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Oxidative and Nitrosative Stresses: Their Role in Health and Disease in Man and Birds

Hillar Klandorf and Knox Van Dyke
*West Virginia University,
USA*

1. Introduction

The concept of oxidative stress (OS) was originally used by Professor Helmut Sies who described it as “an imbalance between oxidants and antioxidants in favor of the oxidants, potentially leading to damage” with the ratio of oxidants to antioxidants as >1 (Sies, 1997). Oxidative/nitrosative stress represents the bodies’ imbalance in the production and the elimination of reactive oxygen and nitrogen species and various reducing or antioxidant chemical systems of the body which destroy reactive intermediates and prevent/or repair the resultant damage. This is a particularly useful concept to establish a common basis for the longevity of a particular species as well as the many different disease states. However, it has also been found to be involved in a variety of other processes including immune protection of the body, gene control, growth as well as cell death. A parallel process is nitrosative stress (NS) which is defined as the ratio of nitrosants to antioxidants as >1 similarly to oxidative stress, but with involvement of reactive nitrogen species. This is a similar process that is involved with a variety of oxygen-nitrogen species causing excessive oxidation and/or nitrosylation compared to antioxidation or reduction. The question thus arises “What endogenous and exogenous strategies are available to cope with the damage associated with chronic oxidative and nitrosative stress?” It is the recombination of short-lived radicals forming new strong oxidants which mainly cause the majority of the driving force for damage in oxidative and nitrosative stresses. Consequences of these particular inflammatory stresses are discussed as are endogenous and exogenous strategies to cope with this burden. Future research in antioxidant/repair therapy will result in the more effective treatment of diseases but it is better used as a preventative strategy. Limitations to the effective management of inflammatory stress are numerous and include the nature of the oxidants generated in association with the form and half-life of the particular antioxidant administered.

2. Localized oxidative and nitrosative stresses

These oxidative and nitrosative stresses (Zorov et al, 2004) could have a more narrowing or selective definition because often these O/N stresses occur locally in a single or selected areas whereas the body as a whole is experiencing control over oxidative and nitrosative stresses and no general damage occurs. So it is easy to conceive of the idea that in a disease state for e.g., damage due to “reactive oxygen” species that cause O/N stresses might occur in a very localized area e.g. a single area of infection.

2.1 What are reactive oxygen and nitrogen species?

This is a term which encompasses molecules composed of oxygen, oxygen and hydrogen as well as oxygen and nitrogen etc. Even oxygen and carbon structures are known to be reactive species and many molecules that are as yet unknown are likely involved as well. Examples of some oxidants should include the following:

Reactive Oxygen Species (Halliwell and Gutteridge, Table 1)

Oxidant	Description
$O_2^{\cdot-}$ (superoxide anion)	Oxygen with an extra electron formed in mitochondrial electron transport with NADPH oxidases and , xanthine oxidase and other reactions. Superoxide forms hydrogen peroxide upon reduction.
H_2O_2 (hydrogen peroxide)	Hydrogen peroxide is formed via dismutation of superoxide (above). Lipid solubility of H_2O_2 aids diffusion across membranes; destroyed by peroxidases.
$\cdot OH$ (hydroxyl radical)	Short lived highly energetic radical formed via Fenton chemistry. It attacks almost all chemicals. It lives and decomposes very quickly essentially where formed.
ROOH (organic hydroperoxide)	Formed by free radical attack on lipids and nucleobases.
RO \cdot (alkoxy) and ROO \cdot (peroxy radicals)	Oxygen centered radicals. Participates in lipid peroxide chain reaction. Production occurs via attack of oxygen radicals on unsaturated lipids.
OCI $^-$ (hypochlorite anion)	Formed from the reaction of hydrogen peroxide and chloride anion with myeloperoxidase. Lipid soluble and highly oxidizing (bleaching effect).
OONO $^-$ peroxy nitrite	Peroxy nitrite formed via the reaction of superoxide anion ($O_2^{\cdot-}$) and nitric oxide (NO^+). Lipid soluble degrades to ($\cdot OH$) and N_2O_2 .
N_2O_3 (dinitrogen trioxide)	Dinitrogen trioxide is formed via the reaction of $\cdot NO$ and NO_2 . N_2O_3 is strongly oxidizing and causes nitrosylation of phenols. It is the anhydride of HNO_2 (nitrous acid).

