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Oxidative Stress And Use Of Antioxidants In Lung Cancer

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Abstract

Numerous diseases, including as atherosclerosis, chronic obstructive pulmonary disease, Alzheimer's disease, and cancer, are made worse by oxidative stress. Preclinical studies have shown that some tiny molecules investigated as antioxidants have therapeutic potential, however clinical trials have yielded disappointing results. A deeper understanding of the mechanisms by which antioxidants function, as well as the locations and times at which they are most effective, may result in a more logical approach to pharmacotherapy. We'll examine the links between illness and oxidative stress, redox signalling, and antioxidant defences, as well as what makes them effective and what can be done to strengthen them, over the following few pages. Additionally, we will discuss some possible pharmacological therapies, physiological signalling, and nutritional components.

Keywords: Oxidative stress, lung cancer, mitochondria, ROS, ageing

Introduction

Oxidative stress has been implicated in the pathogenesis of a variety of diseases, including cancer, age-related degenerative disorders (such as Alzheimer's and Parkinson's), and heart disease. The risk of getting lung cancer rises with the number of cigarettes smoked daily and the number of years smoked, and numerous of the chemicals in cigarette smoke promote oxidative stress by either transferring or producing Reactive Oxygen Species (ROS). The two most common kinds of lung cancer in humans are small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC). Exercise training has been shown to be an effective adjuvant therapy for patients with NSCLC, both before to and after pulmonary resection(1, 2). Numerous variables may influence carcinogenesis, including energy supply, the intensity and frequency of exercise loads, and the degree of exercise-induced oxidative stress.

In Western countries, poor diet is believed to be responsible for 30% of malignancies, making it the second most preventable cause of cancer after smoking. Perioperative complications in individuals with

lung cancer may be anticipated in large part by hunger and fast weight loss. If you're searching for an

antioxidant, micronutrient supplementation seems to have a beneficial impact on lung surgery, even if their role in cancer is still debated. This review will look at lung cancer and oxidative stress, as well as physical activity and diet(3, 4).

What are the roles of reactive oxygen species (ROS) and nitrogen oxides (NO)?

Free radicals are reactive compounds that have unpaired valence electrons in their valence shells. Their life lengths are measured in milliseconds to nanoseconds. Cells may be harmed when a stable molecular electron is extracted to pair with their own electrons, so putting the original molecule into an unstable state. Endogenous antioxidant systems scavenge the minute amounts of free radicals produced under normal physiological conditions. ROS, the most important of which, are radical species formed in biological processes. Apart from being a radical, molecular oxygen (sometimes referred to as dioxygen) has its own unique electrical arrangement. When a single electron is added to dioxygen, the superoxide anion radical (O2•-) is thought to constitute the "primary" ROS. More aggressive "secondary" ROS may be created when chemicals interact directly or through pervasive enzyme- or meta-catalyzed processes(5-7). The concentrations of these compounds in their "steady state" are determined by the interaction of their production and elimination rates by various antioxidants. Previously, it was believed that mitochondria were the primary source of intracellular ROS, but other enzymatic systems, such as Noxs, cytochrome P-450, cyclooxygenase, aldehyde oxidase, dihydroorotate dehydrogenase, tryptophan dioxygenase, nitric oxide synthase, and xanthine oxydase, also play a role. Inflammatory cytokines, growth hormones, environmental contaminants, chemotherapeutics, ultraviolet or ionising radiation, and surgical operations may all result in the generation of reactive oxygen and nitrogen species. It has been shown that cancer is connected to oxidative stress. In cells, both anti- and pro-carcinogenic reactive oxygen species (ROS) may trigger cell cycle arrest, necrosis, and apoptosis, or can inhibit apoptosis and promote angiogenesis and metastasis(8-10). Because NO contains one unpaired electron, it is a highly reactive oxidative biological signalling molecule that is involved in a number of physiological processes, including blood pressure regulation, neurotransmission, and defence mechanisms. NO's half-life in water is rather short (a few seconds). It is synthesised in a range of cell types by nitric oxide synthases (NOS) and is soluble in both aqueous and lipid environments. When the body produces NO, it acts as a critical signalling molecule, affecting a wide variety of cellular activities. In contrast, nitrosative stress, which results from an excess of reactive nitrogen species, is cytotoxic and mutagenic(11-13).

