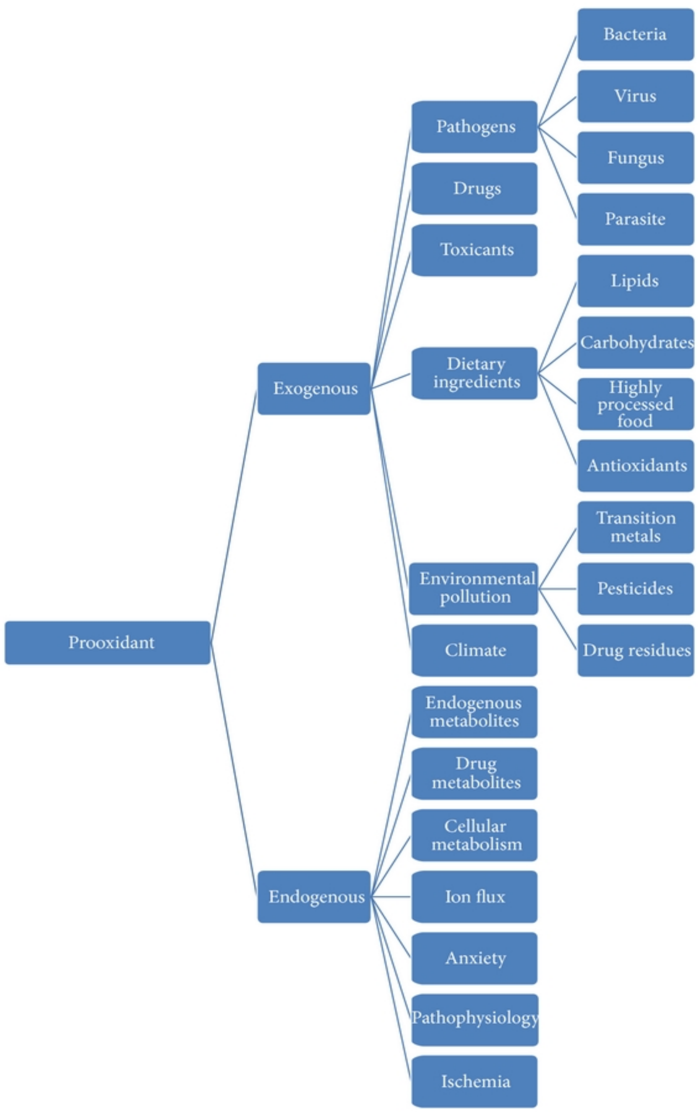

Figure 1 Internal and External Stressors

A prooxidant is defined by Rahal, et al (2014) as parasites or chemicals, natural or manmade, that cause oxidative stress either by generating reactive oxygen species or by preventing antioxidant systems from working properly. The following table shows examples of prooxidants.

SL number	Class	Examples	Mechanism
1	Drugs	Common OTC like analgesic	ROS generation leading to alterations in macromolecules which finally can fatally damage the tissues mainly liver and kidney
2	Transition metals	Examples are magnesium, iron, copper, zinc	Metals induce particular reactions generating excess ROS
3	Pesticide	BHC, DDT, etc.	Stimulation of free radical production, induction of lipid peroxidation, alterations in antioxidant enzymes and the glutathione redox systems
4	Physical exercise	Running, weight lifting, etc.	Relaxation/contraction of muscles and rigorous exercise produce ROS
5	Mental anxiety	Tension, apprehension, stress	Results in imbalance in redox system. Cause of neuro-inflammation and neuro-degeneration, mitochondrial dysfunction, altered neuronal signaling, and inhibition of neurogenesis
6	Pathophysiology	Local ischemia	Gives rise to ROS
7	Environmental factors	Extreme weather, i.e., cold, heat, thunderstorms	During adaptation, mitochondrial membrane fluidity decreases which may disrupt transfer of electrons, increasing production of ROS

Table 1 Different classes of prooxidants and their common mechanism for development of oxidative stress p. 10

Our immune system is a mechanism for destroying invading bacteria and viruses; this mechanism is also a normal part of the biological function of reactive oxygen species. The problem is, these free radicals do not have a specific “stop” mechanism. Without a “stop” mechanism, they can overrun the immune system, causing “collateral damage”, damage to our cells and cellular function, resulting in inflammation and pain (Hanson, 2005). Science is learning that the presence of free radicals seems to be part of the cause of not only many cancers and chronic diseases, but a whole host of other problems associated with aging, such as confusion and difficulty thinking and remembering, cataracts, cardiovascular disease and atherosclerosis, as well as the decline of the immune system (Hanson, 2005). Free radicals are linked to much of the chronic inflammation many people live with on a day-to-day basis.

What are free radicals?

"Free radicals are any species capable of independent existence; there is an unpaired electron which is alone in its orbital (Halliwell, 1994, p. 254)". The most common free radicals known as reactive oxygen species have oxygen atoms in a highly reactive form willing an able to release electrons.