Table 1. REACTIVE OXYGEN/NITROGEN SPECIES (Causing Oxidative and Nitrosative Stress)

1. superoxide (oxygen with an unpaired electron) $O_2^{\cdot-}$
2. hydrogen peroxide (H_2O_2)
3. hydroxyl radical ($\cdot OH$)
4. organic hydroperoxides (ROOH)
5. alkoxy ($RO\cdot$) and peroxy ($ROO\cdot$) radicals
6. hypochlorite (OCl^-)
7. peroxynitrite ($OONO^-$)

Reactive Nitrogen Species (Droge, 2001)

1. nitric oxide ($\cdot NO$)
2. peroxynitrite ($OONO^-$)
3. nitroperoxycarbonate ($ONOOOCO_2^-$)
4. nitrogen dioxide (NO_2)
5. dinitrogen trioxide (N_2O_3)
6. dinitrogen tetroxide (N_2O_4)

2.2 Antioxidants which oppose ROS and RNS

There are two major types of antioxidants systems which act to control damage caused by reactive oxygen and reactive nitrogen species (Sies, 1997). They are chemicals low molecular mass compounds and enzymes - which produce products that eliminate ROS and RNS. The major antioxidants in the bodies of man and various species of animals are the following:

1. vitamin C (ascorbic acid)
2. tocopherols and tocotrienols (forms - alpha, beta, gamma, and delta of both types)
3. glutathione is a tripeptide (reduced form-glycine-cysteine-glutamic acid)
4. urate - salt forms of uric acid
5. vitamin A
6. various thiols eg., N-acetyl cysteine
7. bilirubin
8. ubiquinol-10 (reduced form of coenzyme Q-10)
9. flavonoids
10. estrogens
11. salicylates (aspirin compounds) or non-steroidal antiinflammatories
12. lazaroids-21, aminosteroids
13. mannitol, dimethyl sulfoxide, dimethyl thiourea, hydroxyl radical scavengers
14. various drugs - captopril, beta blockers, calcium antagonists, amiodarone, carvedilol, epinephrine, norepinephrine, dopamine, etc.
15. allopurinol and oxypurinol - xanthine oxidase inhibitors
16. fish oil with omega 3 fatty acids
17. polyphenols from fruits and vegetables, tea etc.
18. melatonin

Endogenous Enzymes or Proteins

1. superoxide dismutase (converts (dismutates) superoxide into hydrogen peroxide)
2. catalases and other peroxidases (degrades organic peroxides e.g. hydrogen peroxide and other peroxidases into water and oxygen)
3. glutathione peroxidase (uses reduced glutathione and hydrogen peroxide to produce oxidized glutathione and water)
4. peroxiredoxins reacts with inflammatory- cytokine- producing peroxides to produce water
5. sulfiredoxin (reduces sulfinic acid to an antioxidant thiolsulfoxide)
6. transferrin and lactoferrin
7. ceruloplasmin,
8. albumen

2.3 Effects of oxidative and nitrosative stresses

When there is a large increase in oxidants or nitrosating compounds, damage to normal cells and tissues can and does occur when the various antioxidant defense mechanisms become depleted. Extracellularly, it is depletion of urate and ascorbate, - while intracellularly, it is the depletion of the reduced form of glutathione that are the most important water-soluble antioxidants. The extent of the antioxidant depletion is the key factor -; small antioxidant perturbations are readily corrected by the cell; , but a large depletion of antioxidants can cause cell death - either apoptosis or even necrosis in cells and tissues. The latter can cause inflammation - either acute or chronic depending on how long the imbalance continues - in oxidants compared to antioxidants.

The induction of oxidative stress via enhanced generation of reactive oxygen species on a continuous basis generally consists of free radicals and peroxides but lesser reactive species like superoxide can be transformed to more reactive species by the reaction with metal ions or other redox-cycling compounds, which can cause damage to cells or tissues. (Figure 1). DNA is a key target of this damage and this could be either somatic or mitochondrial in origin. In particular, mitochondrial DNA repair is less complete than chromosomal DNA repair. Therefore damage to mitochondrial DNA, which controls sugar carbohydrate and lipid metabolism and is key to producing energy in ATP form, can limit energy production. When ATP is depleted, the cell dies via apoptosis or necrosis.

2.4 Oxidant production or depletion

Normally mitochondrial leakage of electrons from electron transport chain to molecular oxygen forming superoxide (S) is about 1- 2% of the total electron flux produced during oxidative phosphorylation during the at production of ATP (Ames et al, 1993). Flavoproteins may contribute some of the total production of (S). Xanthine oxidase generates superoxide when substrates xanthine and hypoxanthine are oxidized. NADPH oxidases and the different cytochrome P-450s also contribute to total production of superoxide.