Nitrosylation reactions that may occur as a consequence of nitrosative stress might alter the structure of the protein, hence impairing its normal activity. NO's role in the course of a tumour from start to promotion is unknown. However, excessive NO induces apoptosis in some types of tumour cells, while inadequate NO promotes vascularity and shields cells from death. When nitric oxide combines with superoxide anion to create peroxynitritrite anion, hydroxyl radical or nitrogen dioxide may be formed. In reaction to free radical exposure, organisms have evolved a variety of defensive strategies, including preventative systems, repair processes, physical defence tactics, and antioxidant defence mechanisms(14, 15). Enzyme antioxidant defences include superoxide dismutase (SOD), which contains three isoforms, catalase (CAT), and glutathion peroxidase (GPX) (GPx). These defences may be altered by exercise, training, nutrition, and ageing. Along with FR quenchers such as ascorbic acid, -tocopherol, and carotenoids, flavonoids, glutathione (GSH), ubiquinone Q10, uric acid, bilirubin, and ferritin, as well as

micronutrients that serve as cofactors for enzymes, non-enzymatic antioxidants include a diverse array of antioxidants. The necessary micronutrients include cobalt, copper, chromium, fluorine, iron, iodine, manganese, selenium, and zinc. Due of copper's ability to acquire and lose electrons, it may also act as a free radical. Antioxidant activity and intracellular levels must coexist in order for organisms to live and maintain health under normal conditions. Cells are characterised by an electron concentration (redox state) that is maintained in a large number of cellular components. The redox state and its oscillations dictate how cells function; also, the term "redox state" refers to the redox environment in which cells operate(16-18).

At the molecular level, stress response mechanisms in cells may be classified as insulin/IGF-1 signalling; sirtuins; target of rapamycin; and AMP-activated protein kinase-dependent pathways. All of these pathways have FoxO1 as a molecular target. These universal transcription factors with a Forehead domain, or FoxOs, are critical in protecting cells from oxidative stress. Each FoxO molecule in mammalian cells is expressed by a separate gene, and they all have an influence on cell differentiation, proliferation, and survival. Insulin, growth factors, hormones, cytokines, and oxidative stress all influence FoxO activity by a variety of post-translational changes, including phosphorylation, ubiquitination, and acetylation(19-21). Excessive oxidative stress or oxidative stress-activated mechanisms that interfere with the activity of FoxOs ultimately overwhelm the antioxidant defence provided by FOxOs.

ROS are well-known for their dual properties of being both harmful and helpful, since they may participate in intracellular signalling and regulation as secondary messengers, which may be both deleterious and advantageous to biological systems. It is true that oxidative stress may affect a range of activities through signal pathway modification, including the manufacture of antioxidant enzymes, repairs, inflammation, apoptosis, and cell proliferation, depending on the kind of antioxidants, the strength, and duration of the redox imbalance. The intensity and duration of stress, as well as the cell type involved, are key determinants of which pathways are activated and the particular outcome reflects the balance of these pathways(22, 23). Numerous signal transduction pathways involve oxidation of proteins at cysteine residues by reactive oxygen species (ROS). ROS are signalling molecules that may participate in any step of the signalling cascade. Amino acid oxidation may have an effect on ERKs, jun N-terminal kinases, p38 MAPK, the Wnt/-catenin signalling pathway, and the activity of transcription factors such as nuclear factor B (NF-B), and AP-1, as well as the activity of transcription factors such as nuclear factor B (NF-B), and AP-1 (NF-B). As a consequence, ROS might play a critical physiological role as a second messenger. In contrast, ROS signalling may be harmful because to the toxicity associated with excessive production of reactive signalling molecules. Numerous illnesses, including cancer, have been associated with oxidative stress. The next section examines how reactive oxygen species (ROS) contribute to the development of lung cancer (Figure 1)(24-26).