Examples of free radicals

Name	Formula	Description
Hydrogen atom	$H^{\cdot}$ (Single dot signifies unpaired electron)	Simplest free radical
Trichloromethyl	$CCL^{\cdot}_3$	Carbon centered radical (unpaired electron on the carbon atom)
Superoxide	$O^{\cdot}_2$-	Oxygen centered radical
Hydroxyl	$OH^{\cdot}$-	Highly reactive oxygen centered radical. Attacks all molecules in the human body
Thiyl	$RS^{\cdot}$	Group of radicals with an unpaired electron residing on sulfur
Peroxyl, alkoxyl	$RO^{\cdot}_2$, $RO^{\cdot}$	Oxygen centered radicals formed during breakdown of organic peroxides
Oxides of Nitrogen	$NO^{\cdot}$, $NO^{\cdot}_2$	Nitric oxide formed in vivo from the amino acid L-arginine. Nitrogen dioxide is made when $NO^{\cdot}$ Reacts with O_2, found in polluted air and smoke from burning organic materials (e.g., cigarette smoke)

Table 2 (Halliwell, 1994, p. 254)

To better understand the role of free oxygen radicals requires a very basic understanding of elements, atoms, and molecules. The following is a brief explanation of the chemistry of elements, atoms, and molecules.

Elements are the basic building blocks of all matter. An atom is the smallest particle of an element. What makes an atom? Atoms are comprised of three sub particles—a proton, which has a positive electrical charge; a neutron, which is neutral, with no electrical charge; and finally, electrons, which have a negative electrical charge (Helmenstine, 2014). Some familiar elements are hydrogen, oxygen, nitrogen and carbon. In all, there are known to be 118 elements, which are found on a table called the “Periodic Table of Elements (Helmenstine, 2014).”

Below is an example of an atom. The protons and neutrons reside together in the nucleus of the atom. There are two protons in the center, depicted by the positive signs, two electrons in the outer area, depicted by the negative signs. The two circles with no symbols are the neutrons.

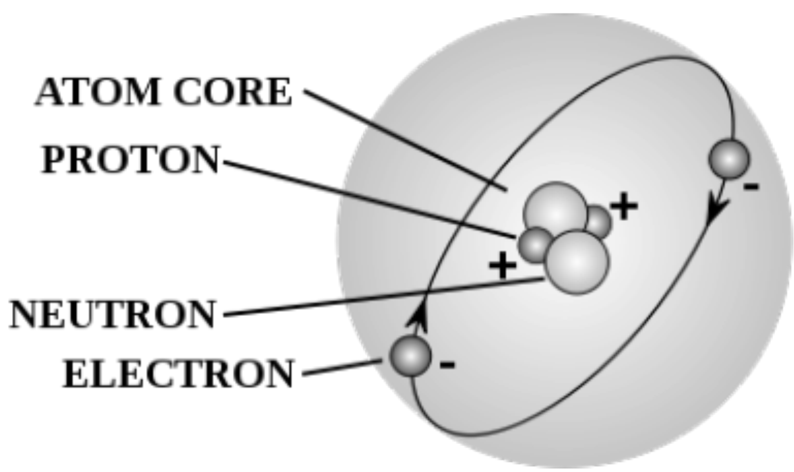

Figure 2 Helium Atom

The proton and the neutron comprise the mass or weight of the atom. Electrons inhabit a space outside the nucleus called the orbital space. This orbital space is like a cloud where electrons live together as pairs, each spinning opposite its partner. This spin holds the electrons in partnership and requires energy, to break the bond that holds the electrons, in order to separate the electrons, which will then allow formation of either different molecules or compounds. An easy way to view this concept is to think of the electrons forming rings, or shells, around the nucleus. Each shell has to be “full” before the next shell can begin to fill with electrons.

Only two electrons can exist in the first energy level, in every atom, except hydrogen; hydrogen only has one electron, therefore hydrogen is very reactive meaning it will readily bind itself to another atom with a free electron in the outer shell.

The next level is the second energy level. In the example of oxygen, there are six electrons in that shell. “Oxygen has two electrons in the second shell that are not spin paired, each residing in a shell (or orbital) by itself (McCord, 2000, p. 652)”. Oxygen likes to bind with many other atoms to form a variety of molecules and to fill pair those two outer shell electrons. But, oxygen is also ready to give up one of those electrons, causing it to become a free radical. When viewed under an electron microscope, the shells resemble a cloud; the cloud is made up of electrons zooming around mostly in pairs. The electrons in the outer shell are the easiest to pull away from the atom as it takes much less energy. Depending on the other atom will determine the number of electrons that will be pulled away to form a molecule.

One of the most common molecules is the water molecule; it is made up of two hydrogen atoms and one oxygen atom. The reason hydrogen and oxygen can come together to create water is fairly simple. Each hydrogen atom has one electron. Oxygen has eight electrons, two in the inner shell and six in the outer shell. In order to create water, each hydrogen atom shares its lone electron with oxygen creating was is called a covalent bond. Wikipedia defines a covalent bond as a chemical bond where electrons are shared (n. a. 2015).