A variety of different oxidases produce hydrogen peroxide with both along with superoxide and hydrogen peroxide and other peroxides contributing to the total of reactive oxygen species.

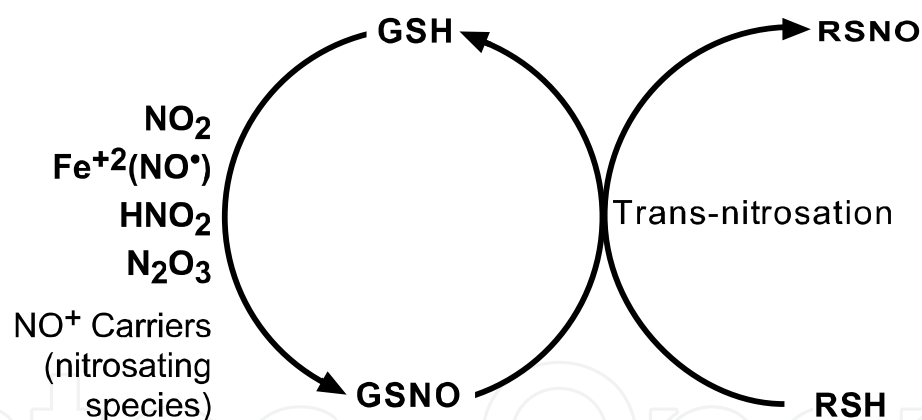
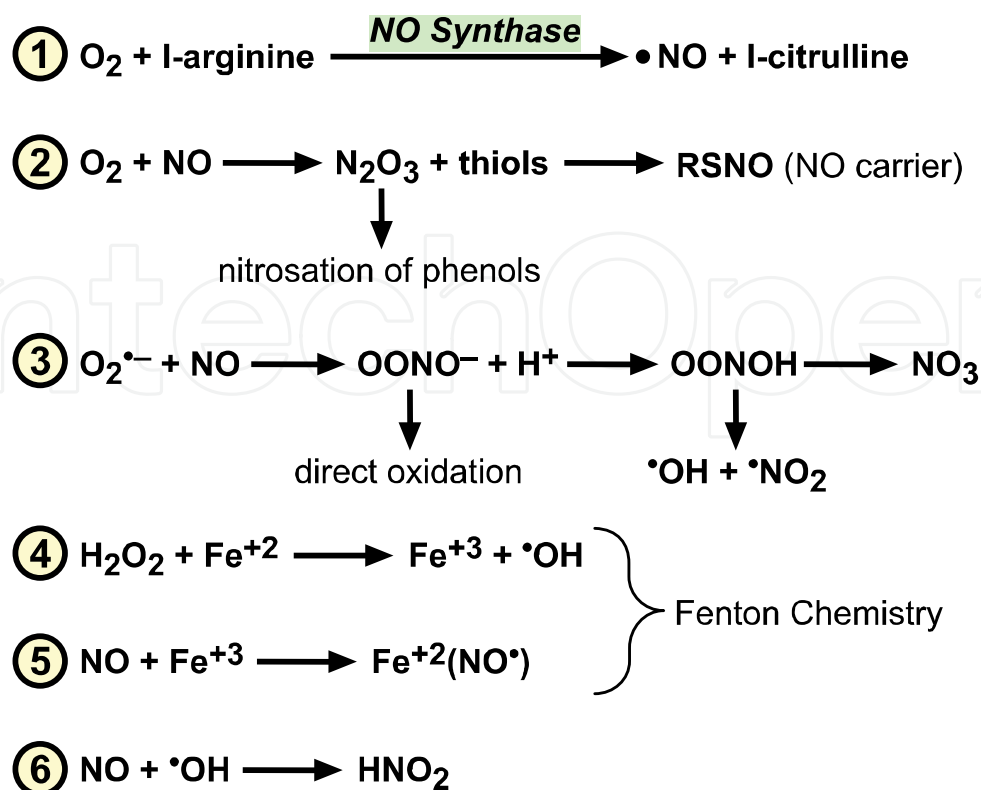


Fig. 1. Reactions leading to the generation of Nitric Oxide and Reactive Nitrogen Species. (Modified from Novo and Parola, 2008)

