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Forum Review

Oxygen, the Lead Actor in the Pathophysiologic Drama: Enactment of the Trinity of Normoxia, Hypoxia, and Hyperoxia in Disease and Therapy

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ABSTRACT

Aerobic life has evolved a dependence on molecular oxygen for its mere survival. Mitochondrial oxidative phosphorylation absolutely requires oxygen to generate the currency of energy in aerobes. The physiologic homeostasis of these organisms is strictly maintained by optimal cellular and tissue-oxygenation status through complex oxygen-sensing mechanisms, signaling cascades, and transport processes. In the event of fluctuating oxygen levels leading to either an increase (hyperoxia) or decrease (hypoxia) in cellular oxygen, the organism faces a crisis involving depletion of energy reserves, altered cell-signaling cascades, oxidative reactions/events, and cell death or tissue damage. Molecular oxygen is activated by both nonenzymatic and enzymatic mechanisms into highly reactive oxygen species (ROS). Aerobes have evolved effective antioxidant defenses to counteract the reactivity of ROS. Although the ROS are also required for many normal physiologic functions of the aerobes, overwhelming production of ROS coupled with their insufficient scavenging by endogenous antioxidants will lead to detrimental oxidative stress. Needless to say, molecular oxygen is at the center of oxygenation, oxidative phosphorylation, and oxidative stress. This review focuses on the biology and pathophysiology of oxygen, with an emphasis on transport, sensing, and activation of oxygen, oxidative phosphorylation, oxygenation, oxidative stress, and oxygen therapy. *Antioxid. Redox Signal.* 9, 1717–1730.

INTRODUCTION

Oxygen is the second most abundant element of Earth's atmosphere. Although indispensable for the aerobic life forms, it also poses a grave danger to life (36, 56). Oxygen, although strongly paramagnetic, at standard temperature and pressure, is a diatomic molecule. The most stable form of the element is the triplet state, whereas the excited one is the singlet state. The allotrope of oxygen, ozone (O_3), is found in the upper layers of the atmosphere where it is produced during electrical discharges or by the solar UV irradiation. Oxygen constitutes almost 21% of the earth's atmosphere. Although the current aerobic life forms absolutely require oxygen for their survival, it has been suggested that life itself shaped the atmosphere, and thereby its oxygen level, as we have it today. The early earth's atmosphere consisted of CO_2, N_2, and H_2O, with traces of H_2. In the prebiotic environment, oxygen supposedly did not exist in the free form (35). During the time of the origin of life, the early photosynthetic organisms released oxygen into the atmosphere and facilitated the evolution of aerobic life forms (36). After many changes, the atmosphere has reached its present gaseous composition, comprising exactly optimal levels of oxygen for sustenance and propagation of life. Although atmospheric oxygen is essential for aerobic life, a few of its derivatives pose a danger to it. Most prominent of them are the free radicals, reactive oxygen species (ROS), and singlet oxygen.

The current review focuses on the role of molecular oxygen

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and its derivatives in pathophysiology. The first section discusses the interdependence of oxygen transport, respiration, and the process of energy generation by using oxygen. It is followed by a brief discussion on oxygen sensing and the oxygenation levels in the body. With an emphasis on ROS and antioxidants, the not-so-noble side of oxygen is visited in light of the environmental toxicity and pathologic disorders. The last section focuses on the therapeutic applications of oxygen.

OXYGEN TRANSPORT, RESPIRATION, AND BIOENERGETICS

Living organisms derive their energy solely from fuel/food substrates, through either anaerobic or aerobic respiration. Anaerobic respiration does not involve the utilization of oxygen; however, it is an inefficient process of energy generation in the form of adenosine-5'-triphosphate (ATP). Conversely, in aerobic organisms, cellular respiration involves enzyme-catalyzed oxidation of fuel substrates, primarily by oxygen, to yield the energy required for biologic processes. Aerobic respiration takes place in two regions of the cell, glycolysis occurring in the cytoplasm, and Krebs' cycle and electron-transport chain (ETS) in the mitochondria (Fig. 1). Glucose, the primary substrate for cellular aerobic respiration, is converted into pyruvate in the glycolytic phase, which is shunted into the Krebs's cycle for oxidative phosphorylation that is undertaken by the ETS in the mitochondrial inner membrane. Oxygen undergoes a four-electron reduction in the ETS, thus generating ATP, the ultimate biologic currency of energy (Fig. 2). The whole process of cellular aerobic respiration yields 28 ATP molecules as opposed to two ATP molecules that are generated during anaerobic respiration. Thus, it is evident that the efficiency of the respiratory substrate (*e.g.*, glucose) utilization to generate the maximal number of ATP molecules is best in the cells during aerobic respiration, in which the involvement of oxygen is essential.

In complex organisms, the delivery of oxygen to the cells in the tissues is controlled by a central processing unit such as the brain. A part of the central nervous system, the medulla oblongata, controls the process of respiration and thereby the delivery of oxygen to the cells. It can alter the process of respiration based on neurosensory feedback. The blood concentration of oxygen, carbon dioxide, and the pH (acid–base equilibrium) also are important in the regulation of respiration.

Overall, the essential basis for respiration at the cellular level is the availability of oxygen. In mammals, including humans, oxygen from the lungs after breathing is carried to the target tissue by the oxygen-carrying protein, hemoglobin. At the target tissue, where the cells actively engage themselves in respiration (oxidative phosphorylation), oxygen is released from the oxygen-bound hemoglobin (oxyhemoglobin) across concentration gradients, and the released oxygen is available to the metabolically active tissues. Thus, the actively respiring cells of the tissue set a concentration gradient of molecular oxygen across several interfaces: between the plasma membrane and exterior, cytoplasm and plasma membrane, and mitochondria and cytosol. Thus, the active cellular mitochondrial respiration creates several stepwise partial pressure gradients (pO_2) of oxygen that drive the influx of oxygen into the cell for metabolic utilization. Therefore, it can be unequivocally concluded that the molecular entry of oxygen into an actively respiring cell is metabolically driven. In other words, if cellular respiration is slowed or arrested, the oxygen gradient created by the cellular respiration ceases, and so does the entry of oxygen into the cell by diffusion. Conversely, the supply of oxygen to the actively respiring cell can be interrupted by blockade of the blood supply such as ischemia. Ischemia causes insufficient or no delivery of oxygen to the target tissues (cell), thus leading to hypoxia or anoxia. In this case, even though pO_2 gradients exist at several strata within the extracellular and intracellular interfaces, because of the lack of blood supply and hence oxygen supply, the cellular respiration is drastically slowed or arrested or both.

Lipids of the cell membranes, including those of the plasma membrane, play a critical role in oxygen entry into the cells. Cholesterol, the nonpolar hydrophobic lipid of the plasma membrane, has been shown to influence the release, transport, and availability of oxygen in red blood cells (RBCs) (17). An increase in the cholesterol concentration of the RBCs has been shown to decrease oxygen transport across the cells, presumably because of a decrease in the membrane fluidity and stiffening of the lipid bilayer (18). An increase in the cholesterol

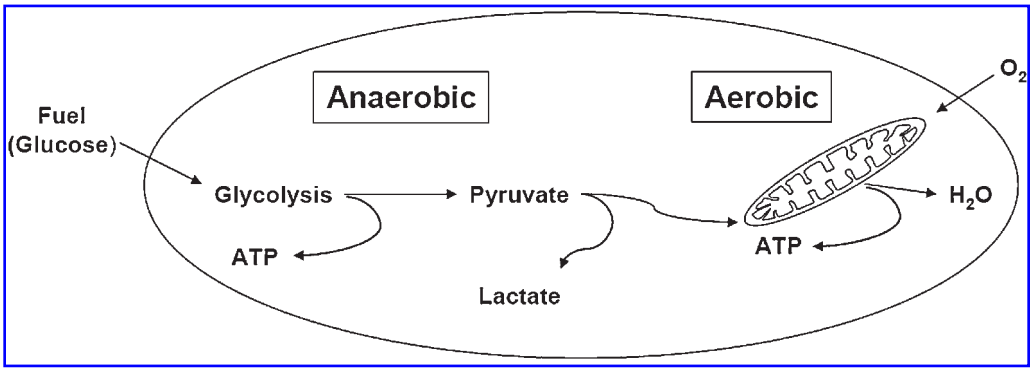

FIG. 1. Cellular respiration showing anaerobic and aerobic pathways of energy generation.

