Oxidative Stress and Vascular Damage in Hypertension

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Metabolism of oxygen by cells generates potentially deleterious reactive oxygen species, including superoxide anion radical, hydrogen peroxide, and hydroxyl radical. Under normal physiologic conditions the rate and magnitude o oxidant formation is balanced by the rate of oxidant elimination. However, an imbalance between prooxidants and antioxidants results in oxidative stress, which is the pathogenic outcome of the overproduction of oxidants that overwhelms the cellular antioxidant capacity. There is increasing evidence that an elevation of oxidative stress and associated oxidative damages are mediators of vascular injury in various cardiovascular pathologies, including hypertension, atherosclerosis, and ischemia-reperfusion. This review focuses on the vascular effects of reactive oxygen species and the role of oxidative stress in vascular damage in hypertension.

Introduction

Reduction-oxidation (redox) reactions generate reactive oxygen species such as superoxide anion ($\cdot O_2^-$), hydrogen peroxide (H_2O_2), hydroxyl radical ($\cdot OH$), and nitric oxide ($NO\cdot$), which act as intercellular and intracellular mediators of signal transduction in physiologic and pathophysiologic processes. In the vasculature, reactive oxygen species modulate vascular tone and structure. $\cdot O_2^-$ and H_2O_2 have been shown to induce vascular contraction [1] and vascular smooth muscle cell growth [2•,3,4], whereas $NO\cdot$ plays a pivotal role in endothelium-dependent relaxation [5•]. Furthermore, oxygen free radicals are proinflammatory an stimulate monocyte migration and formation of oxidized low-density lipoprotein, which is toxic to vascular cells and impairs vascular endothelial function [6]. Consequently, excessive reactive oxygen species may underlie pathologi processes associated with endothelial dysfunction and vascular remodeling, which are characteristic features of small vessels in hypertension. It is becoming increasingly recognized that oxidative stress is a potentially important contributor to vascular damage in hypertension. Links between oxidative stress and hypertension were demonstrated over 15 years ago, when acute hypertension induced by intravenous infusion of vasoconstrictor agents in cats induced generation of superoxide in the brain [7]. Recent studies have shown that in various models of hypertension, generation of reactive oxygen species is increased in the vasculature [8•,9,10], and that treatment with antioxidants or superoxide dismutase mimetics improves vascular function and structure and reduces blood pressure in experimental and human hypertension as well as in pre-eclampsia [11–13].

Biochemistry of Reactive Oxygen Species

Reactive oxygen species are generated as intermediates in redox processes, leading from oxygen to water. The univalent reduction of oxygen yields $\cdot O_2^-$, H_2O_2, and $\cdot OH$ according to the sequence outlined in Figure 1. Superoxide has an unpaired electron in its molecular orbital and is, therefore, known as a free oxygen radical. The unpaired electron imparts high reactivity and renders it unstable and short lived. Superoxide is water soluble and can act either as an oxidizing agent, where it is reduced to H_2O_2, or as a reducing agent, where it donates its extra electron to form peroxynitrite (ONOO-) with $NO\cdot$ [14]. Under physiologic conditions in aqueous solutions at a neutral pH, its preferred reaction is the dismutation reaction that yields H_2O_2. However, when NO is produced in excess, a significant amount of $\cdot\ _2^-$ reacts with $NO\cdot$ to produce ONOO- [15]. Superoxide is membrane impermeable, but can cross cell membranes via anion channels. Hydrogen peroxide is produced primarily from dismutation of $\cdot\ _2^-$. A typical human cell metabolizes about 10^{12} molecules of O_2 per day and generates approximately $3x10^9$ molecules of H_2O_2 per hour. Hydrogen peroxide is lipid soluble, can cross cell membranes, and is stable under physiologic conditions. Hydroxyl radical is a powerful oxidant than can be produced directly from water or from H_2O_2. It is extremely reactive and, therefore, has a very short half-life and does not travel more than a few molecular diameters from it site of formation. Superoxide anion, H_2O_2, and $\cdot OH$ are all produced to varying degrees in the vasculature. These oxygen metabolites, which are tightly regulated under normal conditions, act as second messengers to control vascular function and structure.

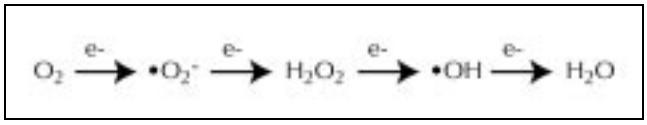

Figure 1. Univalent reduction of oxygen. e—electron; H_2O—water; H_2O2—hydrogen peroxide; $•O_2$—superoxide anion; •OH—hydroxyl radical.