3. Use of antioxidant supplements to prevent or ameliorate diseases

Many studies have used various antioxidants at a variety of doses producing rather equivocal results. Since oxidative stress is a continuous and ongoing problem simply taking one or more antioxidants at less than optimal doses for a given situation one would not expect such a study to be effective. A scientific approach would be to use optimal doses and in a dosage form that was developed in a sustained-release, continuous -release, or time-release mode. The antioxidants should be continuously released during the disease and would be chosen based on the oxidants causing the disease. Not all oxidants are destroyed by a given antioxidant. The antioxidant potential should be matched with oxidant potential

so that destruction of the oxidant is assured. Another matter of importance is to match the kinetics and half-life of a given antioxidant with the production or kinetics of the oxidant. An example of this is vitamin C - which is a water-soluble antioxidant with a short half life. It is necessary to use it in a sustained-release form and take it orally several times a day at evenly spaced times. This occurs to ensure even coverage against continuously produced oxidants e.g. peroxynitrite (OONO-) or dinitrogen trioxide (N₂O₃).

The basic problem using antioxidants as protection against oxidants is that the body produces a continuous variety of oxidants over time with differing oxidative potential (ability to oxidize). In order to counteract the effects of this multiplicity of oxidants, one would need a multiplicity of antioxidants that were available at the same time as the oxidants and at greater doses in a given area of the body. Further, since the antioxidants would not necessarily distribute evenly throughout the body, if the damage from oxidants occurred in a single location e.g., the major joint in the large toe in gout, if the antioxidants did not penetrate well into the joint where massive inflammation could occur due to uric acid crystals, negation of the inflammation probably would not occur. However by taking multiple high dose antioxidants (in time release or sustained release form except for the fat soluble antioxidants-multiple forms of vitamin E, vitamin A or its precursor beta-carotene), damage in the eye by diabetic retinopathy or macular degeneration could slow or possibly be averted.

3.1 Indications for antioxidant therapy

Some important ideas relevant to commencing antioxidant therapy should be contemplated (Rice-Evans and Diplock, 1993) and include the following:

1. Is oxidative damage associated with the disease pathology?
2. Does oxidative stress cause different diseases?
3. Does oxidative damage occur in most diseases?
4. Can the antioxidant reach the site of disease-damage in sufficient concentration?
5. Will the antioxidant (s) utilized to prevent or stop the oxidative process in vivo?
6. Can the doses of antioxidant utilized be tolerated?
7. If the therapy is chronic, will the antioxidant supplements be safe over this time of therapy?

3.2 Examples of phenolic plant antioxidants acting as oxidant destroyers or targets of oxidation and nitration

Many of the highly colored foodstuffs (particularly vegetables and fruits) contain phenols that are highly polyphenolic in nature (Van Dyke et al., 2000). There are a series of polyphenolic compounds found in white, green and black teas. These are compounds like catechin, epicatechin, gallic acid, epigallocatechin or their esters epicatechin gallate, or epigallocatechin gallate or even catechin gallate. Grapes possess a variety of compounds that are either monophenols or polyphenols. These compounds include phenolic acids, stilbenes, flavanols, dihydroflavanols, anthocyanins, flavanol monomers (proanthocyanidins). Flavonoids from grape skins create part of the color and taste of the wine. The non-flavonoids include the stilbenoids e.g. resveratrol, phenolic acids such as benzoic, caffeic and cinnamic acids. Resveratrol in fairly high doses has been touted as an

efficient antioxidant against diseases even when people eat a diet high in fat and carbohydrate. Many Frenchmen live a long life, which is attributed to drinking red wine containing resveratrol and it is thought that this is responsible for “the French Paradox”.

3.3 Major diseases or indications where antioxidant intervention is warranted

3.3.1 Atherosclerosis

Low density lipoprotein particles can be inhibited by antioxidants e.g., probucol, ascorbic acid, vitamins E, and beta carotenes as well as natural flavanoids alone were demonstrated effective against atherosclerosis which is key to inhibiting ischemic heart disease (IHD) (Ames et al., 1993). Flavanoid-rich diets appear effective as a preventative against IHD. The flavanoids which include anthocyanins and tannins are excellent antioxidants as are the non-flavanoids like resveratrol and phenolic acids e.g. benzoic, caffeic and cinnamic acid.

3.3.2 Neurological diseases

Oxidative stress occurs in the brain because of physical damage, viral, bacterial, fungal or parasitic diseases (Floyd, 1999). Different types of physical or anoxic trauma stimulate generation of oxygen and nitrogen radicals that can recombine and produce powerful oxidants or reaction with metals and create other reactive oxygen and nitrogen species. Nitric oxide and carbon monoxide are both known to create major toxicities to the brain in the various areas of the brain associated with senile dementia and Parkinson’s disease as well as the other problems e.g. amyotrophic lateral sclerosis ALS and Huntington’s disease. A variety of antioxidant drugs e.g. selegiline and riluzole as well as lazaroids, trilazad mesylate and tocopherol have shown promising antioxidant effects against these diseases.