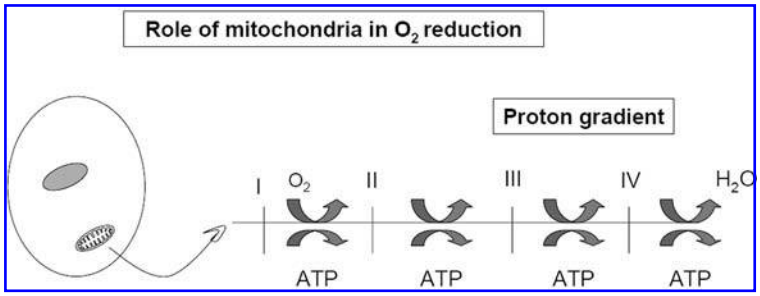

FIG. 2. Sequence of mitochondrial oxygen reduction.

content of the plasma membrane of the Chinese hamster ovary cells has been shown to result in a larger oxygen gradient, further indicating that the cholesterol content of the plasma membrane is crucial in determining the extent of the oxygen gradient across the cellular membrane (48).

NONRESPIRATORY CONSUMPTION OF OXYGEN

Most of the oxygen entering the living cell of an aerobe is expended in oxidative phosphorylation carried out by the mitochondria to generate the currency of energy, ATP. Nonetheless, some of the cellular oxygen acts as an important substrate for several oxygenation reactions catalyzed by oxygenases (monooxygenases and dioxygenases) of nonmitochondrial sources (39). In the majority of these enzymes, iron (Fe) plays a pivotal role in the catalysis of oxygenation. Oxygen activation mediated by heme and nonheme proteins (enzymes) is dependent on the uptake of iron by the cell, iron storage and mobilization, complexation of iron, redox status, and other intricate biotransformation reactions in which the valence of iron dictates the metabolism of molecular oxygen, oxygen activation, and nonmitochondrial oxygenation (39). Oxidation of catechol to *cis*-muconate, biosynthesis of sterols (lanosterol and cholesterol), prostaglandin formation by cyclooxygenase action, lipoxygenase action in the generation of arachidonate metabolites, cytochrome P450–mediated biotransformations, nitric oxide synthase–mediated formation of NO, and metalloporphyrin catalysis are some important examples of nonrespiratory and nonmitochondrial oxygen consumption and utilization by the aerobic (mammalian) cell. A metal-rich cellular environment (containing iron or copper or both) is also known to cause nonenzymatic oxidation of biomolecules including catecholamines, lipids, proteins, and DNA in oxygenated compartments involving the formation of ROS through Fenton-type reactions. These metal-catalyzed oxidative reactions in the cells also contribute to nonrespiratory utilization of cellular oxygen. It should be emphasized here that these pathways involving nonrespiratory and nonmitochondrial utilization of cellular molecular oxygen are extremely crucial for cellular physiologic homeostasis and are also important in pharmacologic, toxicologic, and pathophysiologic settings.

OXYGEN SENSING

Oxygen sensing is an intrinsic phenomenon to maintain oxygen homeostasis in the body. Organisms constantly sense the change in body-oxygen concentration and respond correspondingly: the perception of hypoxia, resulting in increased ventilation through increased breathing rate. Oxygen sensing occurs at two levels: (a) global (organ and organism), and (b) local (cellular and tissue) levels. A few models are proposed to explain the mechanism of sensing and to identify the sensor.

The carotid body model explains the global oxygen-sensing mechanism at the global/ organism level. The carotid body, situated in the carotid artery, is the primary sensor of oxygen concentration in the mammals (80). Glomus cells of the carotid body are depolarized in response to hypoxia and initiate a sequence of events. However, several local oxygen-sensing mechanisms at the local (tissue, cellular, organelle, and molecular) level have been proposed; these include the cellular oxygen-sensing units (mitochondria), membranes (chelation of iron and potassium channel inhibition), efflux of ATP at the afferent nerves, reactive oxygen intermediates, nitric oxide, carbon monoxide, and neurotransmitters (54). Different mechanisms have been proposed, suggesting the operation of these events. One of the mechanisms indicates the involvement of high-conductance calcium and voltage-gated potassium channels (47). Recent evidence points to the existence of a sensor molecule that is located in the vicinity of these channels (47). Another controversial hypothesis proposes that the mitochondrion is the organelle of oxygen sensing (7, 54, 90). Nitric oxide is also believed to act as a sensor molecule that interacts with mitochondrial complexes (54). A connection between involvement of CO_2 (23, 54) and CO (47) in oxygen sensing has also been shown. NAD(P)H oxidase has also been suggested as a possible oxygen sensor (90). All these studies acknowledge that ROS are involved in the oxygen-sensing process, but the exact role of ROS in oxygen sensing is yet to be addressed, especially in hypoxia (90). Although most of the investigations conducted in this area are directed toward hypoxia sensors, a few studies have also focused on understanding the nature of hyperoxia sensors. These studies have revealed p38MAPK as the upstream regulatory switch of hyperoxic ROS generation and effector (78, 92). Although p38MAPK and Src kinase have been shown to regulate the upstream activation of NAD(P)H oxidase in endothelial cells exposed to hyperoxia, the exact reasons that mo-

lecular oxygen is activated to ROS during hyperoxic exposure must be established (25, 78).

A fascinating novel mechanism of adjusting to the fluctuating pO_2 at the cellular and tissue levels has been put forth (50, 84, 85, 92). In mammalian organs, the pO_2 has a broad range (between 90 and <3 torr) under normoxic states (85) and thereby allows normoxia to become an adjustable variable. Cells, in response to the chronic moderate hypoxia, are able to tune themselves to the lowered pO_2 by adjusting their normoxia set point, resulting in a state called "perceived hyperoxia" (relative elevation of pO_2) on reoxygenation (85). This mechanism of adjusting to marginal relative increase in pO_2 through perceived hyperoxia by cells has been shown to induce the differentiation of cardiac fibroblasts to myofibroblasts through the p21-mediated signaling (84). In a survival model of rat heart focal ischemia–reperfusion (I-R), the activation of perceived hyperoxia-sensitive genes has been revealed in the I-R region of the heart tissue (85). By using the laser microdissection pressure catapulting technique coupled with the real-time PCR analysis, the induction of p21 gene by perceived hyperoxia has been shown in both fibroblasts and cardiomyoctes of the heart subjected to *in vivo* I-R (50). Hence, perceived hyperoxia plays a crucial role in myocardial remodeling and healing (92).