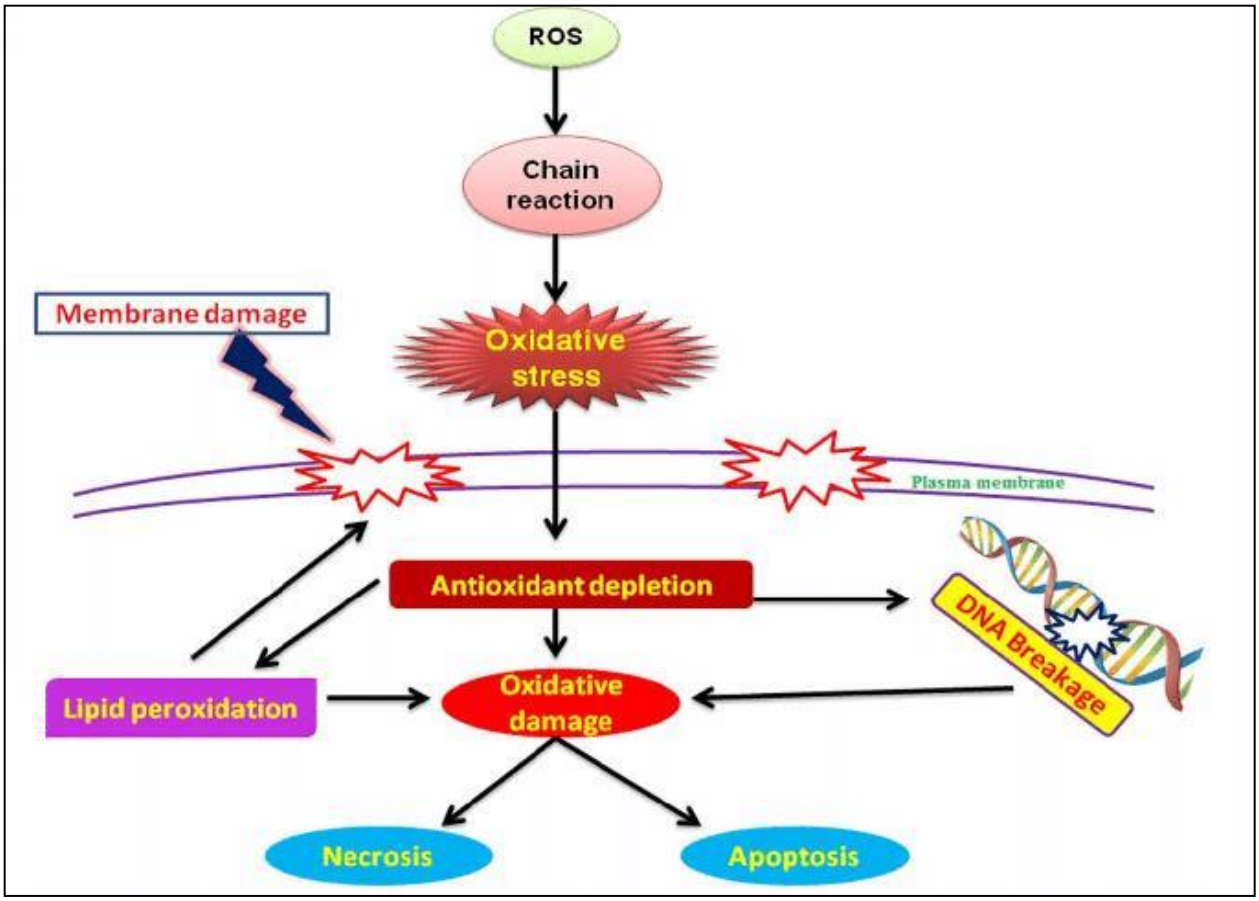

Figure 1: Oxidative stress mechanism

ROS and lung cancer

Lipid peroxidation may have significant consequences, especially for the lung, since the lipoperoxyl radical may reorganise in response to oxidative stress (ROO). By inducing oxidative DNA damage, reactive oxygen species may contribute to the development of cancer. Apart from single or double stranded breaks, purine pyrimidine or deoxyribonucleotide substitutions, and DNA cross-links, ROS-induced DNA damage results in the activation of signal transduction pathways, replication errors, and genomic instability associated with carcigononosis(27-29).