Vascular Production of Reactive Oxygen Species

Superoxide anion

Superoxide can be produced from numerous sources in the vessel wall [16••,17], including 1) the mitochondrial respiratory chain of enzymes, such as nicotinamide adenine dinucleotide dehydrogenase (NADH) and ubiquinone Q-cytochrome B complex; 2) small molecules that are normal cellular constituents, such as flavins, thiols, and catecholamines; 3) metabolic byproducts associated with metabolism of arachidonic acid, including cyclooxygenase, lipoxygenase, and cytochrome P450 monooxygenase; 5) xanthine oxidase, which oxidizes xanthine and hypoxanthine to form $•O_2^-$, H_2O_2, and uric acid; and 6) NADH/NADPH oxidase (Fig. 2). Of the many sources of reactive oxygen species, it appears that a nonmitochondrial membrane-associated NADH/NADPH oxidase is the major source of $•O_2^-$ in vascular cells [18••].

Vascular reactive oxygen species are produced in endothelial, adventitial, and vascular smooth muscle cells and derived primarily from NADH/NADPH oxidase, which is a multi-subunit enzyme [10,18••,19] (Fig. 2). This enzyme transfers electrons from NADH or NADPH to molecular oxygen, producing $•O_2^-$. The neutrophil NADPH oxidase is composed of at least five subunits: two cytosolic components (p47phox and p67phox), a plasma membrane-associated cytochrome b558 composed of two subunits (p22phox and gp91phox), and a small molecular weight protein (either rac-1 or rac-2) [20]. In resting cells, th components of the oxidase are segregated into cytosolic and membrane components; during activation, however, the cytosolic components translocate to the plasma membrane and assemble with membrane-bound components, resulting in the active $•O_2^-$ generating system. The molecular structure of vascular NADH/NADPH oxidase differs from that of the neutrophil oxidase. In endothelial cells, gp91phox, p22phox, p47phox, and p67phox are detectable by reverse transcriptase (RT)-polymerase chain reaction (PCR) testing, but only p22phox is detectable by Northern blot analysis, and only the cytosolic components are detectable by Western blot analysis [21]. In human arteries and isolated cultured-rat vascular smooth muscle cells, p22phox, which is regulated by glucocorticoids, is abundantly expressed, but gp91phox does not appear to be present [22,23]. However, mox1, a homologue of gp91phox, has been found by RT-PCR testing in vascular smooth muscle cells [24••]. Thus, mox1, which generates reactive oxygen species and participates in mitogenic responses to growth factors, may be the vascular counterpart of neutrophil gp91phox.

Hydrogen peroxide and hydroxyl radical

The main source of H_2O_2 in vascular tissue is the dismutation of $•O_2^-$, as seen in Figure 3. This reaction can be spontaneous or it can be catalyzed by superoxide dismutase (SOD). The SOD-catalyzed dismutation is favored whe the concentration of $•O_2^-$ is low and when the concentration of SOD is high, which occurs in normal conditions. Three mammalian SODs have been identified and the genes cloned and characterized: copper/zinc SOD (SOD1), mitochondrial Mn SOD (SOD2), and extracellular SOD (SOD3) [25••]. The concentration of SOD in the extracellular fluid is lower than in intracellular fluid. Therefore, $•O_2^-$ can survive longer and travel further once it gains access to the extracellular space. In biologic systems, H_2O_2 is scavenged by catalase and by glutathione peroxidase. Glutathione peroxidase utilizes reduced glutathione to convert H_2O_2 to water, and catalase converts H_2O_2 to water without requiring cofactors. In the presence of iron-containing molecules such as Fe^{2+}, which act as a redox catalyst, H_2O_2 can also be reduced to generate the highl reactive •OH (Haber-Weiss or Fenton reaction) [14] (Fig. 4). Hydroxyl radical is highly reactive, and unlike $•O_2^-$ and H_2O_2, which travel some distance from their site of production, •OH induces local damage where it is formed. Because of its extremely high reactivity, there are no specific scavengers of •OH.