3.3.3 Ischemic reperfusion injury

Reperfusion is the re-establishment of blood flow after stoppage (Dhalla et al, 2000). Once blood flow has been stopped ischemia develops, and restoration promotes production of reactive oxygen and nitrogen species causing toxicity. This phenomenon is particularly important in hypoxic states e.g. in organ transplantation i.e. heart or kidney etc. when the heart is reperfused, post ischemic stunning or contractile dysfunction, reperfusion arrhythmias and damage to the lining of vessels via endothelial injury occurs. Excessive thrombolysis associated with death occurs within 24 hours post transplantation. Antioxidants can inhibit this process associated with vascular disease and their use is mandatory. Of note, reperfusion injury can be prevented by a procedure termed ischemic preconditioning (Marin-Garcia, 2011). The practice is based on the observation that if the blood flow to an organ such as the heart is halted for a period less than five minutes and then restored, the cells downstream gain permanent protection from a second ischemic insult. For this protection to occur three cardioprotective proteins must be induced in response to the oxidative stress. 1. *iNOS*, which increases nitric oxide. NO in turn reacts with the superoxide radicals generated in response to the oxidative stress to generate the harmful nitrogen radical peroxynitrite. NO may also suppress mitochondrial respiration, while also inducing: 2. *HO-1* (heme oxygenase) which produces carbon monoxide (CO). In turn, CO induces: 3. *ecSOD* (extracellular superoxide dismutase) which inactivates the superoxide radical and peroxynitrite as well as inducing more *iNOS*. These types of studies further highlight the importance of endogenous antioxidants in the amelioration of oxidative stress.

3.3.4 Diabetes mellitus

Diabetes is actually caused by excessive production of excessive nitric oxide reactive oxygen and nitrogen species in or close to the pancreatic beta cells (which produce, store and release insulin) (Van Dyke et al., 2010). Once the beta cells die, the body is deficient in insulin. Therefore, insulin must be restored by injection or inhalation. Alpha cells (which produce glucagon) take the place of the beta cells and excessive glucagon causes an increase in blood glucose from sources like glycogen breakdown to exacerbate the problem. Oxidative stress from lack of the control of blood glucose occurs which depletes the antioxidant load. This creates the need for antioxidant supplementation to counteract the oxidant stress. Once the diabetic state is established, there is a deficiency of nitric oxide in the vascular system of diabetics. Since sufficient nitric oxide supply is necessary to maintain proper blood pressure - when the endothelial cells (which line the blood vessels) are damaged they produce insufficient nitric oxide to maintain proper vasodilation. Therefore blood pressure increases and hypertension occurs. Antioxidants like ascorbic acid and the various forms of vitamin E (tocopherols and tocotrienols) inhibit the auto-oxidation of glucose and glycation of blood proteins e.g. Hemoglobin A1C. Therefore antioxidant therapy can ease the toxic state which occurs in diabetes Type I or II.

3.3.5 Inflammatory diseases

Acute or chronic inflammation plays a role in most if not all disease states. This is because it is a response to damage caused by different entities be it infective (bacteria, viruses, fungus or parasites) or non-infectious - e.g., different forms of arthritis (Chade et al., 2004). Since the major inflammatory cells like neutrophils and/or macrophages generate a variety of reactive oxygen and nitrogen species as well as release various proteases tissue damage and destruction occur. Inflamed joints and even tissues e.g. inflammatory bowel diseases occur. These problems also occur in a variety of liver, kidney and pancreatic diseases etc. Preliminary clinical trials using antioxidants appear to be helpful in ameliorating the damage and pain caused by these diseases.

3.3.6 Hypertension

High blood pressure is mainly caused by having excessive vascular constrictors relative to vasodilators (Vasdev et al., 2007). The major vasoconstrictor is known to be a peptide called angiotensin II and the major vasodilator is nitric oxide. The problem is nitric oxide (.NO) has a very short half life of a few seconds or less. Therefore, it must be made produced continuously in the vasculature via endothelial cells lining the blood vessels. The body produces. NO by oxidizing the amino acid L-arginine using oxygen and the enzyme endothelial NO synthase. There must be a continuous supply of sufficient l-arginine and if there are l-arginine-like NO synthase inhibitors in the vasculature e.g., (asymmetric dimethyl arginine) less nitric oxide is made produced creating leading to hypertension (figure 2). If excessive amounts of the constrictors are generated hypertension would also develop. Therefore, long acting l-arginine supplements and angiotensin II production or receptor inhibitors are effective. Calcium channel blockers and beta receptor blocking drugs are antioxidants and have been proven effective in hypertension (Godfraind, 2005, Aruoma et al., 1991).