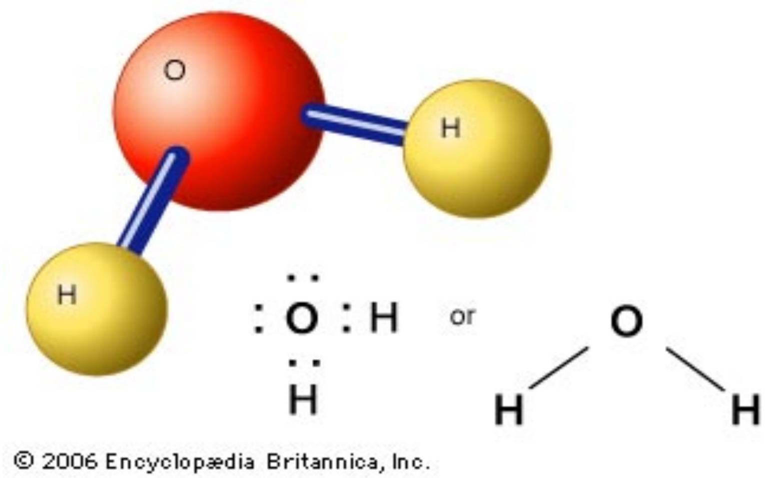

Figure 3 Water molecule

Electrons and protons have opposite charges, they are attracted to one another, and the attraction is what creates the element. The attraction between electrons and protons is highly charged. As the electrons spin in the orbitals, the electrons furthest from the protons can be manipulated easier because the pull to hold an electron in place is not as strong. When there is a single electron in an orbital space, the molecule is highly reactive because the lone electron is always searching for a partner in an effort to regain a stable stance. This ability to move is referred to as chemical reactivity.

According to Hanson (2005), reactivity is dependent upon a number of factors. Some factors are temperature—the higher the temperature the faster molecules move carrying more energy; concentration of reactants—the greater the concentration of reactants the faster the reactions will be. Reactivity means how fast a molecule reacts in a given reaction. In addition to reactivity, there is also selectivity (Hanson, 2005). This is important because free oxygen radicals are not selective about what they react with. The reactivity coupled with the lack of selectivity is the reason why free oxygen radicals are so dangerous; the reactions of free oxygen radicals will damage any cells that it comes in contact with (Hanson, 2005).

Rahal, et al (2014), describe some of the internal functions that cause the production of reactive oxygen species. While these functions can and do contribute to damage of proteins, DNA, the lipid peroxidation of cellular membranes, the reactive oxygen species have a vital function in our metabolic and biologic functions. Table 2 shows internal stressors, which cause the production of reactive oxygen species.

Leakage of free radicals	Membrane-bound enzymes	NADPH oxidase
	Electron transport systems	Mixed function oxidases
Activation of oxygen	Soluble cell constituents	Transition metals, thiol containing proteins, quinine derivatives, epinephrine, metalloproteins, hemeproteins, and flavoproteins
	Xenobiotic metabolizing enzymes	Cyt P_{450}-dependent monooxygenases, Cyt , and NADPH-dependent cytochrome reductases
ROS generation/propagation	Soluble cytosolic enzymes	Xanthine oxidase, superoxide dismutase, catalase
	Phagocytic cells	Neutrophils, macrophages, and monocytes involved in inflammation, respiratory burst, and removal of toxic molecules
	Local ischemia	Damaged blood supply due to injury or surgery

Table 3 Endogenous Stress Mediators of Oxidative Stress

The human body has defense systems for combating free radicals, including free oxygen radicals. One defense system is antioxidants. Antioxidants “scavenge” free oxygen radicals and help minimize the formation of reactive oxygen species (Hanson, 2005).

What are antioxidants?

According to Lobo et al (2010), antioxidants are considered stable molecules that are able to donate an electron to a free radical, thereby scavenging the free radical and stopping the free radical from causing further damage. Free radical chain reactions are stopped by antioxidants.

Antioxidants are a powerful defensive system because they scavenge free radicals, can donate hydrogen or an electron, decompose peroxide, grab singlet oxygen, inhibit dangerous enzyme activity, and act as metal-chelating agents (Lobo et al, 2010).

Some antioxidants are produced in the body through normal metabolic action in the body. Enzymes drive these normal metabolic actions. However, most antioxidants are found naturally in a variety of whole foods, specifically in fruits and vegetables as well in a number of micronutrients known as vitamins; the most common vitamins that provide a system for scavenging free radicals are vitamin E (alpha-tocopherol), vitamin C (ascorbic acid), and Beta carotene. These vitamins are not produced by the body and must be supplied through diet (Lobo, et al, 2010).