The activity and expression of enzymes that regulate production of reactive oxygen species are regulated by cytokines, growth factors, and vasoactive agents. Of particular signifi cance is angiotensin (Ang) II, which is implicated in the pathogenesis of hypertension. Ang II stimulates activation of NADH/NADPH oxidase and H_2O_2 production and induces growth via redox-sensitive pathways in cultured vascular smooth muscle cells [2•,4,18••] (Fig. 5AB). These effects are blocked by diphenylene iodonium, an inhibitor of flavin-containing enzymes [2•,18••]. Mechanisms whereby Ang II activates vascular oxidase are unclear, but arachidonic acid metabolites have been implicated [3]. In addition, we recently demonstrated that phospholipase D-dependent pathways regulate vascular NADH/NADPH oxidase [2•]. Platelet-derived growth factor (PDGF), and the inflammatory cytokine tumor necrosis factor (TNF)-α, also activate the NADH/NADPH oxidase system in vascular smooth muscle cells, whereas increasing levels of catalase or the antioxidant glutathione prevents PDGF-mediated production of reactive oxygen species [26,27]

Vascular Effects of Reactive Oxygen Species

Reactive oxygen species play a pivotal role in intracellular signal transduction (Tables 1 and 2). $•O_2^-$ and H_2O_2 activate many growth-related signaling pathways in vascular smooth

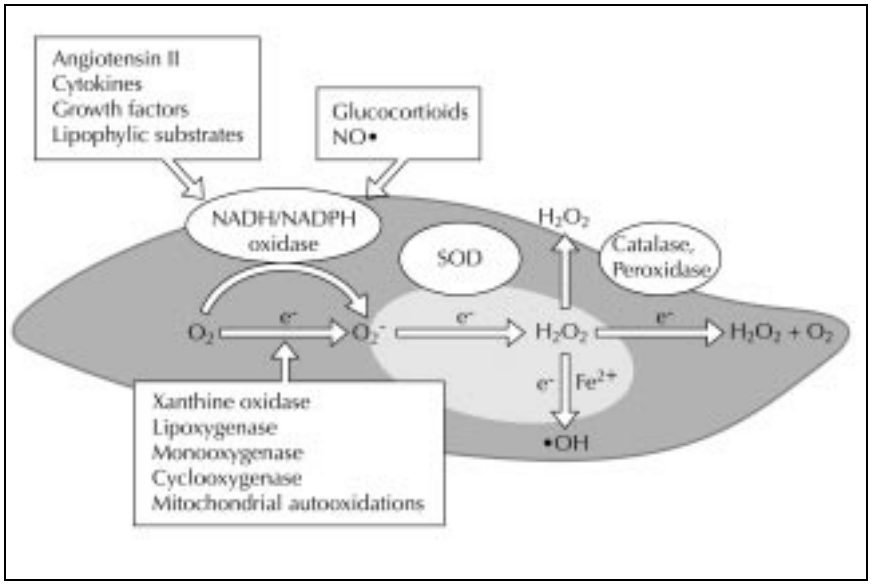

Figure 2. Regulation of reactive oxygen species production in vascular smooth muscle cells. The major source of vascular superoxide anion ($\bullet O_2^-$) is nicotinamide adenine dinucleotide (NADH)/NADPH oxidase, a multisubunit enzyme that is membrane-associated. Many other enzyme systems, such as xanthine oxidase, cyclooxygenase, lipoxygenase, monooxygenase, and mitochondrial enzymes of oxidation-phosphorylation, also produce $\bullet O_2^-$, but their role is minor in vascular cells. Extracellular stimuli, such as angiotensin II, activate (+) NADH/NADPH oxidase, whereas glucocorticoids and nitric oxide (NO•) inhibit (-) enzyme activity. Hydrogen peroxide (H_2O_2), but not $\bullet O_{2-}$, is lipid soluble and can freely cross the cell membrane. e—electron; O_2—diatomic oxygen; •OH—hyroxyl radical; SOD—superoxide dismutase.

$$2 \bullet O_2^- + 2H^+ \longrightarrow H_2O_2 + O_2$$

Figure 3. Dismutation of $\bullet O_2^-$ is the main source of H_2O_2 in vascular tissue. H^+—hydrogen ion concentration; H_2O_2—hydrogen peroxide; O_2—diatomic oxygen; $\bullet O_2$—superoxide anion.

$$H_2O_2 + Fe^{2+} \longrightarrow \bullet OH + OH^- + Fe^{3+}$$

Figure 4. Reduction of H_2O_2 by iron-containing molecules to •OH. Fe—iron; H_2O_2—hydrogen peroxide; OH^-—negative charged hydroxyl ion; •OH–hyroxyl radical.