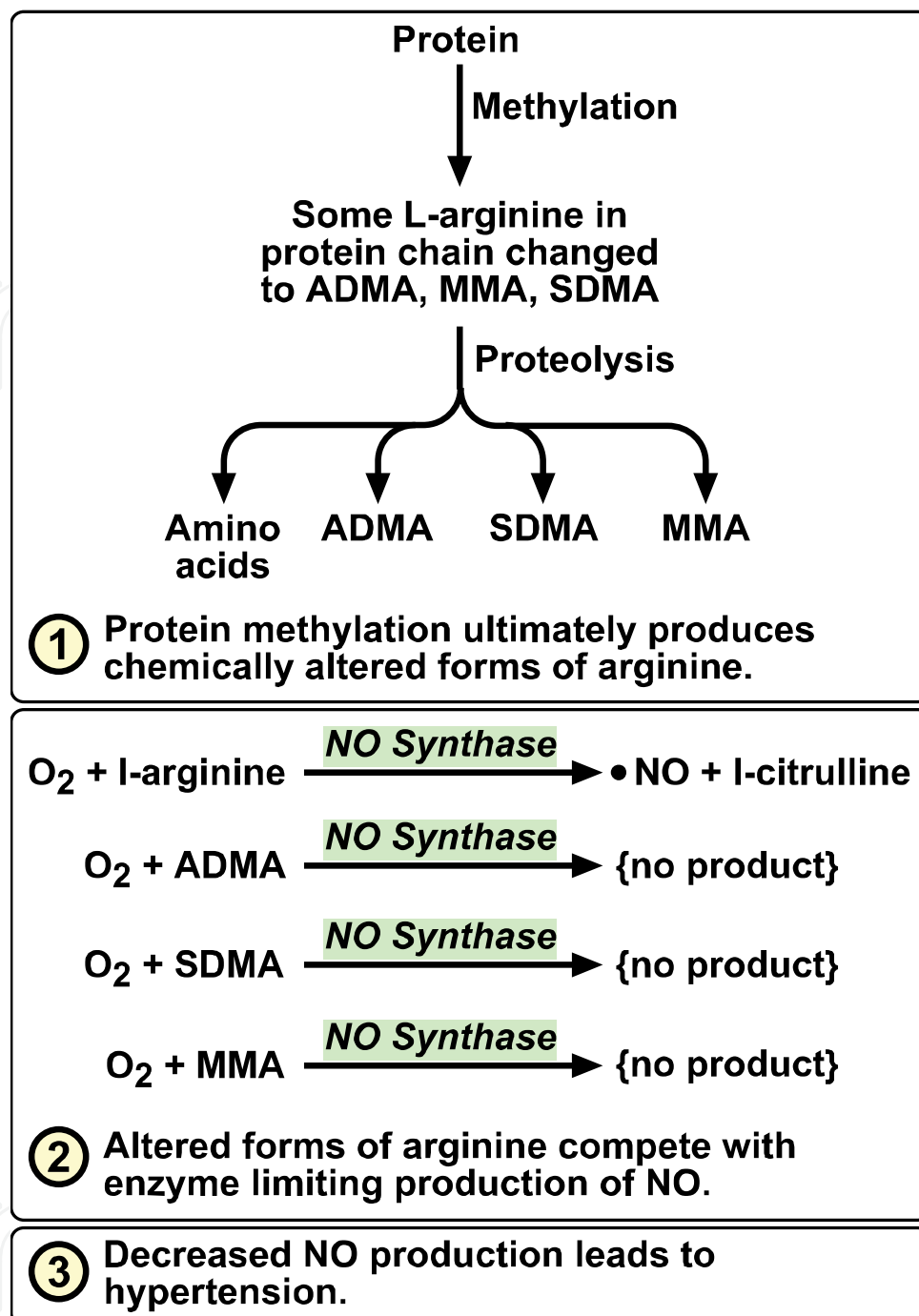


Fig. 2. Reactions leading to reduced NO production

3.3.7 Other pathological problems

Examples include sepsis and shock which cause hypoxia of vital organs, inflammation, and endothelial damage. Even with standard therapy, these patients are likely to develop adult respiratory distress syndrome (ARDS). This problem certainly is associated with activation of neutrophils and macrophages causing oxidative stress via production of oxidants and release of proteases. If these cells could be prevented from entering the areas linked to the disease, it would be effective therapy since which would control the damaging mechanisms.