Fluctuating changes in the local oxygen concentration (pO_2) include adaptive strategies in the system (cell/organ) toward protection from or lessening of the damage. Hypoxia-inducible factors (HIFs), transcription factors, and important regulators of hypoxia-induced gene expression have been thoroughly studied as the key elements in setting the adaptive mechanisms in systems facing hypoxic insult (2). The adaptive responses to hypoxic stimulus have been identified to be mediated by a wide spectrum of oxygen-sensing signaling cascades involving the phagocytic NADPH oxidase, mitochondrial ETS, cytochrome *c* oxidase, HIF prolyl hydroxylase, and HIF asparaginyl hydroxylase (2). These oxygen-sensing elements have different degrees of oxygen-sensing abilities and, depending on the type of the cell, they are compartmentalized in the cell to exert adaptation to variations in the tissue pO_2 through complex cell-signaling cascades. Oxygen sensing is an important process that is required for normal functioning of the body, fetal development, adaptation to abnormal oxygen levels in the body as a response to the ambient oxygen levels, and pathologic conditions. Impaired oxygen sensing in humans has been shown to be associated with a growing number of pathologic states including cancer, hypertension, sleep apnea, heart failure, stroke, and sudden infant death syndrome (94). Overall, it should be emphasized that the oxygen-sensing mechanisms at both the global and local levels are interdependent.

OXYGENATION LEVELS IN THE BODY

Aerobic organisms cannot survive without oxygen. If the oxygen concentration in the body decreases below a certain critical level or if it supersedes a threshold, the normal physiologic processes are disrupted. Thus, it is clear that the normal physiologic functions of the body operate under a tight regulation of oxygen concentration, and any imbalance therein leads to abnormal organism physiologic functions. Adaptation of a cell or an organism in response to changing ambient concentrations of oxygen is regulated by complex networks of signaling pathways and gene expressions (94).

Normoxia, the level of oxygen (pO_2) required for normal physiologic processes to occur, is the optimal level for oxygen in the body. Hypoxia is defined as oxygen deficiency in the body that results because of the difference between oxygen supply and oxygen consumption. Several types of hypoxia are classified according to the condition that causes the particular hypoxic state (46). Hypoxia triggers a cascade of cellular responses, including the production of transcription factors. In a majority of the circumstances, hypoxia leads to complete starvation of the cells and consequently to cell death. Hypoxic condition, when treated at the right time, can lead to the rescue or recovery of certain regions of the tissue. Hypoxia can lead to serious disorders such as stroke or myocardial infarction, and if left untreated, develops into anoxia, which is defined as the complete lack of oxygen. Hyperoxia arises when the oxygen level is higher than the normoxic level. Hyperoxic levels of oxygen in the body can be detrimental to the tissues. Notable adverse effects of hyperoxia are injury to the lungs and vital organs and CNS damage. Prolonged hyperoxia leads to death, presumably because of ROS and oxidative damage. Both hypoxia and hyperoxia are shown to be associated with the production of ROS in the cells.

Here, it is important to note that although a few guidelines are accepted, no absolute values of oxygen levels (pO_2) define hypoxia or hyperoxia (46). The oxygen requirement of an organ, a tissue, or a cell depends on its physiology and function. Therefore, the levels of oxygen dictating hypoxia/hyperoxia change according to the system (cell/tissue/organ) being studied. For example, brain and muscles require different levels of oxygen to exhibit normoxic and hypoxic states. These specific oxygen levels, under clinical settings, can also be influenced by the health of the individual. It is evident that the control of cellular and tissue oxygenation levels also depends on the regulation of oxygen-sensing mechanisms at the global and local levels. Extensive work is warranted to define the tissue-specific levels of oxygen and associated normoxic, hypoxic, and hyperoxic conditions for different organs and tissues.

REACTIVE OXYGEN SPECIES

Atmospheric molecular oxygen, a free radical itself, is relatively nonreactive because of spin restrictions. This property prevents materials from undergoing spontaneous combustion in an ambient oxygen-rich atmosphere. Molecular oxygen undergoes four-electron reduction to water. This four-step reduction generates intermediates that are commonly and collectively called ROS. ROS include radical as well as nonradical chemical species. By definition, any chemical species (atom or molecule) with an unpaired electron is described as a free radical (56). Typical oxygen free radicals are superoxide ($O_2^{-\cdot}$), hydroxyl radical ($^{\cdot}OH$), peroxyl radical ($RO_2^{\cdot}$), and hydroperoxyl radical ($HO_2^{\cdot}$) (Table 1). The nonradical ROS are hydrogen peroxide (H_2O_2), hypochlorous acid, singlet oxygen, and ozone. Reactive nitrogen species (RNS) such as peroxynitrite ($ONOO^-$) and nitric oxide (NO) are also included at times

TABLE 1. CHARACTERISTICS AND SOURCES OF REACTIVE OXYGEN SPECIES

ROS	*Symbol*	*Free radical*	*Lifetime*	*Source*
Superoxide	$O_2^{-\cdot}$	Y	10^{-6} sec	Mitochondria, cardiovascular system
Hydrogen peroxide	H_2O_2	N	Stable	Cellular reactions
Hydroxyl	$^{\cdot}OH$	Y	10^{-9} sec	Fenton reaction
Peroxyl	$ROO^{\cdot}$	Y	1 sec	Oxidative damage to lipids, proteins, sugars, *etc.*
Nitric oxide	$NO^{\cdot}$	N		Mitochondria, endothelial cells
Peroxynitrite	$ONOO^-$	N	10^{-3} sec	From superoxide and nitric oxide
Singlet oxygen	$^1O_2$	N	10^{-6} sec	Formed during chemical reactions
Ozone	O_3	N	Stable	Present in the atmosphere

among the ROS (Fig. 3). The members of the ROS family have different specificities for reactants with different degrees of chemical reactivities and wide ranges of lifetimes. Therefore, their reactivities and effects in the biologic systems vary broadly.

ROS are generated by both enzymatic and nonenzymatic catalysis. The enzymatic sources xanthine oxidase, NADPH oxidase, cyclooxygenase, lipoxygenase, myloperoxidase, glucose oxidase, nitric oxide synthase, and uncoupling of the mitochondrial ETS also generate ROS, especially the superoxide radical (Fig. 4). Several enzymes have been identified as sources of generation of ROS during the course of metabolism. Drug and xenobiotic metabolism by the microsomal cytochrome P450 system has been shown to cause the formation of ROS. Autoxidation of small molecules such as catecholamines has been shown to generate ROS. ROS also are produced on exposure to radiation (ionizing, UV). The list of pathologic conditions (diseases) is ever increasing, showing the involvement of generation of ROS.

$$O_2 + e^- \longrightarrow O_2^{-\cdot} \quad \text{(R1)}$$

$$O_2 + 2e^- + 2H^+ \longrightarrow H_2O_2 \quad \text{(R2)}$$

$$O_2 + 3e^- + 3H^+ \longrightarrow H_2O + {}^{\cdot}OH \quad \text{(R3)}$$

$$O_2 + 4e^- + 4H^+ \longrightarrow 2H_2O \quad \text{(R4)}$$

$$O_2^{-\cdot} + O_2^{-\cdot} + 2H^+ \longrightarrow O_2 + H_2O_2 \quad \text{(R5)}$$

$$O_2^{-\cdot} + H_2O_2 \longrightarrow O_2 + {}^{\cdot}OH + OH^- \quad \text{(R6)}$$

$$M^{n+} + H_2O_2 \longrightarrow M^{(n+1)} + {}^{\cdot}OH + OH^- \quad \text{(R7)}$$

Molecular oxygen is activated either by a nonenzymatic process (ionizing radiation) or by enzymatic catalysis into the superoxide anion (R1). The superoxide anion is dismutated by superoxide dismutase into hydrogen peroxide (R2). The four-electron reduction of molecular oxygen leads to the formation of water (R4). Superoxide also undergoes spontaneous dismutation (disproportionation) into molecular oxygen and hydrogen peroxide (R5). Superoxide reacts with hydrogen peroxide (Haber–Weiss reaction) to form molecular oxygen, hydroxyl radicals, and hydroxyl ions (R6). Transition metals (Cu^+, Fe^{2+}, Co^{3+}) catalyze the degradation of hydrogen peroxide (Fenton reaction) into hydroxyl radical and hydroxyl ion (R7). Hydrogen peroxide, although nontoxic, generates one of the most reactive ROS, the hydroxyl radical species ($^{\cdot}OH$) in biologic systems in the presence of redox-active transition metal(s), especially Fe^{2+}. The hydroxyl radical has been shown as the initiator of several ROS-mediated reactions in biologic systems.

