Oxidative Stress and Sleep Apnea-Hypopnea Syndrome

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Introduction

Sleep apnea-hypopnea syndrome (SAHS) is associated with an increased risk of cardiovascular disease.[1-4] The pathogenic bases for this association are unknown, but one of the possible mechanisms involved is oxidative stress.[5] It has been suggested that the intermittent hypoxia and episodes of hypoxia/reoxygenation that accompany apneas may lead to increased vascular release of free radicals, favor the process of formation of atheromata, and increase the risk of cardiovascular disease in patients with SAHS.[6,7] In this review we present some general concepts concerning the genesis of oxidative stress in the vascular wall and the existing evidence for the involvement of this process in the pathogenesis of cardiovascular disease in patients with SAHS.

Oxidative Stress

General Considerations

Although free radicals or reactive oxygen species (ROS) have well defined physiological functions (such as generating oxidative bursts in neutrophils or activating growth-related intracellular signal transduction pathways), they are highly reactive molecules that can damage cells.[8] The unchecked production of ROS can be a source of disease through the alteration of macromolecules (lipids, proteins, carbohydrates, and nucleic acids) and diverse cellular processes (membrane function, enzyme production, or gene induction). ROS are produced during metabolic reactions when the cells of the organism transform food into energy, especially under conditions of hyperoxia, intense exercise, and ischemia. They are also produced through exposure to certain external agents, such as ionizing radiations, ultraviolet light, or tobacco smoke. The most important inorganic ROS are molecular oxygen (O_2), superoxide anion radical (O_2^-), hydroxyl radical (HO^-), and its immediate precursor, hydrogen peroxide (H_2O_2); the most import organic ROS are peroxyl radical (ROO^-), organic hydroperoxide (ROOH), and lipid peroxides.[8-10]

The organism possesses antioxidant defense systems whose function is to eliminate free radicals immediately. In addition, there are certain ingested antioxidants that the organism cannot synthesize (Table). An antioxidant is defined as any substance which, when present at concentrations lower than those of an oxidizable substrate, significantly delays or prevents the oxidation of that substrate. The substrate contains organic and inorganic molecules found in living cells, such as proteins, lipids, carbohydrates, or DNA.

TABLE
Types of Antioxidants*

Internal	External
Enzymatic	
Superoxide dismutase	Carotenes and carotenoids (vitamin A)
Glutathione peroxidase	Tocopherols (vitamin E)
Catalase	Ascorbic acid (vitamin C)
Other enzymatic systems involved in redox reactions	Flavonoids
Glutathione reductase	
Methionine reductase	
DT diaphorase	
NADPH-dehydroascorbic acid reductase	
DNA repair enzymes	
Non-enzymatic	
Uric acid	
Albumin	
Bilirubin	
Ceruloplasmin	
Reduced glutathione	
Transferrin	
Ubiquinones	

*NADPH indicates nicotinamide adenine dinucleotide phosphate.

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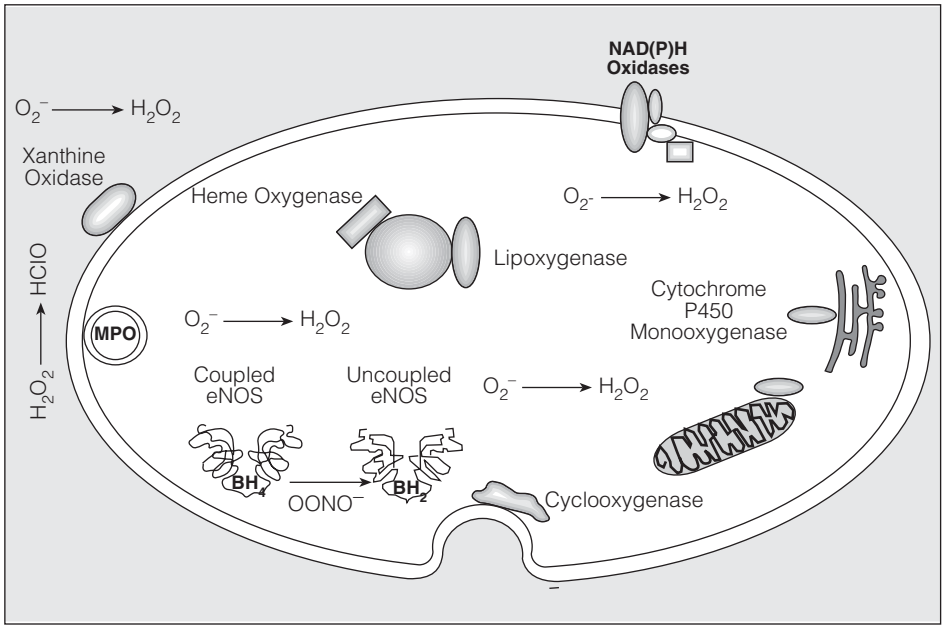