muscle cells, including phosphorylation of mitogen-activated protein arterial pressure (MAP) kinases (p38 and ERK5), induction of protooncogenes *c-fos, c-myc,* and *c-jun* and activation of the AP-1 transcription factor [16••,28]. H_2O_2 also induces PDGF stimulation of STATs, activation of Akt by Ang II, phosphorylation of epidermal growth factor receptor, activation of tyrosine kinases and tyrosine phosphatases, and activation of *ras* [16,28]. These signaling events mediate redox-sensitive growth in vascular smooth muscle cells and are particularly important in Ang II-stimulated proliferation and hypertrophy, which contribute to vascular wall thickening and remodeling in hypertension [2•,29]. The vascular growth-promoting actions of oxidative stress are further supported by studies that demonstrated antioxidants dose-dependently reduce cell viability and enhance apoptosis [30]. At high concentrations, H_2O_2 is also associated with apoptosis, which could further contribute to vascular remodeling [31,32]. The dual role of reactive oxygen species in vascular growth is probably related to the severity of oxidative stress, to the particular species present, and to the antioxidant status in the tissue under consideration [32].

The integrity of vascular smooth muscle cell morphology depends on the organization of membrane myofilaments. Oxygen radicals can damage the cellular cytoskeleton, causing severe morphologic and structural alterations. Superoxide anion and H_2O_2 polymerize hyaluronic acid as well as regulate activity of vascular smoot muscle-derived matrix metalloproteinase (MMP)-2 and MMP-9 to degrade proteoglycans and collagen [33]. These processes influence extracellular matrix composition and arterial wall structure.

In addition to the effects on vascular growth and structure, reactive oxygen species are capable of modulating vascular functional contractile and dilatory responses. Oxygen radicals mobilize C $^{2+}$ from sarcoplasmic and mitochondrial stores [34] and activate the Na^+/H^+ exchanger to promote intracellular alkalinization [35]. These signaling events are major determinants of vascular smooth muscle contraction and probably underlie mechanisms, whereby $\bullet O_2^-$ and H_2O_2 directly stimulate contraction [1]. Reactive oxygen species also regulate vascular tone by influencin endothelium-dependent relaxation. Nitric oxide, a free radical, is a potent endogenous vasodilator. The integrity of endothelium-dependent dilation depends on the balance between NO• and $\bullet O_2^-$. Because NO• can be scavenged by $\bullet O_2^-$ to form ONOO-, conditions associated with increased $\bullet O_2^-$, such as hypertension, can induce vascular damage by reducing the beneficial effects of NO• and by increasing the injurious effects of ONOO-, which can be protonated t peroxynitrous acid, the products of which are highly reactive oxygen species. Under these conditions, acetylcholine-induced dilation is impaired, vasoconstriction is increased, lipid peroxidation is induced, expression of vascular cel adhesion molecule (VCAM-1) and monocyte chemotactic protein (MCP-1) is increased, and adhesion of leukocytes is favored. These redox-sensitive changes contribute to endothelial dysfunction and vascular damage. The role of NO• in endothelial cell function and control of vasomotor tone