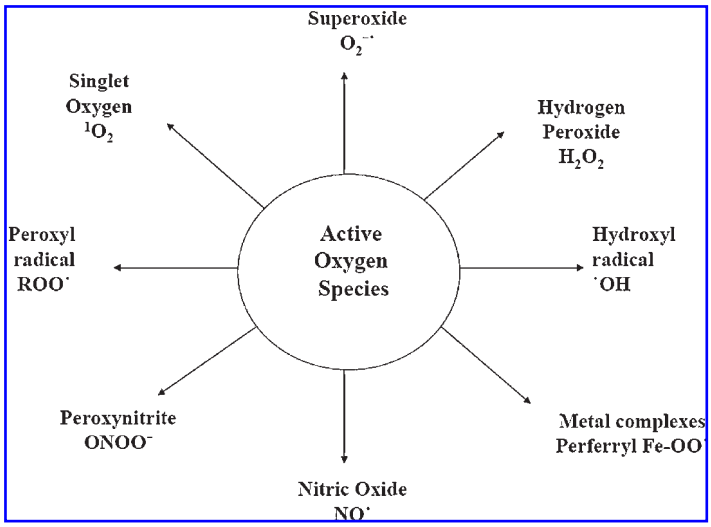

FIG. 3. Molecular oxygen giving rise to different oxygen species (ROS/RNS).

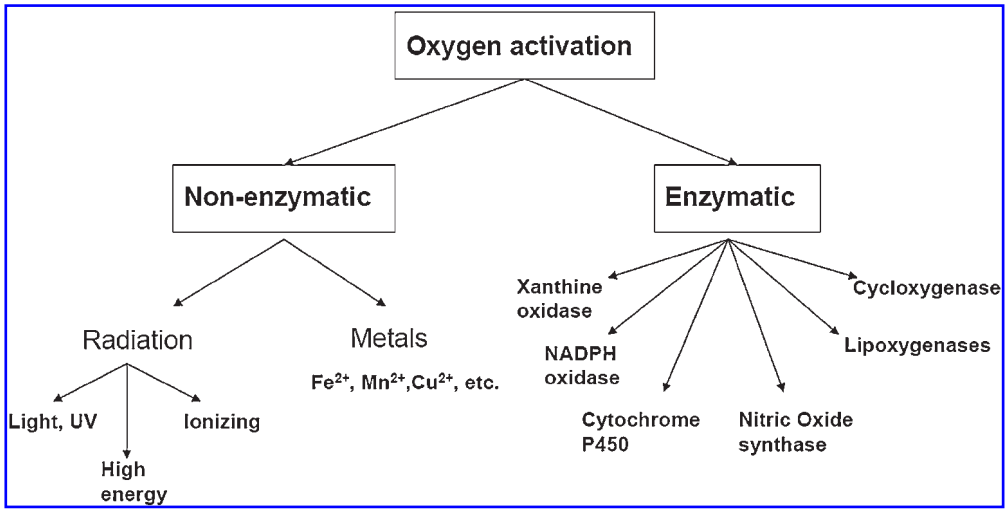

FIG. 4. Activation of molecular oxygen by nonenzymatic and enzymatic mechanisms.

Therefore, redox-active transition metals play an important role in the catalysis of the formation of ROS from molecular oxygen. ROS are highly reactive and capable of reacting with almost every molecule in the organism. The reactivity of ROS with biomolecules leads to the damage of lipids, carbohydrates, proteins, and DNA (Fig. 5). Lipid peroxidation of the membrane phospholipids by ROS is a highly damaging chain reaction. Cellular carbohydrates are also attacked by ROS. Thus, the ROS-induced damage to biomolecules has implications in many pathophysiologic disorders that arise because of free radical–mediated alteration of cellular molecular events. Proteins, upon oxidation by ROS, give rise to myriad products that are

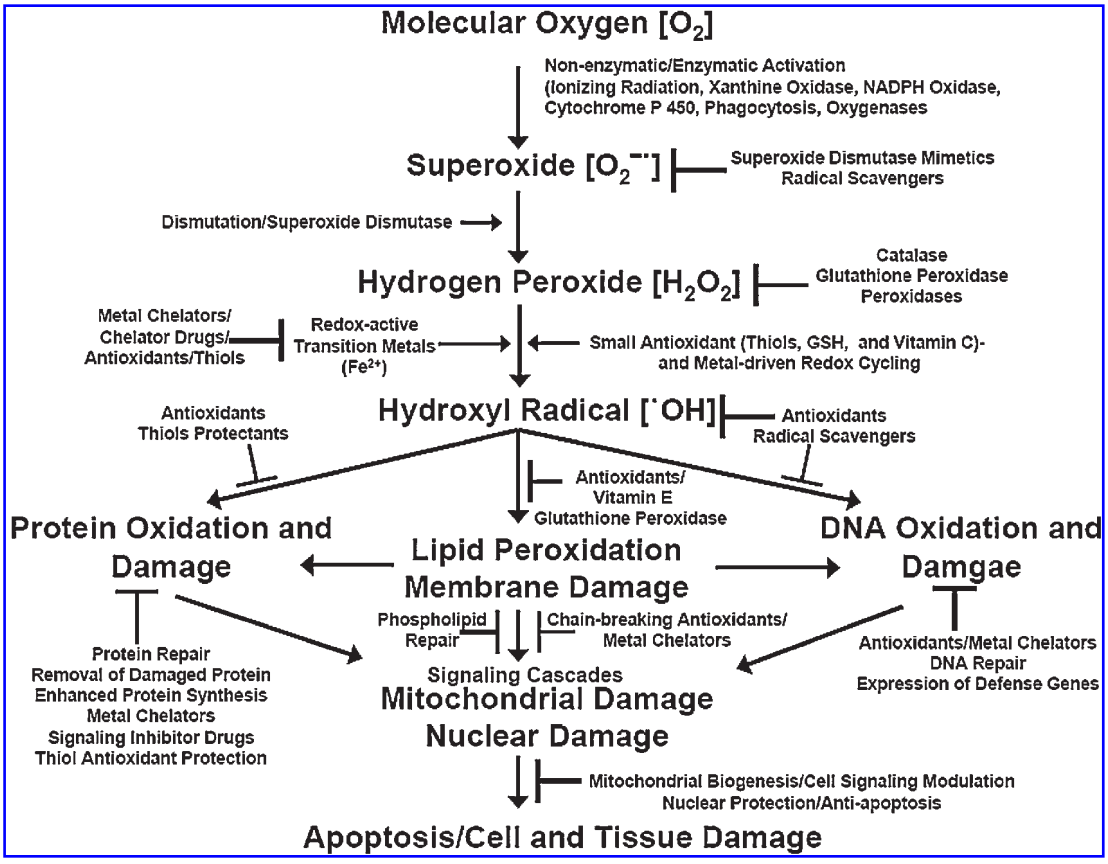

FIG. 5. Formation, reactivity, and toxicity of ROS.

either reactive themselves or form free radicals following their interaction with other molecules. DNA damage is also induced by ROS, especially by the highly reactive hydroxyl radical, which leads to base damage, single-strand breaks, and formation of crosslinks, which have been shown in chemical-induced mutations and carcinogenesis. Hence, oxygen plays a pivotal role in the ROS-mediated biomolecular oxidative modifications as the ROS are derivatives of oxygen.