Figure. Potential sources of reactive oxygen species. Many enzymes—such as those that participate in mitochondrial electron transport, xanthine oxidase, cyclooxygenase, lipoxygenase, myeloperoxidase, cytochrome P450 monooxygenase, uncoupled epithelial nitric synthase (eNOS), heme oxygenase, peroxidase, nicotinamide adenine dinucleotide (NADH), and nicotinamide adenine dinucleotide phosphate NAD(P)H oxidases—produce reactive oxygen species. Depending on their location in the cell, these reactive oxygen species are generated intracellularly, extracellularly, or in specific intracellular compartments. MPO indicates: myeloperoxidase; O_2^-, superoxide anion radical; H_2O_2, hydrogen peroxide; $OONO^-$, peroxynitrite; BH_4, tetrahydrobiopterin; BH_2, dihydrobiopterin. (Adapted with permission from Griendling et al.[12])

A shift in the balance between free radicals and antioxidant systems in favor of free radicals leads to what is known as oxidative stress, which plays an important role in numerous degenerative processes, such as aging, arteriosclerosis, or cancer.[8-10] ROS are key players in the development of vascular diseases, including arteriosclerosis, hypertension, and postangioplasty restenosis.[11] It is now clear that many ROS are produced in the arterial wall, and that, alone or in combination, they contribute to the various abnormalities associated with vascular disease.[12,13]

Reactive Oxygen Species and the Vascular Wall

There are various ROS that play major roles in vascular physiology and pathophysiology. The most important of these are nitric oxide (NO), O_2^-, H_2O_2 and peroxynitrite ($ONOO^-$).[12] ROS are involved in some of the basic functions of the arterial wall. NO is a crucial mediator in endothelium-dependent vasodilation, while O_2^- and H_2O_2 intervene in the growth, differentiation, and apoptosis of smooth muscle cells.[14,15] Furthermore, $ONOO^-$–induced lipid peroxidation and protein nitration are early atherogenic events.[16] Each of the ROS is derived from specific chemical or enzymatic reactions (Figure). NO is produced in endothelial cells by the activation of the enzyme epithelial nitric oxide synthase (eNOS), but macrophages and smooth muscle cells can express inducible NO synthase and contribute to the production of NO. NO is a crucial mediator in endothelium-dependent vasodilation. It also participates in the process of platelet aggregation and in maintaining the balance between growth and differentiation of smooth muscle cells. The eNOS enzyme can be activated by diverse vasodilating hormones and physical forces. The expression of inducible NO synthase in macrophages and smooth muscle cells causes an increase in cytokine concentrations that give rise to a local inflammatory response. Under certain conditions, eNOS is uncoupled due to a deficiency of tetrahydrobiopterin, an essential cofactor, and O_2^- is produced instead of NO. In other words, NO synthase enzymes are potential sources of NO and O_2^-, depending on environmental conditions.[13,17,18]

All vascular cells produce O_2^- and H_2O_2. O_2^- is the result of the single-electron reduction of oxygen by a variety of oxidases. When O_2^- is produced along with NO, they rapidly react to form the highly reactive molecule $ONOO^-$. $ONOO^-$ is an important mediator of lipid oxidation—such as the oxidation of low-density lipoproteins (LDL), which has significant proatherogenic effects.

In the absence of NO, O_2^- is rapidly dismutated to a more stable ROS, H_2O_2, by superoxide dismutase and is then converted to H_2O by catalase or glutathione peroxidase.[12,13] The effects of O_2^- and H_2O_2 on vascular function depend on the amounts produced. When they form intracellularly in small quantities, they can act as second messengers to modulate the function of biochemical mechanisms that participate in smooth muscle cell or fibroblast growth processes. High ROS production can damage DNA and cause cellular toxicity and apoptosis, as has been demonstrated in both endothelial and smooth muscle cells.[12] In addition to mitochondrial production of ROS, various enzymes —such as nicotinamide adenine dinucleotide (NADH) or nicotinamide adenine dinucleotide phosphate (NADPH) oxidases—can synthesize O_2^- and H_2O_2. Enzyme activity can be modified by various stimuli. Thus, angiotensin II, tumor necrosis factor-α, thrombin, and