Lobo et al (2010) describes two mechanisms for antioxidant activity. One mechanism is called a "chain-breaking mechanism (p. 9). A primary antioxidant donates an electron to a free radical. In the second mechanism, a free radical species initiator is removed by preventing a chain reaction initiating catalyst (p. 9). The antioxidants provide defensive action at different levels: preventive, radical scavenging, repair and de novo, and adaptation (Lobo et al, 2010).

According to Pizzorno & Murray (2014), using antioxidant supplementation in order to stop the production of free radicals is considered counterproductive because there are physiologic levels of reactive oxygen species needed for maintaining homeostasis. Examples are the production of nitric oxide and superoxide, which have a role in maintaining the body's defenses and homeostatic mechanisms.

I looked at research beginning in the late 1990s through as recent as 2012 however, there is no standard mechanism for understanding and detailing how the body responds to oxidative stress, the production of free radicals and the use of antioxidants to balance the production of oxidants. Research cannot use data from in vitro studies or animal studies and is turning to other mechanisms such as the use of genetically modified animals and the analysis of global changes in gene expression (Pizzorno & Murray, 2014).

Methods

The information included in this review of current scientific literature was gathered through an extensive search of peer-reviewed scholarly journals and current medical texts. I did not limit my time frame as some of the research conducted in the 1990s is still being cited today. For my literature review, I used the following key terms to search for peer reviewed articles to use to support my paper: inflammation, free oxygen radicals, reactive oxygen species, oxidative stress/redox balance, chronic illness, and antioxidants. I used ProQuest, LIRN, Google Scholar, PubMed, and Google. In addition to these websites I also referred to *The Textbook of Natural Medicine, 4th Ed*., *Krause's Food and Nutrition Care Process, 13th Ed*., and *Understanding Medicinal Plants: Their Chemistry and Therapeutic Action*.

Results

Reactive oxygen species are free radicals and free radicals are a product of oxidative stress. Oxidative stress is normal in aerobic metabolic functions but can result in deleterious reactions causing lethal damage to proteins, DNA and lipids.

There are numerous causes of oxidative stress. One of the most extreme causes is severe malnutrition; without proper nutrition such minerals as copper, manganese, zinc, and selenium and vitamins are not absorbed by the body. These minerals and vitamins participate in scavenging certain free radicals, working as antioxidants (Halliwell & Cross, 1994). Other toxins, which contribute to oxidative stress, are medications, such as carbon tetrachloride, and herbicides such as paraquat (Halliwell & Cross, 1994). A well-documented toxin that contributes to oxidative stress is cigarette smoking.

There is evidence supporting various tissue injuries which a linked to oxidative stress and damage. The following cause tissue damage: heat, trauma, ultrasound, infection, radiation exposure (x-ray), elevated oxygen levels, toxins, exercise to excess, and ischemia. The resulting damage are: an increase in radical-generating enzymes and or their substrates; activation of phagocytes, activation of enzymes phospholipases, cyclooxygenases, and lipoxygenases; dilution and destruction of antioxidants; release of “free” metal ions from sequestered sites; release of heme proteins (hemoglobin and myoglobin); and disruption of electron transport chains and increased electron leakage forming the superoxide radical (Halliwell & Cross, 1994, p. 9). Finally, there are a number of environmental air pollutants that contribute to causes of oxidative stress.

Again, free radicals are the products of oxidative stress. Hydrogen is the most reactive of the free radicals. It has only one electron and willing gives up this one electron and, actively avails itself to bond with atoms. The good thing about hydrogen is that it essentially provides stability to other atoms and molecules. However, where it is the most influential is when it combines with an oxygen atom to create the hydroxyl radical.

The hydroxyl radical is the most lethal of the free radicals. According to Halliwell & Cross (1994), hydroxyl radical is so reactive that it reacts with all biological molecules and the damage caused by the hydroxyl radical cannot be avoided. This radical attacks proteins, carbohydrates, DNA, and lipids. When the hydroxyl radical attacks DNA it causes such problems as single-strand breaks, base modifications, and conformational changes. Our thymine and guanine are most susceptible to modification (Ahsan, Ali, & Ali, 2003). There do not appear to be any redeeming reactions from the hydroxyl radical and no particular scavenger antioxidants to control the presence of hydroxyl radicals.

Halliwell & Cross (1994) continue, explaining that superoxide is also very reactive except in aqueous solutions. Superoxide is actually a product of our immune system. The radical is a product of phagocytic cells, that is, neutrophils, monocytes, macrophages, and eosinophils. Its role with phagocytes is to stop harmful viruses and bacteria. Research supports the presence superoxide in other instances as well. For example, this radical has appears to have a role in which it is produced by lymphocytes and fibroblasts and may be involved in intercellular signaling and growth regulation (Halliwell, 1994).

Nitric oxide is known to be the result of metabolic functions. It acts as a vasodilator agent and may be an important neurotransmitter. Other important actions that nitric oxide performs are regulation of vascular smooth muscle tone helping to control blood pressure.