Metals with the ability to bind to critical thiols may potentially change DNA bases, enhance lipid peroxidation, disrupt the calcium-sulphydryl balance, and generate free radicals. DNA damage has been proven to occur when reactive nitrogen species (RNS) such as peroxynitrites and nitro oxides are present. Mitochondrial reactive oxygen species (ROS), mitochondrial gene mutations, and the insertion of mitochondrial genes into nuclear DNA have all been shown to cause oxidative damage and DNA changes in mitochondria. All three of these processes may be referred to as carcinogenesis. Additionally, the normal regulatory systems of the cells may be interrupted, which may result in the development of cancer. High NO levels may promote apoptosis in certain tumour cells, but low NO levels can protect cells against apoptosis, as has been established most clearly in lung cancer. Due of the lung's closeness

to the outside world, both exogenous and endogenous reactive oxygen species (ROS) may be harmful to it(30-32). Even now, the mechanisms by which oxygen radicals cause lung damage are being investigated and debated. Genetic variations in the metabolism of tobacco-derived carcinogens increase an individual's risk of getting lung cancer. Tobacco smoke exposure may induce lung cancer in nonsmokers. As a result of chronic cigarette smoke inhalation, leucocytes and reactive oxygen and nitrogen species have been shown to accumulate in the airways (ROS and NO). DNA may be mutated as a result of NO's interaction with reactive oxygen species (ROS) and protein nitridation (Figure 2)(33-35).