Although ROS have been identified for their harmful actions, studies over the years have shown that ROS are also important in various normal physiologic processes that occur at the cellular and organism levels. ROS have been shown to activate cellular growth factors in vascular smooth muscle cells (5). They are instrumental in the elimination of dysfunctional proteins by oxidizing them and are also essential for functions of cellular organelles (70). ROS are involved in aging and programmed cell death. They also act as signaling molecules (55) and are highly critical in the immune functions (55). ROS are important in the regulation of various physiologic processes (33). On the flip side, the involvement of ROS has been identified in several diseases and disorders, as either the cause or the effect or both. The link between ROS and various diseases is discussed later in this review.

ANTIOXIDANTS

Antioxidants, by definition, either slow or inhibit free radical–mediated oxidative reactions through different mechanisms. Their primary function is to protect the body from the harmful effects of the ROS and maintain redox homeostasis in the body of the organism. The antioxidants in the body can be grouped into two categories, enzymatic and nonenzymatic. The important enzymatic antioxidants include superoxide dismutase (SOD), catalase, glutathione peroxidase, glutathione reductase, and thioredoxin (10). Nonenzymatic antioxidants are thiols (*e.g.*, glutathione, GSH), protein thiols; vitamins A, B_6, $B1_2$, C, and E; selenium; folic acid; and β-carotenoids (60). The various components of the antioxidant defense system are interrelated and have to work together to ensure adequate protection of the cell. Antioxidant defense mechanisms range from the very simple to a complex network of redox switches. It has been shown that these networks are activated by the oxidants themselves (107). Antioxidant networks sense imbalance in the redox environment and immediately work to regaining equilibrium (56).

The benefits of antioxidants stem from the fact that they lessen or abolish the excess ROS in the cells, leading to the prevention of aging, cardiovascular diseases, and cancer, wherein oxidative stress has been shown as the important causative factor. Many studies have been performed to understand the mechanisms governing these antioxidant protective effects, and the possibility of using antioxidants as drugs and preventive agents in major pathologic conditions is rapidly emerging. The majority of the antioxidants (small molecule and redox active), depending on the environment, can act as either prooxidants or antioxidants. This antioxidant paradox is very critical for the utilization of the molecule as an effective and safe antioxidant. In a metal-rich and oxygen-rich environment, the antioxidant becomes a prooxidant, generates ROS, and causes oxidative stress. Therefore, caution should be exercised while using excessive (mega) doses of redox-active antioxidants either as dietary supplements or as preventive nutraceuticals.

MITOCHONDRIA, ROS, SIGNALING, AND APOPTOSIS

Although mitochondria function as the powerhouse of the cell in generating most of the cellular energy currency (ATP), these organelles are also capable of converting molecular oxygen (2–3% of the total consumed oxygen) into ROS by a one-electron reduction mechanism and also generate NO through the action of mitochondrial nitric oxide synthase (NOS), which also uses molecular oxygen as a substrate (43). Thus, mitochondria are also endangered by oxidative, nitrative, and nitrosative stresses. Therefore, mitochondria play a pivotal part in the survival and death of the cell, in which molecular oxygen is a critical player. Mitochondrial SOD plays a crucial role in the flux of cellular H_2O_2 and establishment of the cellular redox state and vital functions (19). The redox status and the presence of transition metals also contribute to the mitochondrial oxidative reaction, which ultimately determines the homeostasis, survival, or death (apoptosis) of the cell. ROS-mediated signaling cascades from mitochondria to nucleus have been emerging as one of the most important regulators of aging and diseases in humans, which can be tightly balanced by antioxidants to scavenge the highly reactive mitrochondrially generated active oxygen metabolites.

DISEASES AND DISORDERS ASSOCIATED WITH OXYGEN AND ROS

Formation of ROS and the associated oxidative stress have been identified as the major players in the mediation of a majority of disorders caused by the lack or excess of oxygen. Oxidative stress is a condition in the body that arises when the antioxidant–oxidant balance is altered and redox equilibrium is disturbed, leading to the overwhelming production and action of free radicals. Thus, oxidative stress leads to the damage of the biologic system at the molecular, cellular, organ, and organism levels. The relation between oxidative stress, ROS production, different oxygenation levels, and the disease state(s) in the body is very complex. Most times, the determination of the causality, which is controlled by several factors affecting various organ/tissue systems in the body, apparently is not simple.

Redox homeostasis undergoes changes because of a plethora of factors. Conditions including disease states, lack or excess of oxygen, infection, inflammation, toxic insults, and respiratory burst can very well alter the redox homeostasis. This starts a cascade of responses, including the induction of transcription factors such as HIF-1. Under certain conditions, the tissue/organ uses repair strategies to restore the altered redox homeostasis, but sometimes the balance is not restored, leading to pathologic condition(s).

The brain is highly susceptible to insults, which lead to alterations of the redox status through different mechanisms (83). The brain has a high demand for oxygen and therefore, a greater chance exists for ROS production in the brain. Comparatively, the brain has low antioxidant enzyme activity, especially that of catalase. Second, the brain has higher levels of membrane polyunsaturated fatty acids, which are susceptible to free radical–mediated peroxidative attack. All these conditions contribute to a greater susceptibility of the brain tissue to the ROS-induced oxidative stress that involves elevated toxic radical species formation, membrane lipid degradation through lipid peroxidation, protein oxidation, and oxidative DNA damage (29). The cerebrospinal fluid has low-molecular-weight iron and copper complexes, and neurons have nonheme iron. These transition metals catalyze the reactions that generate oxygen free radicals through the Fenton reaction. Thus, the brain encounters the oxidative stress caused by ROS to a greater extent (83). This risk increases even further during a hemorrhagic stroke.

Oxidative stress is involved in most of the neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS) (Table 2) (1, 29, 61, 83, 95). Oxygen also is involved in vascular diseases and disorders including, but not limited to, atherosclerosis, peripheral vascular disease, ischemia, ischemia–reperfusion injury, congestive heart failure, and stroke (22, 44, 61). Atherosclerosis is a process that involves the blocking of blood vessels by plaque (made up of low-density lipoprotein, LDL, and cellular debris) build-up along the vessel wall. One of the widely accepted mechanisms is that the oxidation of LDL by ROS leads to atherosclerotic lesions (79). Enzymes present in the vessel wall, including NAD(P)H oxidase, myloperoxidase, and lipoxygenases, use molecular oxygen to generate ROS (98). Thus, ROS induce/initiate the events leading to a cascade of oxidative reactions involving lipid peroxidation. Although the cause–effect relation between lipid oxidation and atherosclerosis is not yet clearly established (98), it is clear that interaction of lipids with oxygen-derived species before or after the initiation of the lesions is a major concern. Attempts have been made to administer antioxidant therapy, but no clear evidence of its efficacy has been observed (14).

Atherosclerotic lesions can block the blood supply to a tissue or part of an organ, which leads to ischemia. Ischemia deprives the tissue of oxygen and nutrients (26). Tissue ischemia has been shown to generate free radicals (ROS), deterioration of membranes, and uncoupling of the mitochondrial electron transport, leading to the loss of oxidative phosphorylation. These events ultimately cause cell death. The two most critical conditions that arise from ischemia are myocardial ischemia and ischemic stroke. Myocardial ischemia (oxygen starvation of heart tissue) arises from either a disproportionate increase in oxygen demand or interruption of blood flow to the cardiac tissue. It leads to the formation of an infarct (scar tissue) that hinders the cardiac function. This further develops into different disorders, including cardiomyopathy and congestive heart failure, which are the leading causes of death in the United States. Ischemic stroke is the response of the brain to oxygen deprivation. Hemorrhagic stroke is caused by the rupture of a blood vessel. Atherosclerotic plaques have been identified as causative factors in the onset of the ischemic stroke. Ischemic stroke is observed to develop into a hemorrhagic one if not treated in time. Stroke results in neuronal death in the ischemic region, and depending on the nature and the extent of the damage, the cerebral functions and consequently various functions of the body are affected. Oxidative stress is regarded as a major player in the poststroke events that lead to neuronal death (30, 61).