Hydrogen peroxide is not considered a free radical. The problem is when high levels of hydrogen peroxide are produced the hydrogen peroxide attacks cellular energy-producing systems (Halliwell, 1994). It has the ability to cross biological membranes and form the hydroxyl radical. Hydrogen peroxide creates the hydroxyl radical through interaction with certain metal ions such as iron and copper (Ahsan, Ali, & Ali, 2003).

Our mitochondria are the powerhouses of our cells and their function is an aerobic function. There is a process called the “electron transport chain” within the mitochondria. The electron transport chain is a “series of proteins in the inner mitochondrial membrane that move an electron from a higher to a lower energy level and create a proton gradient (Copstead, & Banasik, 2013, p. 1125).” An effect of the electron transport chain is the production of reactive oxygen species due to leakage of electrons from the mitochondria. This leakage can result in an inflammation of tissue and tissue damage (Ahsan et al, 2003).

In Addabbo, F., Montagnani, M., & Goligorsky, M. S., (2009), they talk extensively about the activities of our mitochondria. Mitochondria are aerobic organisms and their function produces oxidative reactions through a respiratory chain complex (Addabbo et al, 2009). Rahal, et al (2014) explain that up to 1-3% of our pulmonary intake of oxygen are converted to reactive oxygen species; these free radicals provide important physiological functions although, it is the excess production of free radicals which cause damage to our cells. The free radical most frequently produced by the mitochondria is the superoxide radical. Its production reduces the function of the mitochondria.

As our bodies work to keep us healthy, activity within our immune system is linked to the overproduction of free radicals. Ahsan et al, (2003) indicated that when our immune system is compromised our system is thrown into a state of oxidative imbalance. In addition, our neutrophils (the cells that destroy bacteria), while doing their job of killing invading microbes, cause an increase of reactive oxygen species resulting in oxidative damage and inflammation.

There is evidence that these compromises in our immune system are contributing to a variety of autoimmune diseases. Research from Ahsan et al, (2003) state that reactive oxygen species are a center of investigative research as "plausible causative agents in the pathogenesis of several human degenerative diseases (p. 400)." As stated early, the hydroxyl radical is a key component of chronic inflammatory conditions. The supposition is that chronic inflammatory diseases such as Rheumatoid Arthritis and Systemic Lupus Erythematosus "have DNA-anti-DNA antibody complex (es) deposited into tissue, causing inflammation. In response, phagocytes release reactive oxygen species at the site of injury and because of their reactivity may penetrate the cellular membranes thereby reacting with the nuclear DNA (Ahsan et al, 2003, p. 400)."

In our normal metabolic and biologic functions, signals are sent to cells throughout our body to control the proliferation of cells and maintain homeostatic balance. These signals communicate messages to a number of different life processes. Some of the processes send messages to hormones for a variety of functions; there are messages for immune killing, reactive oxygen species, genetic and physical trauma, and oncogene expression (Ahsan et al, 2003). This function is called programmed cell death or apoptosis. During apoptosis, cells shrink, the chromatin condenses, DNA are cleaved and fragmented, and blebs or bulges develop on the exterior of the cell membrane (Ahsan et al, 2003). In some autoimmune diseases there appears to be a breakdown in communication and the cells that are supposed to go through a programmed cell death fail to complete the process leaving cell fragments and electron leakage. Again, the autoimmune diseases are contributing to the production of reactive oxygen species and damaging inflammation (Ahsan et al, 2003).

Rahal et al (2014) point out that our immune system calls upon reactive oxygen species, as well as reactive nitrogen species, to combat pathogens that threaten the health and wellness of the body; however, the reactive oxygen species do not differentiate between good cells and bad cells, often triggering a chain reaction of damage that does not stop until some type of termination product is produced.

Discussion

As organic systems evolved, which include any organism that uses oxygen or has an aerobic function, the organisms developed a defense system to protect against the damage caused by oxygen toxicity (Halliwell, 1994). The defense system is antioxidants produced naturally by the human body and found in various food sources, most notably fruits and vegetables. Antioxidants are referred to as scavengers because they interact with free radicals to provide the stop mechanism to halt chain reactions. The beauty of the human body is that we naturally produce a number of antioxidants in the form of enzymes and these enzymes function regularly to protect our cells from the ravages of oxidative stress. As long as the antioxidants are not overrun by an overproduction of reactive oxygen species our bodies function just fine. It is the over production of reactive oxygen species that put us into harms way.

There has been much research on the benefits of antioxidants. In Halliwell (1994), he writes that the damage caused by the hydroxyl radical affects all organisms and the vast majority of our antioxidant defense system combats exposure to the hydroxyl radical. Halliwell (2012) later writes that our bodies produce many antioxidants in the form of enzymes. The common enzymes are superoxide dismutase, catalases, reduced glutathione, and peroxiredoxins. Other antioxidants, are not synthesized in the human body. These compounds are found as vitamins, most notably vitamin E (alpha-tocopherol) and vitamin C (ascorbic acid).