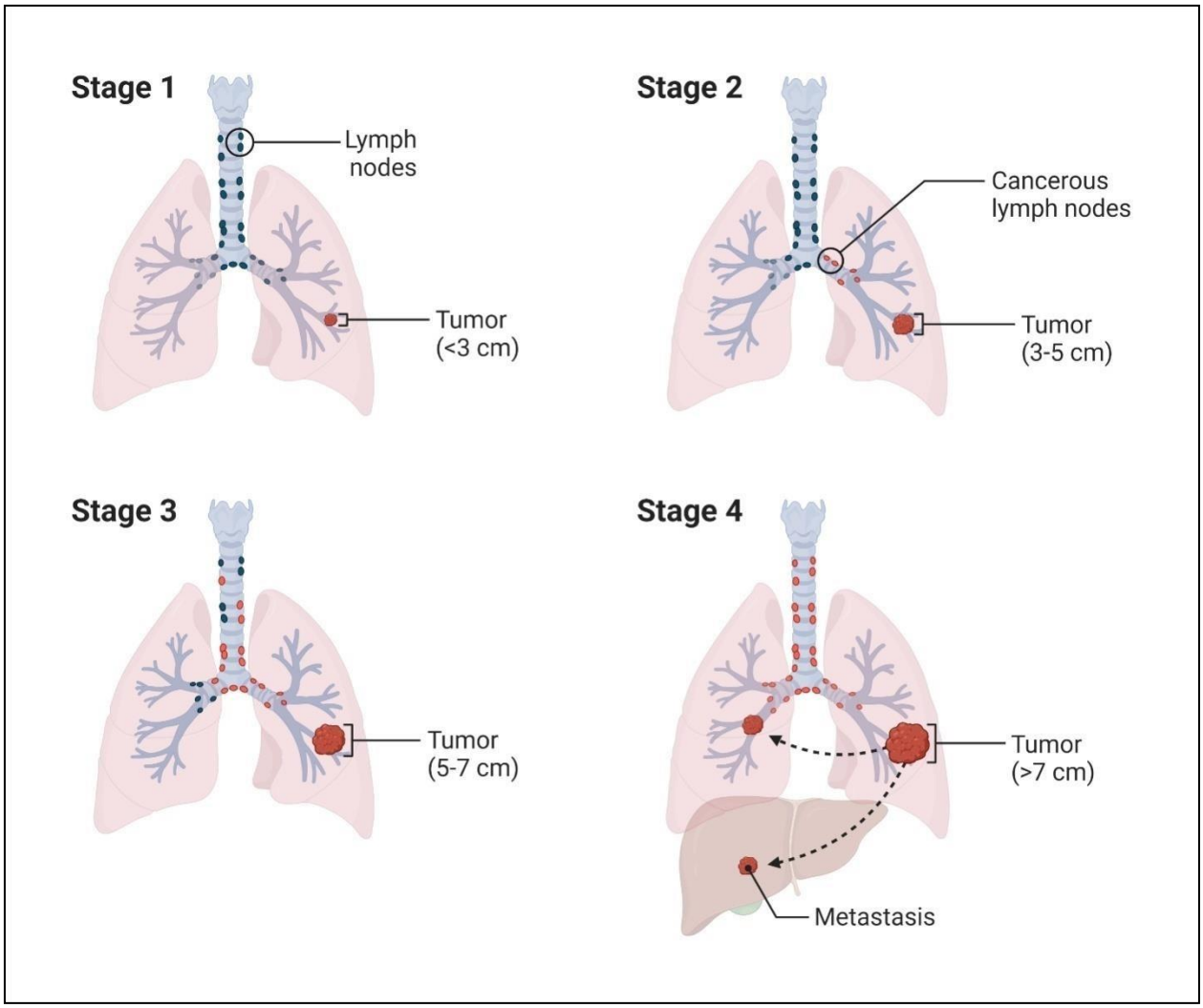

Figure 2: Lung cancer stages

Similarly, smoking depletes the body's supply of antioxidants. Fewer carcinogens have been linked to lung cancer than cigarette smoke, including arsenic, polycyclic aromatic polysaccharides (PAS), and diesel pollution. When breathed, these carcinogens may induce oxidative damage to DNA, which may result in DNA breakage. Oxidant pollution may contribute to lung disease by activating signalling pathways. When paired with contaminants and reactive oxygen species, increased MAPK signalling may result in inflammation in some individuals (ROS). Radon, a naturally occurring air pollutant created by

the radioactive decay of uranium-238 and spread throughout the Earth's crust, has been identified as a lung carcinogen(36-38).

Additionally, changes in the DNA sequence, copy number, and methylation of promoters have been seen in lung cancer studies. Numerous genes, including the EGF receptor (EGFR), Ras, P53, glutathione S-transferase (GSS), histone deacetylases (HDAC), and N-acetyltransferase (NAT), have been associated with an elevated risk of lung cancer in smokers(39-41).

The antioxidant defences' function in health and illness

Antioxidant enzymes, substrates for these enzymes, and damage repair have all evolved in organisms as a first line of defence against oxidative stress. These defences become more effective in the presence of oxidants and other electrophiles, increasing their capacity to detoxify and repair oxidative damage. Antioxidant therapy is based on the administration of medicines that enhance these defences.

The induction of antioxidant enzymes has been studied in terms of regulatory mechanisms, disease effects, and potential therapeutic inducers. These studies were extensive and exhaustive. The induction of antioxidant genes GCLC, GCLM, and SOD1 via activator protein 1 (AP-1), peroxisome proliferator-activated receptor (PPAR-), and nuclear factor-B (NF-B) is the most significant finding in this area, followed by the induction of HO1 via HMOX1 and glutamate–cysteine ligase and SOD1 via NF-B. •OH, ONOO-, and HOX are all reactive oxygen species that immediately endanger the structural and functional integrity of cells. Exogenous small molecules are incapable of removing these oxidants efficiently due to their rapid reaction with membrane lipids, proteins, and nucleic acids(42-44). There has been a great deal of misunderstanding about OH scavengers. Even though oxidative stress results in the creation of •OH, the concept that foreign molecules scavenge these radicals in biological systems is erroneous. ' Diffusion limits are calculated for all organic compounds that react uniformly with •OH. As a consequence, no chemical has a greater capacity for scavenging •OH than the hundreds of molecules found in every biological system. For a medicine to be 50% effective, all of these endogenous components must be present in equal or greater amounts. Preventing the formation of •OH is the only effective method of avoiding damage. Two tactics that may be useful in this endeavour include preventing O2•- generation and removing O2•- and H2O2-. Along with blocking the synthesis of ONOO- and •OH, removing O2•- and H2O2 prevents the formation of HOX(45-48).