Reperfusion injury occurs when oxygen is reintroduced into an ischemic area through the circulation. This reperfusion of oxygen triggers generation of ROS that damage the previously ischemic tissue. This condition, although largely associated with the heart, also occurs in any reperfused ischemic tissue. It is routinely observed in the brain after ischemic stroke, and in the liver (93), and is a concern in plastic as well as transplant surgeries. No consensus exists over how the ROS are formed from oxygen after reperfusion; however, various mechanisms have been proposed (13, 20). Two of the most important mechanisms include the involvement of xanthine oxidase and NAD(P)H oxidase. During ischemia, generation and accumulation of a substrate gives rise to ROS in the presence of oxygen, causing extensive tissue damage, leading to apoptosis (65). Reports exist on the use of antioxidants as well as xanthine oxidase inhibitors (14, 77) to attenuate the ROS-induced damage in the reperfused, postischemic tissue. Another approach is to reperfuse the heart with blood that has a regulated amount of oxygen to minimize oxygen-mediated damage after reperfusion with oxygen-rich fluid.

Emphasizing the role of SOD, the action of free radicals, and an imbalance of antioxidant enzymes in cancer were introduced by Oberley and Buettner (76) as central to cancer as early as 1978, long before the terms "ROS" and "oxidative stress" were

Table 2. Involvement of ROS-Mediated Oxidative Stress in Neurologic Disorders

	Alzheimer's disease	*Parkinson's disease*	*Amyotrophic lateral sclerosis (ALS)*
Oxidative damage to DNA	Yes	Yes	Yes
Increased levels of 8-OHdG	Yes	Yes	Yes
Lipid peroxidation	Yes	Yes	?
Mitochondrial dysfunction	Yes	Yes	Yes
Increased iron levels in the brain	?	Yes	Yes
Change in the activity of SOD	Yes	Yes	Yes
Increase in protein carbonyls	Yes	Yes	Yes

From refs. 1, 29, 61, 83, and 95.

in the lexicon of the field. Toyokuni and co-workers, in 1995 (104), put forth the hypothesis that oxidative stress has a role in cancer. Since then, considerable progress has been made in understanding the role of ROS and oxidative stress in cancer, tumor growth, and cell proliferation (11, 16, 99, 106). The damage of proteins, lipids, and DNA has been shown to be associated with cancer. Low oxygen levels in the tumor are known to influence the growth of the tumor through angiogenesis (64), induction of several genes, and transcription factors such as HIF-1 (42, 53, 66, 99, 108). Oxidative stress influences cancer metastasis by decreasing the attachment of cells to basal lamina (52), increasing cell migration (52), modifying vascular permeability (16), and activating the membrane metalloproteinases (72, 73).

Oxidative stress plays a crucial role in eye diseases. Retinopathy of prematurity is associated with a high oxygen concentration (hyperoxia) that causes retinal vascularization during subsequent years of life (102). However, it has also been suggested that other factors, including low vitamin E concentration in premature infants, birth weight, gestational age, and exposure to light, contribute to premature retinopathy. Trials have been proposed to probe the lower oxygen-saturation values (SpO_2, 85–89%) as safer levels as opposed to the currently used high-end SpO_2 levels (91–95%) to reduce the severity of premature retinopathy (102). Conversely, retinal hypoxia has been suggested as a contributing factor in retinal neovascularazation in the ischemic proliferative retinopathies, with a special emphasis on diabetic eye diseases (97). Vitrectomy and panretinal photocoagulation, the two treatment strategies, have been demonstrated effectively to reduce or minimize diabetic retinal neovascularization through improvement of retinal oxygenation. Ironically, the same molecular oxygen has two different personalities such as (a) causing retinopathy in premature infants at elevated levels, and (b) improving retinopathy among diabetics by enhancing oxygen delivery, wherein the former requires reduction of the dose of oxygen delivery, and the latter requires the elevation of oxygen levels.

Oxidative stress is an important factor to be considered in diabetes (6, 62, 69, 75), renal disorders (63), autism (68), age-dependent diseases such as arthritis (57, 103), and many more diseases and disorders. This warrants a thorough understanding of the mechanism of disease regulation by oxidative stress and effective therapies for the same.

OXYGEN, HYPEROXIA, AND LUNG DISEASES

It has been increasingly evident that oxygen, especially in the hyperoxic state, plays a major role in several lung diseases/disorders among humans (9, 12, 27). Oxidative stress mediated by the oxygen-derived reactive metabolites (ROS) has been identified as the trigger of such oxygen-induced lung diseases (82). In addition to ROS, RNS are also shown to participate in the oxidant-induced lung diseases, and antioxidant defense mechanisms have been identified as important in the protection of oxidative stress–mediated lung diseases (27). Antioxidant defense systems, especially glutathione peroxidase, have been identified to be upregulated during oxidative stress in the lung, which could serve as an important protector against oxidant-mediated lung injury. Oxidative stress has also been implicated in asthma. Among the antioxidant defenses, adaptive responses have been identified as the prominent players in offering a defense against oxidant-induced asthma, which may also provide insights into identifying antioxidant, antiasthma, therapeutic strategies (12). An association between the complement proteins, phagocytosis, ROS, and the pathophysiology of lung diseases (asthma and acute respiratory distress syndrome, ARDS) has been recognized (87).

Pulmonary oxygen toxicity is associated with the influx of phagocytotic inflammatory cells in the lung, enhanced expression of cytokines, and regulation of hyperoxia-induced acute lung injury that could offer insights into the development of therapeutic strategies for oxygen toxicity in lung (9). Signaling mechanisms in lung epithelium play a crucial role in the oxidant-mediated lung diseases, including asthma, cystic fibrosis, bronchitis, and chronic obstructive pulmonary disease (COPD) (71). Mitogen-activated protein kinases (MAPKs) have been identified as important signaling switches in the oxidant-mediated pulmonary diseases and can be possible target candidates in pharmacologic intervention into such pathologic states. As the inflammatory cells generate and release ROS, both the inflammation and cancer of the lung seem to be tightly associated with the oxidative stress that induces the activation of proteases and DNA damage (96). Oxygen activation into ROS and RNS and subsequent participation of these highly reactive metabolites in COPD and oxidative stress–mediated respiratory diseases have been emphasized (32). Nuclear factor, erythroid 2–related factor 2 (Nrf 2), a transcription factor belonging to the Cap'n'collar/basic leucine Zipper (CNC-bZIP) family of transcription factors, has been shown to activate antioxidant protective mediators that are likely therapeutic candidates for acute respiratory distress syndrome, pulmonary fibrosis, lung cancer, and emphysema, in which oxidative stress has been identified as a crucial player. Overall, it has become very clear that oxygen is a critical player in oxidative stress–mediated lung injury and diseases.