There are four levels of antioxidant defense. The first line of defense is known as preventive antioxidants. From Lobo et al (2010), we learn that preventive antioxidant suppress the formation of free radicals. The function is not yet completely understood, however, what is known is that hydroperoxides and hydrogen peroxide are reduced to water and alcohols by the following enzymes: glutathione peroxidase, glutathione-s-transferase, phospholipid hydroperoxide glutathione peroxidase (PHGPX), and peroxidase.

In the second line of defense, antioxidants hunt for active radicals in order to suppress the chain initiation and break up any chain propagation reactions (Lobo et al, 2010). Some of these antioxidants tend to bond well with water and some tend to bond well with fats. The following compounds bond well with water: vitamin C, uric acid, bilirubin, albumin, and thiols which contain sulfur; the fat loving compounds are vitamin E, considered to be the most potent scavenger, and ubiquinol (Lobo et al, 2010). Lipid peroxidation causes production of unstable fat molecules and has been linked to chronic illnesses as atherosclerosis, hemolytic anemias, and ischemic reperfusion injuries (Insel et al, 2014). Vitamin E donates an electron to a free radical, stopping the chain reaction formation (Insel et al, 2014).

The third line of defense is found as repair enzymes. According to Lobo et al (2010), proteinases, proteases, and peptidases, enzymes that break up long chain proteins, found in the cytosol and mitochondria, recognize, degrade and remove proteins that were modified by oxidation while preventing the accumulation of oxidized proteins. This is important since DNA is a protein. Other enzymes called glycosylases and nucleases can repair damaged DNA (Lobo et al, 2010).

There are some well-known enzymes that play a vital role in protecting cells from oxidative stress and enzymes are produced in the body. These enzymes are superoxide dismutases, catalase, and glutathione systems.

There are three forms of superoxide dismutase in humans. The role of superoxide dismutase (SOD) is to convert the superoxide radical to oxygen or hydrogen peroxide. The first known form of superoxide dismutase is SOD1, found in the cytoplasm; it needs to have copper and zinc to function. Another form of SOD is SOD2, found in the mitochondria. It needs manganese to function. The third SOD is SOD3, which is extracellular. SOD3 also requires copper and zinc to function (Pizzorno & Murray, 2012). SOD2 is found in acute inflammation while SOD3 is has a role regulating vascular reactive oxygen species in our vessel walls (Lobo et al, 2010). Though humans produce SOD, it can be found in greater abundance in plants, one of the many reasons that at least five servings of fruits and vegetables are recommended daily.

Catalase is an iron-dependent enzyme. Catalase is found in every organ with a very high concentration in the liver. Its role is to acts as a catalyst in order to break down hydrogen peroxide to water and oxygen (Lobo et al, 2010). Studies show that catalase working with SOD may protect the lungs from ischemic injury, protect the intestines from damage by reactive oxygen species, and protect cells from damage brought about by radiation. (Pizzorno & Murray, 2014).

The glutathione systems are made up of the following enzymes: glutathione, glutathione reductase, glutathione peroxidase, and glutathione-S-transferase; they are contain selenium co-factors; the glutathione systems will not function properly without selenium. These enzymes are found in all organic organisms, to include plants, animals, and microorganisms.

The primary role of these systems is to breakdown hydrogen peroxide and lipid hydroperoxides. They are found in the liver and are believed to working in detoxification metabolism (Lobo et al, 2010). Of these enzymes listed, glutathione is one of the most important cellular antioxidants. In our cells it is found as glutathione reductase.

Glutathione is not an enzyme but a protein known as a peptide. Glutathione is synthesized in cells from the constituent amino acids (Lobo et al, 2010). It reduces metabolites and enzyme systems reacting with oxidant, acts as a detoxifying agent, quenches free radicals, and regulates the internal redox environment of cells (Pizzorno & Murray, 2014; Lobo et al, 2010). When glutathione is reduced it reacts directly with singlet oxygen, hydroxyl radicals, and superoxide radicals, forming oxidized glutathione. Unfortunately with aging, glutathione levels decline, which in turn gives rise to a variety of chronic conditions such as diabetes, macular degeneration, gastrointestinal disorders, and neurodegenerative diseases (Pizzorno & Murray, 2014).

There are many non-enzymatic antioxidants that exist in both the intracellular and extracellular environment. Many of these non-enzyme antioxidants are found in the form of micronutrients such as vitamins and minerals as well as a few hormones.

Since we cannot produce all the necessary antioxidants within our bodies, we obtain the majority of antioxidants in the food we eat. One of the most important antioxidants we get from food is ascorbic acid, better known as vitamin C. Vitamin C is a critical antioxidant and is recommended in the control of a number of chronic illnesses.

Vitamin C, a water-soluble vitamin that is able to react with a number of reactive oxygen species; superoxide, singlet oxygen, hypochlorite, and sulfur radicals. Vitamin C breaks the chain reactions found in free radicals, providing protection to lipids and other cellular membranes because it actively scavenges peroxyl and hydroxyl radicals (Pizzorno & Murray, 2014). Chronic illnesses that have experienced positive efficacy of vitamin C are cardiovascular disease, hypertension, cancer, neurodegeneration, diabetes, and cataracts. Vitamin C is found in citrus fruits, various melons, sweet potatoes, green vegetables, chili peppers, and various other fruits and vegetables.