Antioxidants neutralize the products generated in association with the inflammatory response and help in control the damages.

3.3.8 Cancer

Large scale epidemiological studies have indicated high dietary antioxidant diets are less likely to cause human cancer (Frei, 2004). In particular, lung cancer is an example. Particularly when people smoke, DNA damage occurs, this can often be prevented using antioxidants. However, when beta carotene was used cancer lesions increased. This is not surprising since beta carotene is not a particularly effective antioxidant unless high doses are used and these can create toxicity, even cancer.

3.3.9 HIV – Human immunodeficiency virus infection

Patients with HIV infection displaying AIDS have comprised immune systems (T lymphocyte amounts are greatly reduced) associated with both decreased reduced glutathione levels and enhanced expression of tumor necrosis factor alpha (TNF-alpha) (Fuchs et al, 1991). This stimulates reproduction of HIV while raising the antioxidant level suppresses the production of the virus. Giving a variety of antioxidants e.g. vitamin C, vitamins E, N-acetyl cysteine (reverses the rate limiting step in glutathione biosynthesis) causes a reduction in production of virus. The addition of a strong and lasting Nf-kappa β inhibitor to the mixture of antioxidants can lower the HIV viral level to undetectable. Therefore simple antioxidants can play a large role in viral reproduction. When these viruses are replicating with high efficiency, the protective antioxidant load decreases drastically. This phenomenon occurs with other viruses as well.

3.3.10 Other diseases

Vitamin E (tocopherol) appears to limit the retinopathy of prematurity consequent to the exposure of high levels of oxygen (Robertson, 2010). Reduction in the amount of intraventricular hemorrhage occurs upon treatment with vitamin E. Senile macular degeneration and cataracts may be preventable using antioxidant supplement therapy. Neonatal -distress -syndrome incidence decreases with vitamin E- (tocopherol) supplements.

3.3.11 Aging

Since ultraviolet attack and oxidative stress over time are certainly responsible in premature aging it is not surprising that antioxidants given at the correct doses and in sustained release forms several times per day would effectively slow damage over time (Ames et al., 1993) Tocopherols (vitamins E), aminoguanidine (Iqbal et al.), vitamin C, N-acetyl cysteine NAC and low dose retinoids can be helpful to prevent premature aging of the skin. Recent studies have suggested that administration of probiotics can also ameliorate inflammatory skin diseases (Hacini-Rachinel et al, 2009). Emerging studies suggest that probiotics induce regulatory T cells, which reduce inflammation by suppressing effector T cell function.

3.3.12 Drug toxicity

In cases where the major protective antioxidant glutathione is depleted by overdose of a drug -e.g. acetaminophen (Tylenol), by taking or injecting increased amounts of N-acetyl

cysteine at the correct time serious toxicity to the liver can be avoided (Daly et al., 2008). This occurs because the N-acetyl cysteine (NAC) increases the amount of glutathione available and therefore prevents the toxicity of a toxic metabolite. If a drug depletes glutathione to dangerously low levels, toxicity can be avoided if N-acetyl cysteine NAC is given in the correct amount and quickly enough. Alcohol can decrease antioxidant reserves as well as acetaminophen.

An imbalance of oxidant damage / antioxidant protection has been described in congestive heart failure, and chronic renal failure. Further, eclampsia, chronic peritonitis, respiratory diseases and a variety of hematological disorders are known to involve redox similar imbalances.

4. Damage by oxidants and roles of antioxidants in animals

Animals have similar connections to oxidative stress that happens in man. However, birds have a remarkable longevity for their body size despite an increased body temperature, higher metabolic rate, and increased blood glucose concentrations compared with mammals (Holmes and Austad, 1995). Theoretically, birds should sustain a much higher degree of oxidative damage and processes leading to senescence such as glycoxidation of proteins and nucleic acids (Monnier et al., 1991). For example, a mouse that weighs approximately 20 g is equal in body size to a canary and yet the mouse will live 3 years as with one-twentieth the oxidative burden as opposed to the canary that will live 20 years (Holmes and Austad, 1995). This suggests that birds have developed a mechanism to cope with reactive oxygen species (ROS) assault by either reducing the amount of ROS produced or by a more efficient endogenous antioxidant defense system.