OXYGEN, OXIDATIVE STRESS, AND ENVIRONMENTAL TOXICITY

Oxygen toxicity has been established under toxicologic conditions in several model systems *in vivo*, wherein ROS induce the damage at the molecular, organelle, cellular, and organ levels. Ionizing radiation–induced ROS generation and associated oxidative stress and injury are well established. Environmental toxicants [gaseous pollutants including sulfur dioxide and oxides of nitrogen, ozone, heavy metals and metallic dusts, biologic contaminants such as pollen, bacteria, toxins, spores, fungi, animal dander and viruses, agrochemicals, polycyclic aromatic hydrocarbons, organic compounds, volatiles, solvents, urban particulate matter (PM), fibers, and diesel exhaust gases], after their entry into the body, induce the formation of ROS from molecular oxygen either through enzymatic catalysis in a metal-rich environment or through metabolic formation by biotransformation (Fig. 6). The route of entry into the body is a critical factor in the induction of oxidative stress. Inhalation of

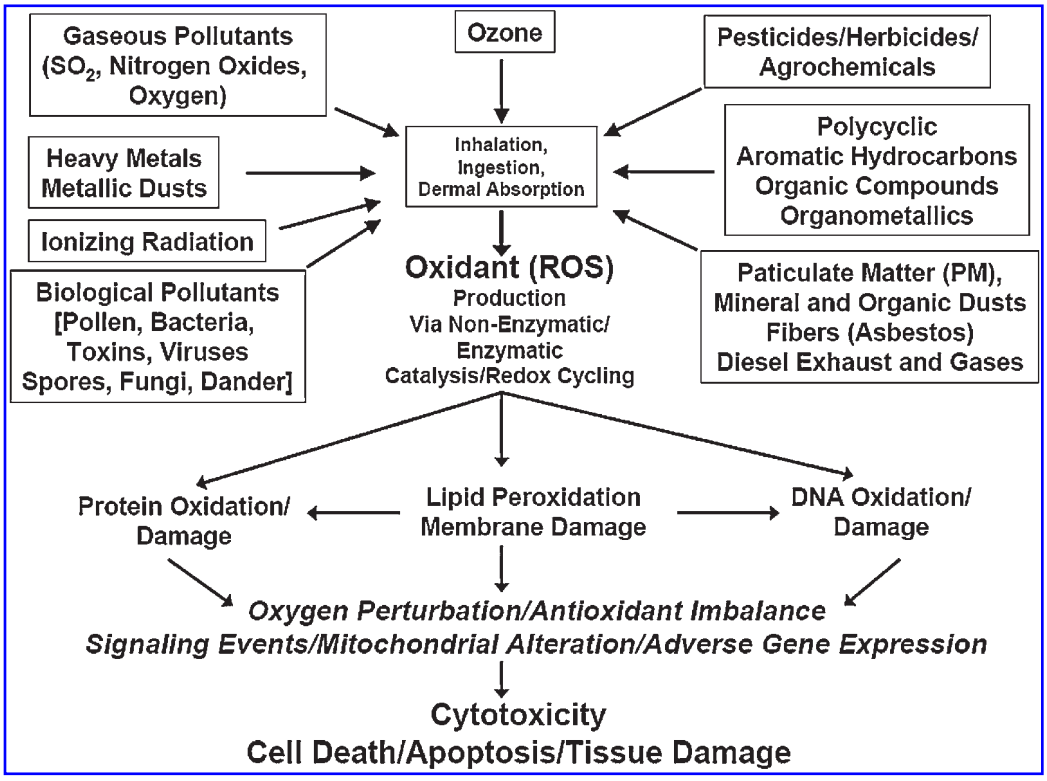

FIG. 6. Toxicity of environmental chemicals through ROS generation and oxidative stress.

airborne toxic substances has been shown to cause oxidative stress through ROS formation in the respiratory tract, lung, and other tissues. Ingestion or dietary absorption or dermal uptake of several toxic chemicals has been shown to cause oxidative stress in different organs. Oxidative stress at the cellular level results in ROS/RNS-mediated membrane lipid peroxidation, thiol-redox alterations, altered enzyme activities, and DNA damage, which lead to tissue damage and the loss of physiologic function(s) of organs. Several important signaling cascades at the cellular level have been shown to cause the toxic insults of the toxicants upon entry. Gaseous pollutants (oxides of nitrogen, carbon monoxide, carbon dioxide, hydrogen sulfide, oxides of sulfur), in conjunction with molecular oxygen, have a profound impact on the cellular, molecular, and biochemical machinery tuning the production of reactive free radicals, ROS, and RNS, which cause serious havoc in the body (81). Redox cycling in the biologic systems, including humans, has been shown to play an important role in the toxicity of environmental pollutants after their entry into the system. Redox cycling has been implicated in the generation of ROS through NADPH-cytochrome P450 reductase catalysis and associated DNA damage during diesel exhaust–particulate treatment (51). Flavoenzyme-catalyzed redox cycling of 2,4,6-trinitrotoluene (TNT) metabolites in TNT metabolite cytotoxicity has been emphasized (86). The widely used bipiridylium herbicide, paraquat, has been shown to exert its toxicity in animals and humans through redox cycling–mediated superoxide generation (40). Overall, it should be emphasized that the oxygen status of the system is very critical during the redox cycling of the environmental chemicals because of their adverse effects through ROS generation and oxidative stress. Air pollution by noxious gases and heavy metals has been shown to cause adverse health effects, including respiratory disorders and diseases, among urban dwellers in the industrialized countries (91).

Asthma has been shown to be associated with air pollutants including airborne particulate matter (PM) and ozone; individual genetic susceptibility and antioxidant defense systems play a pivotal role (67). Ambient PM pollutants (2.5–10 μm) in air have been emerging as notorious environmental airborne toxicants that are associated with cardiopulmonary mortality and morbidity in the United States and industrialized cities of the world (101). Airborne PM has been shown to induce the formation of ROS and oxidative stress in the respiratory tract, causing pulmonary inflammation. It has also been emphasized that PM in the air exacerbates pulmonary inflammation among susceptible individuals with asthma and COPD (101). Analysis of the urban PM in the air has revealed the presence of biologic materials (pollens and bacteria), organic compounds, hydrocarbons, ions, acids, gases, and transition metals adsorbed to a carbonaceous core (101). Inhalable PM has been shown to cause the formation of ROS and to induce oxidative stress and oxidant injury. Inhalation of particles from environmental or occupational exposure has been shown to increase the risk of lung cancer, probably because of the particle-induced ROS formation and associated genotoxicity (49). Environmental exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin and other planar halogenated hydrocarbons has been shown to cause cardiovascular embryotoxicity (38). Electron paramagnetic resonance analysis has revealed the generation of ROS induced by respirable airborne PM that is catalyzed by transition metals and quinone re-

dox cycling involving Fenton-type reactions (105). Ultrafine airborne PM (<0.1 μm) has gained a great deal of attention in recent years as a serious airborne pollutant of the urban environs, which epidemiologically is associated with the risks of myocardial ischemia, cardiac arrhythmia, hypertension, decreased heart rate, inflammation, and thrombosis (31). Although the animal experiments and epidemiologic data suggest a strong correlation between ambient airborne PM pollution and cardiopulmonary and cardiovascular toxicity/diseases, the causative chemical species in the PM and the precise underlying mechanisms must be identified and established (8). Nevertheless, the involvement of molecular oxygen and ROS in the PM-induced cardiopulmonary and cardiovascular toxicity/diseases is emerging.

OXYGEN THERAPY

Oxygen can be used as a therapeutic agent to assist recovery from the conditions that are linked to oxygen insufficiency (Fig. 7). Oxygen can be delivered in one of two ways, supplemental oxygen therapy or hyperbaric oxygen therapy, chosen as required. In supplemental oxygen therapy, the patient is given oxygen through inhalation to counteract the oxygen insufficiency in the blood/tissues. The therapy can be applied over the short term for recovery from certain conditions or over the long term for chronic respiratory disorders. Oxygen is supplied either from a concentrator or as compressed gas or from a liquid oxygen source. This therapy helps to increase the arterial oxygen levels and thereby alleviate the adverse effects of hypoxic conditions. It improves sleep, reduces shortness of breath, and decreases the risk of heart failure for patients with severe respiratory problems. Oxygen therapy is useful in conditions such as asthma, COPD (41), emphysema, bronchitis, lung cancer, cystic fibrosis, pulmonary hypertension (58), and congestive heart failure. Oxygen is also used for resuscitation of newborns, but controversies exist about the necessity for and frequency of its use (28, 88). Portable oxygen cylinders are used as a breathing aid during physical activities such as mountain climbing (for high-altitude hypoxia) and deep-sea diving.