Vitamin E is a fat-soluble vitamin. It is most often found in vegetable oils and wheat germ. Vitamin E is actually two set of four compounds known as tocopherols and tocotrienols. The compound known as alpha tocopherol is the only one that contributes to meeting the needs of humans and is the most common form found in food (Insel et al, 2014). Vitamin E does accumulate in the liver. Rather, adipose tissue contains almost 90% of vitamin with the remainder found in every cell membrane in every tissue (Insel et al, 2014).

As an antioxidant, vitamin E has the vital role of protecting cellular membranes from lipid peroxidation, which are unstable lipid molecules that have excess oxygen (Insel et al, 2014) and can initiate chain reaction of free radical formation. In order to protect the cellular membrane, vitamin E donates an electron to the free radical. Vitamin E is a chain reaction stop mechanism. It should be noted however that vitamin does have some contraindications. For people with hypertension it can aggravate the condition while those who are receiving anticoagulants or vitamin K, it can cause increased bleeding (Pizzorno & Murray, 2014). There is still much research needed to support the positive efficacy of vitamin E in the treatment of a number of chronic illnesses, but it has been shown to improve the immune system especially in health elderly people (Pizzorno & Murray, 2014).

Vitamin E is found is many plant and animal sources such as wheat germ and wheat germ oil, safflower oil, cottonseed oil, and sunflower seed oil. Spinach has one of the highest levels of vitamin E as do sunflower seeds, almonds, canned tomato sauce and mangos.

Carotenoids are naturally occurring and are found in fruits and vegetables with deep yellow and orange color. They are also found in many green vegetables such as spinach. The most common carotenoid beta-carotene, found in cantaloupe, carrots, and squash. Beta-carotene is a potent antioxidant and has been linked to a reduction in aging, cancer, atherosclerosis, cataracts, macular degeneration, bone loss, and diabetes.

There are countless other naturally occurring antioxidants that I have not delved into but are extremely important. Many of these other naturally occurring antioxidants are found as micronutrients, minerals, and non-nutritive antioxidants called polyphenols. Consumption of functional foods provides the avenue for adding these antioxidants to our nutritional health.

Conclusions and Recommendations

As a student of nutrition I have been on a quest to learn how to manage food and nutrition to combat various chronic illnesses as well as weight loss and menopause. This project presented me with an opportunity to delve into an area I knew little about and showed that lack of knowledge can be dangerous. Reactive oxygen species play a vital role in our metabolism yet must be kept in check. Stress affects us in many forms and the damage caused by reactive oxygen species and oxidative stress are what make reactive oxygen species and free radicals deleterious to our health and well-being.

When I began this project I intended to show the damage caused by oxidative stress as a result of the over production of reactive oxygen species but this has been a bumpy road and since the early stages of this literature review, I have come to understand very important things about reactive oxygen species. I was under the misguided impression that reactive oxygen species are a metabolic response causing untold damage to our cells, in effect wreaking havoc and resulting in premature cellular death as well as the destruction of vital aspects of human life including by not limited to DNA; I thought all we needed to was stop our unhealthy behavior and to “right a wrong.”

There is truth to this information. Our overindulgences: smoking, drinking to excess, overeating and not consuming enough fruits, vegetables, and healthy, unrefined grains, not moving or exercising enough, and relying on medications rather than holistic healing choices, are causing an unhealthy overproduction of free radicals such as reactive oxygen species and oxidative stress.

However, oxidative stress is a natural metabolic function that evolved as aerobic beings evolved on planet earth. We experience oxidative stress every day. It is true that oxidative stress is linked to all inflammatory diseases: arthritis, vasculitis, systemic lupus erythematosus, adult respiratory distress syndrome, ischemic diseases, stroke, intestinal ischemia, hemochromatosis, AIDS, emphysema, organ, transplantation, gastric ulcers, hypertension and preeclampsia, neurologic diseases (MS, Alzheimer’s, Parkinson’s, ALS, muscular dystrophy), alcoholism, and smoking related diseases (McCord, 2000). The reason that oxidative stress contributes to this list of chronic diseases is oxidative metabolism is a normal function of a cell's metabolism and if a cell is injured or our mitochondria suffer injury; the production superoxide and the hydroxyl radicals are often a result (McCord, 2000). Research has shown that superoxide has a vital role in the defense against invading microbes and its role is very important. McCord (2000) describes how superoxide is cytotoxic, giving phagocytes the ability to detect and destroy invading microorganisms, acting like an antibiotic. But, in the action of protecting the body, another lethal action takes place. Neutrophils are also produced but they attack not only the invading microbes, but also any cell healthy or not that get in the way. There is no distinction between healthy and damaged cells and so many phagocytes are on the offensive that the result is often an overproduction of reactive oxygen species.