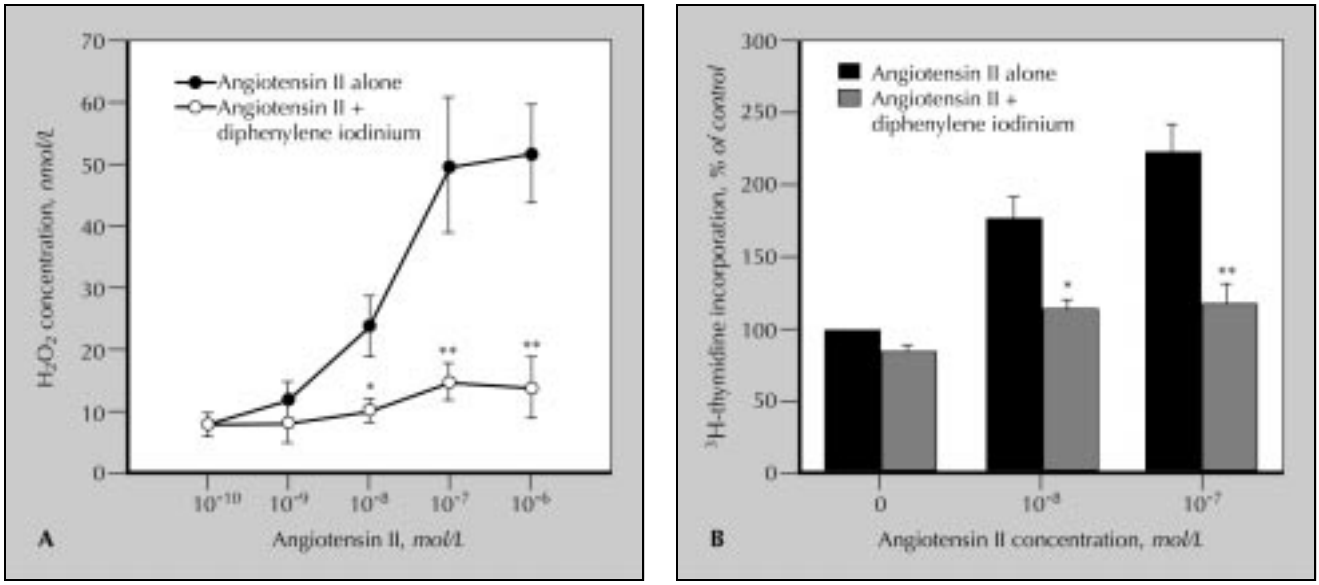

Figure 5. Angiotensin II increases production of hydrogen peroxide (H_2O_2) and induces DNA synthesis via nicotinamide adenine dinucleotide (NADH)/NADPH oxidase in human vascular smooth muscle cells. **A**, Line graphs demonstrate effects of angiotensin II on H_2O_2 production in human vascular smooth muscle cells. Cells were loaded with the fluorescent dye DCFDA (8 µmol/L), and fluorescence measured withexcitation wavelength of 495 nm and emission wavelength of 520 nm. In some experiments cells were pretreated for 20 minutes with the NADH/NADPH oxidase inhibitor diphenylene iodinium (DPI) (10^{-5} mol/L). * $P < 0.05$; ** $P < 0.01$ versus angiotensin II counterpart. **B**, Bar graphs demonstrate effects of angiotensin II in the absence and presence of DPI (10^{-5} mol/L) on ^{3}H-thymidine incorporation, a measure of DNA synthesis. * $P < 0.05$; ** $P < 0.01$ versus angiotensin II counterpart. *Adapted from* Touyz and Schiffrin [2•].

has recently been reviewed and the reader is referred t these references for further details [5,25,36].

Superoxide Generation in Hypertension

Recent evidence suggests that hypertension is associate with increased vascular oxidant stress in hypertension, particularly in Ang II-dependent hypertension. Ang II stimulates $\bullet O_2^-$ formation by increasing the activity of NADH/NADPH oxidase in cultured rat and human vascular smooth muscle cells, and in intact aortas of rats made hypertensive by Ang II infusion [8•,19]. In aortas from hypertensive rats, p22phox mRNA expression and NADH/NADPH oxidase activity are increased [37]. Ang II strongly upregulates extracellular-SOD activity, protein, and mRNA expression, which modulate the oxidative state of the vessel wall in hypertension [38•]. Ang II-induced, but not norepinephrine-induced, hypertension is ameliorated by treatment with membrane-targeted forms of SOD [8•]. Liposome-encapsulated SOD also enhanced in vivo responses to acetylcholine and in vitro responses to endothelium-dependent vasodilators in Ang II-treated rats [8•]. These data further suggest that hypertension caused b chronically elevated Ang II is mediated via oxidative stress-dependent processes.

Reactive oxygen species have also been implicated in other models of experimental hypertension. Increased oxidative stress has been demonstrated in aortic and mesenteric vessels of stroke-prone spontaneously hypertensive rats (SHR), SHRs [9,39], and in renal proximal tubules of SHRs [40]. In 14- to 17- week-old stroke-prone SHRs, which have severe hypertension, the amount of urinary 8-hydroxy-2'-deoxyguanosine (8-OhdG), a biomarker of the total systemic oxidative stress in vivo, is significantly elevated [41]. In addition, various studies have demonstrated that antioxidants decrease vascular $\bullet O_2^-$ generation, improve endothelial dysfunction (especially in conduit arteries), and reduce blood pressure in experimental and human hypertension [11,42–44]