Another type of oxygen therapy is hyperbaric oxygen therapy (HBO). In HBO, the patient is given 100% oxygen at >1 Atm pressure, which helps overcome hypoxia by increasing the level of oxygen dissolved in plasma. Consequently, it is indicated for many conditions that have hypoxic complications, such as air embolism, carbon monoxide poisoning, wound healing, and decompression sickness. HBO helps wound healing by decreasing edema by vasoconstriction, killing bacteria, and promoting angiogenesis (15, 37). It is also used in the treatment of diabetic foot ulcers (45). HBO has also been found useful as adjunct therapy in treating tumors with radiotherapy, chemotherapy, and phototherapy (3). Most of these advantages come about by decreasing the hypoxia of tumors. The use of HBO in treating carbon monoxide poisoning, burns, and crush injury has also been evaluated (89). Another indication of HBO is in decompression sickness (37).

From experimental and clinical observations, it is increasingly evident that brain trauma and aerobic metabolism are linked (4). Impairment of oxygen delivery and subsequent mitochondrial dysfunction in the brain due to hypoxia have been identified as critical players in traumatic brain injury. This situation arises because of arterial hypoxia or decline in cerebral blood flow or both (4), which also lead to 80–90% of deaths among patients. Therapeutic strategies including the elevation of cerebral perfusion pressure, increasing arterial pO_2 (hyperbaric oxygen), and normobaric hyperoxia have been developed to improve the oxidative metabolism of the traumatized brain. Of these, normobaric hyperoxia has been emphasized as a choice of therapeutic strategy to rescue the brain from traumatic injury (4).

During the transition from NREM to REM sleep, an enhancement in cerebral blood flow and brain glucose uptake with lowered increase in oxygen influx have been noticed (59). It has been suggested that the diffusion of oxygen is limited under this condition, which is also supported by observations of hypoxic regions in the brain due to microregional brain capillary hypoxia and subsequent anaerobic glycolysis. Hypoxia greatly reduces REM sleep time, whereas hyperoxia increases the same. Thus, a decrease in the arterial pO_2 or oxygen transport or both poses a threat to REM sleep under pathologic conditions (59). Therefore, it is increasingly becoming evident that the oxygenation of blood and brain, in a concerted fashion, regulates the sleep patterns among humans.

Humans, during high-altitude exposure, face high-altitude hypoxia, and although genetic differences exist among humans, adaptation to chronic high-altitude hypoxic hypoxia has been observed (34). Even though temporary oxygen supplementation

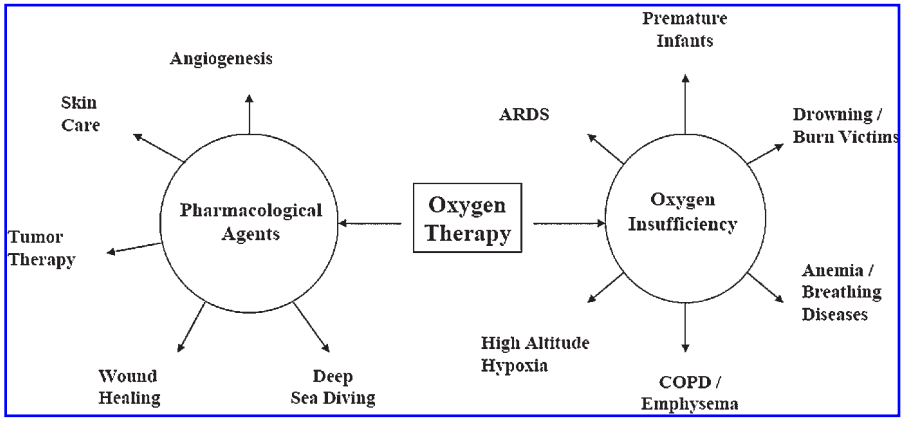

FIG. 7. Use of oxygen in therapy.

for high-altitude hypoxia is used, the molecular mechanism of hypoxia adaptation, involving epigenetic regulations such as antioxidant status, transcription, translation, and posttranslational modifications, operate among humans venturing in high-altitude expeditions.

COPD is closely associated with oxidant generation, oxidative stress, and inflammation (82). Oxidative stress during COPD leads to inactivation of antiproteases, inactivation of surfactants, excessive mucus secretion, oxidative deterioration of the membrane lipids, lung epithelial damage, extracellular matrix alterations, and apoptotic cell death. Therapeutic strategies involving antioxidant administration to treat COPD have been suggested. However, it has been debated whether to treat COPD patients with the 28% oxygen masks used by paramedics, which might exacerbate the hyperoxic condition in patients by overoxygenation (74).

Phagocytosis of bacteria by leukocytes and the synthesis of collagen also use molecular oxygen as an important substrate (24). Immediately after surgery, during the postoperative period (due to several factors such as hypoventilation as a result of pharmacologic depression, hypoxia, and shivering-induced elevation of the metabolic rate), ambient oxygen supply apparently is insufficient. Therefore, perioperative oxygen supplementation is recommended for better recovery of the patient.

The importance of oxygen in wound healing is becoming increasingly evident. The interplay between hypoxia and hyperoxia in wound healing of the skin in experimental animal models has been highlighted (100). A combination of growth factors and molecular oxygen is recommended for skin wound healing. The important role of HIF-1 in such combination wound-healing therapy has been emphasized. The use of oxygen is not without complications. Reports exist of complications with short-term oxygen therapy (21) and with hyperbaric therapy (37). This warrants prudent use of oxygen therapy.

CONCLUSIONS

It is unequivocally established that molecular oxygen is an absolute requirement for the survival of aerobic life forms, including humans. Although oxygen is one of the most important ingredients in the generation of the currency of energy (ATP), oxygen transport, cellular oxygenation, and oxygen sensing are crucial phenomena in the regulation of mitochondrial oxidative phosphorylation. Besides its participation in the generation of ATP, molecular oxygen can also be transformed into highly reactive ROS, which either play instrumental role in the normal physiologic functions or can be detrimental to the organism, depending on the oxidant–antioxidant balance. The levels of tissue and cellular oxygenation are tightly balanced by cellular oxygen consumption, complex signaling cascades of oxygen sensing, and oxygen transport and also maintain the normal state of the oxidative phosphorylation. Under conditions of fluctuating tissue and cellular oxygenation states (hypoxia and hyperoxia), molecular oxygen goes astray and is transformed into ROS, which are detrimental to physiologic homeostasis. This abnormal phenomenon is often encountered in a plethora of pathophysiologic conditions and diseases. A thorough understanding of the behavior of molecular oxygen at the levels of oxygenation, transport, sensing, oxidative phosphorylation, and ROS production in normal physiologic conditions and pathophysiologic settings offers better strategies of treatment of several disorders and diseases in which oxygen is a lead player.

ABBREVIATIONS

ALS, amyotrophic lateral sclerosis; ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; ETS, electron transfer chain; HBO, hyperbaric oxygen; HIF, hypoxia-inducible factor; LDL, low-density lipoprotein; MAPKs, mitogen-activated protein kinases; NO, nitric oxide; NOS, nitric oxide synthase; NREM, non–rapid eye movement; PM, particulate matter; RBCs, red blood cells; REM, rapid eye movement; RNS, reactive nitrogen species; ROS, reactive oxygen species; SOD, superoxide dismutase; TNT, 2,4,6-trinitrotoluene.

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