SODs and enzymes that detoxify hydrogen peroxide (H2O2) and lipid hydroperoxides serve as the first line of defence against oxidative stress. There are, however, significant discrepancies between extracellular fluids and cells, and these distinctions have therapeutic implications. Extracellular SOD (EC-SOD, SOD3) is often detected at the outer membranes of cells but is not present in all extracellular fluid. Reduced formation of potentially hazardous ONOO- by SOD mimics is effective in extracellular fluids because it conserves •NO, which is required for vasodilation and other key physiological activities(49-51). The additional catalase activity of the majority of SOD mimics also catalyses the removal of H2O2, which EC-SOD cannot accomplish due to the outer surface binding of some cells to EC-SOD. These include cytosolic SOD1 in the cytoplasm, mitochondrial matrix SOD2 in the mitochondria, and catalase in peroxisomes (and cardiac mitochondria). GPXs are capable of reducing lipoperoxides, and two of them

(GPX4 and PRDX6) are also capable of reducing phospholipid hydroperoxides. Endogenous SODs remove O2•- at a rate millions of times quicker than the majority of other O2•- interactions in cells, which explains why scavenging of O2•- by tiny molecules is essentially nonexistent. Certain cells' outer surface binds to EC-SOD, which also outcompetes any prospective O2•- scavenger. SOD mimics, on the other hand, are effective in environments devoid of substantial EC-SOD. When O2•- is eliminated, the more damaging ONOO- is averted, but the medically necessary •NO is preserved. At first look, this may not seem to be a significant increase in antioxidant protection. Combinations of SOD and catalase activity provide an advantage over SOD alone(52-55).

Thyoredoxin (TRX), glutathione (GSH) synthetase, glutathione reductase, and thioredoxin reductase all use NADPH to reduce GSSG, forming the second line of antioxidant defence. Because first- and second-line enzymes govern redox signalling and homeostasis, respectively, removing H2O2 would impair cellular function.

In comparison to small molecules, the 15 enzymes that degrade H(2)O(2) and lipid hydroperoxides, as well as the two enzymes that degrade phospholipid hydroperoxides, remove much less H(2)O(2). While ebselen is a GPX mimic, a number of its rate constants are comparable to those of enzymes(56-59). According to certain research, ebselen may also reduce ONOO-. Oxidative stress, on the other hand, may deplete cells' GSH concentrations, which are generally millimolar. Endogenous GPXs and analogues perform better when supplemented with cysteine or other GSH precursors, since cysteine is a limiting element in the formation of GSH. The therapeutic effect of boosting GSH production may also be realised by stimulating GCL, the enzyme that inhibits GSH synthesis. Scientists have been looking for strategies to activate the NRF2 transcription factor and induce GCL for more than two decades(60-63).

Challenges and limitations in targeting oxidativestress

Several of the antioxidant defences and strategies discussed above provide significant opportunities to prevent or mitigate disease associated with oxidative stress. However, there are a number of factors that limit our ability to employ antioxidants therapeutically(64, 65).

Oxidative stress has a detrimental effect on the body

The capacity of a person to profit from antioxidant defences is dependent on the amount of oxidative stress present. While oxidative stress is often cited as a cause in the development of disease, decreasing it may have minimal impact. While antioxidants increase antioxidant defences and decrease markers of oxidative stress, they have little to no effect on pathology as a result. This limitation is critical for measuring antioxidant defences in clinical trials. The purpose of this study is to see if antioxidant strategies can be developed to assist relieve some of the symptoms of the condition, but not its core cause. Product development based on small molecules that are chemical antioxidants but do not function as such in vivo will ultimately fail to exhibit substantial advantages beyond what an adequate diet of antioxidant enzyme-inducing small molecules can achieve. This disappointment will impede the development and dissemination of really effective medicines(66-70).