As the research has shown, most every metabolic function in aerobic life results in the production of reactive oxygen species. The human body is an amazing engineering work of art. As aerobic organisms evolved through time, our bodies developed defense mechanisms to combat the damage caused by reactive oxygen species. However we do not have to succumb to the ravages of oxidative stress and the damage caused by reactive oxygen species.

In order to heal the damage caused by oxidative stress and the overproduction of reactive oxygen species, we have to first be willing to modify our behavior. This may mean selecting and working with a health and wellness coach to help reduce the physical stressors in our life from work, family responsibilities, poor nutrition and lack of movement, then learn how to first improve our nutrition in an effort to consume healthy, wholesome food where we can find antioxidants, found in foods such as fruits and vegetables, whole grain cereals, spices, palm and soybean oil, cod liver oil, sprouts, green peppers, honey, and walnuts (Zhang, 2014), or by adding micronutrients to our diet such as vitamin C, vitamin E, B-carotene, urate (uric acid) and coenzyme Q10. Some of the best natural sources of antioxidants are found in berries of all kinds, cherries, citrus fruits, prunes and olives (Lobo et al, 2010). Antioxidants are a way to keep balance between the natural metabolic functions of reactive oxygen species and the overproduction of reactive oxygen species; however, over consuming an antioxidants may be toxic, causing more damage than the reactive oxygen species (Zhang, 2014). As with everything in life, we have to find a healthy balance to heal damage caused by our overindulgences.

As I continued researching the effects of oxidative stress and free radicals I found my research winding me down a different path. There is truth to the overproduction of reactive oxygen species being bad for us, but there will always be a certain unavoidable level of oxidative stress; however, we can make a stand against the damage. As long as we breathe we will produce oxidative stress on our bodies. By becoming willing to take a hard look at how we are living we can minimize the damage to our bodies and in doing this we can even experience an exciting prospect. We can potentially stop living a life of chronic illness and pain. The more we can understand about the effects of reactive oxygen species and how to reduce the oxidative stress brought about by normal metabolic function, we healthier and potentially live longer.

Our bodies do produce a fair number of antioxidants but there are a number of antioxidants that must come from our diet. Halliwell (1994) finished his study with an important discussion regarding the nutritional implication of antioxidants. He discussed plant constituents that have antioxidant activities found as polyphenols. In his follow up article from 2012 he left us with two very important points to think about.

The first point is if you smoke stop. Smoking causes a cascade of free radical chain reaction and severely increases oxidative damage. The second point is to avoid hypercholesterolemia, hyperglycemia, and obesity. These three chronic illnesses are rife with oxidative damage in our cells. Finally, he points our that dietary antioxidants are very important to our overall health. Without the correct balance of antioxidants we will become ill. The goal for each of us should be to eat a variety of foods that are high in fruits and vegetables, sprouted grains, and functional foods, which are foods that provide health benefits beyond basic nutrition (Insel et al, 2014). The key to functional foods is the health protective effects provided by phytochemicals, which are substances found in plants but are not essential to life (Insel et al, 2014).

I wish I had begun this journey sooner. There is so much still to learn about nutrition and the effect food has on our overall health. Rahal et al (2014) points out protection from oxidants has become a focus point in research and understanding the mechanism of action of various antioxidants in herbs as well as fruits and vegetables. Oxygen derived prooxidants and antioxidants have an important role in normal metabolism and several chronic disease states (Rahal et al, 2014).

Finally, what of the therapeutic role of antioxidants? From Pizzorno & Murray (2014), using antioxidant supplements has been linked to both innate and humoral immunity. In addition, the specific goals of antioxidant supplementation are two fold: correct any imbalances in a person's nutritional status; second, support the body's defense systems. Research suggests that multiple, complementary antibiotics are more effective at protecting one's health because antioxidants often work together to overcome free radical damage.

Nutrition is not a one size fits all. With the full spectrum of the human genome now being studied, nutrition research has to branch out. The two current areas of research that can offer so much more information on the efficacy of nutrition, are nutrigenetics and nutrigenomics.

Nutrigenetics studies how we respond physiologically to specific nutrients. It is considered "personalize nutrition." Alternatively, nutrigenomics focuses on specific nutrients and how they effect the genome as a whole (Pizzorno & Murray, 2014). Hopefully these two areas of research will help each of us learn how to optimize our nutritional intake to overcome stress, oxidative stress, chronic disease, and slow down the process of aging.

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Figure 1 General classification of prooxidants, p. 3. Rahal, A., Kumar, A., Singh, V., Yadev, B., Tiwari, R., Chakraborty, S., & Dhama, K. (2014, January). Oxidative Stress, Prooxidants, and Antioxidants: The Interplay. *Biomedical Research International*, *2014, Article ID 761264*.

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Figure 3 Water molecule. Oxygen: Water Molecule. [Art]. In *Britannica Online for Kids*. Retrieved from http://kids.britannica.com/elementary/art-89381

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