Like other species, birds rely on both exogenous and endogenous antioxidant defense systems. Exogenous antioxidants are obtained primarily from the diet and other environmental factors. For example, in another species, apes eat a diet that is generally high in fruits and vegetables. It has been stated that a chimpanzee eats about 5 grams of vitamin C a day. Generally they are quite healthy which could be attributed in part to a high antioxidant load which protects them against viruses, and other infectious diseases. In birds, endogenous antioxidant enzymes include superoxide dismutase, glutathione peroxidase and the product of the enzyme xanthine oxidase, uric acid. Uric acid is a potent antioxidant and it is arguably, the dominant antioxidant defense mechanism for birds (Seaman et al., 2008, Stinefelt et al., 2005, Machin et al., 2004, Simoyi et al., 2002, Klandorf et al., 2001). Uric acid is the end product of purine degradation. Due to the evolutionary lack of urate oxidase expression, also known as uricase, birds (comparable to reptiles, higher primates, and humans) do not convert uric acid to allantoin. It is the loss of uricase in association with increased uric acid concentrations that can be linked to a prolonged life span.

5. Future directions in antioxidant therapy

The idea that antioxidant therapy is effective against disease because it only inhibits or destroys free radicals is partially defective and incomplete (Firuzi et al., 2011). Free radical oxygen and nitrogen compounds do exist but usually are quite short-lived and are generally quite difficult to detect, especially the high energy radical compounds that cause real damage. The radicals exist for a short time and recombine with other radical compounds

that have free electrons to produce oxidants that can cause major damage. A simple example is the reaction of the nitric oxide radical and oxygen radical superoxide forming peroxy nitrite anion (Fig. 1).

It is the recombination of short-lived radicals- forming new strong oxidants which mainly cause the majority of the driving force for damage in oxidative and nitrosative stresses.

5.1 Limitations using antioxidant/repair therapy to treat diseases

1. It is helpful if one understands what oxidants are being generated in order to select the proper antioxidants. The doses of antioxidants must be in the therapeutic range.
2. A mixture of antioxidants should be chosen at the correct doses to eliminate the toxins formed in the disease.
3. The timing of the antioxidants has to be linked with an understanding of the half-life of each antioxidant.
4. The use of time- release or sustained -release supplements should be used so that their blood level of the different antioxidants remains relatively constant.
5. Have sufficient levels of various antioxidants at the sites of action where oxidative and nitrosative stresses occur.
6. Use increased levels of repair chemicals to prevent permanent damage (particularly for DNA) e.g. nicotinic acid.
7. It is best to use dietary antioxidant supplementation as a preventative and not as a treatment of diseases.

As Benjamin Franklin stated “An ounce of prevention is worth more than a pound of cure”.

6. Conclusion

Oxidative stress represents the bodies' imbalance in the production and the utilization of reactive oxygen and nitrogen species and various reducing or antioxidant chemical systems of the body which destroy reactive intermediates and prevent/or repair the resultant damage. It is the recombination of short-lived radicals forming new strong oxidants which mainly cause the majority of the driving force for damage in oxidative and nitrosative stresses. The ability of an organism to survive these cumulative insults can be linked to both exogenous and endogenous sources of antioxidants, which can be further linked to longevity of species. Future directions in antioxidant/repair therapy will be the more effective treatment of diseases; however they are better used as a preventative strategy. Limitations to the effective management of inflammatory stress are numerous and include the nature of the oxidants generated in association with the form and half-life of the particular antioxidant administered.

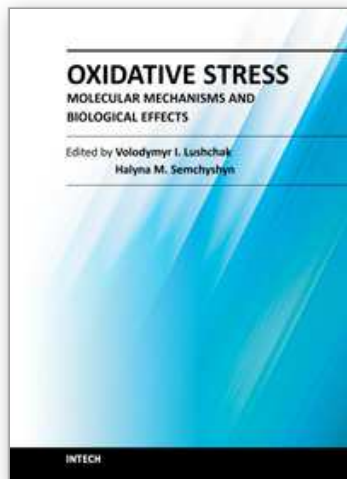
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Since the discovery of free radicals in biological systems researchers have been highly interested in their interaction with biological molecules. Denoted in 1980, and due to fruitful results and ideas, oxidative stress is now appreciated by both basic and applied scientists as an enhanced steady state level of reactive oxygen species with wide range of biological effects. This book covers a wide range of aspects and issues related to the field of oxidative stress. The association between generation and elimination of reactive species and effects of oxidative stress are also addressed, as well as summaries of recent works on the signaling role of reactive species in eukaryotic organisms. The readers will gain an overview of our current understanding of homeostasis of reactive species and cellular processes they are involved in, as well as useful resources for further reading.

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University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
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InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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