Scavenging using micromolecules

Due to the incapacity of small molecules to scavenge free radicals, antioxidant defence is severely limited. Antioxidants' claims of being able to eliminate hydroxyl radicals from the body are meaningless, since almost all chemicals react with hydroxyl radicals in the same way. To reduce the formation of •OH, one of the most effective methods is to eliminate H2O2. Due to the high rate constant of reaction 3 (2O2•- + 2H+ H2O2 + O2) (which is at least 105 times that of the majority of O2•- reactions save those involving •NO237), scavenging O2•- in cells is difficult. To put it another way, the majority of intracellular agents would be unable to compete with the 15 enzymes involved in reactions 4–6 (2H2O22H2O + O2, H2O+2Trx(SH)2TrxS2, and H2O+ 2GSHGSSG + 2H2O). Scavenging as an effective antioxidant defence mechanism in cells is effectively ruled out kinetically(71, 72). If oxidative stress occurs outside the body, SOD and catalase-like mimics with a relatively high kinetic rate constant may be beneficial. The rate constants of the SOD and catalase mimics, on the other hand, are around 105 times that of conventional cysteine-rich proteins. The addition of a lipophilic cationic group to SOD mimics enables them to accumulate in high concentrations in the mitochondrial matrix, where overexpression of natural SOD2 has been demonstrated to enhance H2O2 production. Additionally, the long-term consequences of increased mitochondrial SOD activity are unknown.

Vitamin E is the only dietary antioxidant capable of scavenging small molecules from lipid hydroperoxyl radicals due to the high concentration of vitamin E in membranes. There has been little success with antioxidant therapies that have been shown to work in non-human animal models or cell culture. The quantity of exogenous substances present in vitro and in vivo is considerably different. Laboratory animals are given modest doses of vitamin E and selenium, which produces a setting in which antioxidants function more as vitamins that prevent deficiency than as medications that cure deficiency(73-76).

Mito-Q, which is synthesised by conjugating ubiquinone with a lipophilic cationic group, may accumulate in mitochondria and function similarly to vitamin E there. Ubiquinone's non-physiological ascension has immediate ramifications, but the long-term effects are unclear(77-79).

Conclusion

Numerous diseases are linked to oxidative stress, necessitating the development of effective antioxidant treatment. While the employment of tiny molecules has been mostly ineffective, the discovery that the rationale behind their use is based on errors that may be overcome gives reason for hope. Improved techniques of antioxidant defence will arise from a greater knowledge of the function of H2O2 in physiological signalling, as well as from a reduction in the synthesis of •OH and ONOO- by reducing their precursors H2O2 and O2•-. Additional consideration should be given to the limitations identified in this review, including the debate over whether oxidative stress is the primary or secondary cause of pathology, the negligible effect of nearly all small molecules as scavengers, the difficulty of achieving effective in vivo concentrations, and the aging-related decline in the ability to increase NRF2 activation. Scavengers of O2•- and H2O2 at the intracellular and mitochondrial levels are potential agents. SOD, as well as SOD-catalase and GPX analogues, seem to be beneficial, and various medications are now undergoing clinical trials. SOD functions as an antioxidant. To maintain GSH, the substrate for GPXs, precursors such as NAC and GSH esters may be employed. Indeed, NAC is already being used in people

to treat a range of disorders and toxicities, but there are currently no clinical trials with GSH esters. Along with antioxidant enzyme mimics and GSH, NRF2 signalling in cells promotes the generation of endogenous antioxidant enzymes and de novo GSH synthesis. Our hope is that this examination of antioxidant treatment may act as a spark for a more rational approach to this worthwhile endeavour.

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