Table 1 Vascular effects of reactive oxygen species

Altered vascular tone
Altered endothelium-dependent responses
Altered vessel reactivity
Increased vascular growth
Increased endothelial permeability
Increased monocyte/macrophage infiltration
Platelet aggregation

Table 2 Signal transduction pathways regulated by reactive oxygen species in vascular smooth muscle cells

Activation of tyrosine kinases (*eg*, Src family kinases)
Inhibition of phosphotyrosine phosphatases
Phosphorylation of mitogen-activated protein kinases, particularly BMK1 and p38
Activation of small G proteins (*eg*, p21 ras)
Activation of NF-κB
Mobilization of intracellular Ca^{2+}
Activation/inhibition of Na^+/H^+ exchanger

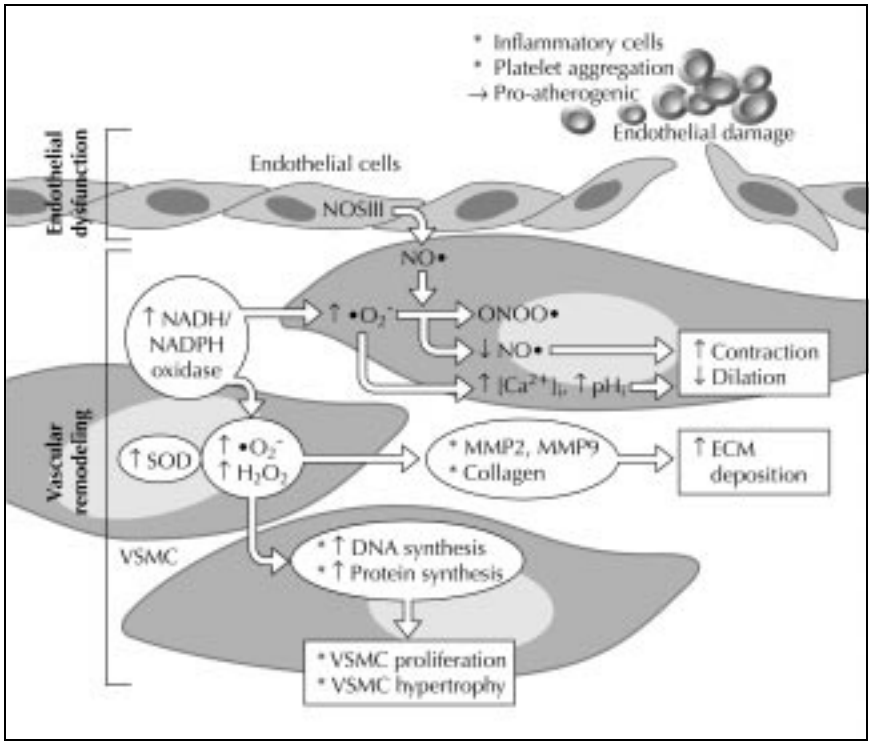

Figure 6. Diagram demonstrating possible mechanisms whereby reactive oxygen species induce vascular damage in hypertension. Increased production of vascular superoxide anion and hydrogen peroxide (H_2O_2) results in increased quenching of nitric oxide (NO•), with resultant increased ONOO-, reduced NO•, and altered endothelium-dependent relaxation. Oxidative stress also activates growth-signaling pathways to stimulate vascular smooth muscle cell growth and increased connective tissue deposition, leading to vascular wall thickening and remodeling. Increased reactive oxygen species increase intracellular free Ca^{2+} concentration ($[Ca^{2+}]i$) and induce intracellular alkalinization, which stimulates vascular smooth muscle contraction. Endothelial dysfunction, increased reactivity, and vascular remodeling are characteristic features of vascular damage in hypertension. ECM—extracellular matrix; NOS III—endothelial nitric oxide synthase; SOD— superoxide dismutase; VSMC—vascular smooth muscle cell; ↑—increase; ↓—decrease.

Role of Reactive Oxygen Species in Vascular Damage in Hypertension

Arteries are capable of structural and functional changes in response to changes in hemodynamic conditions. Arterial remodeling is mediated via the synthesis and release of locally produced growth and vasoactive factors, and is an adaptive process occurring in response to chronic changes in arterial pressure or flow. In hypertension, the arterial system undergoes structural remodeling that is characterized by hypertrophy of the arterial wall and increased wall-to-lumen ratio and associated decreased arterial distensibility. When the remodeling process becomes maladaptive, further vascular damage ensues in hypertension, which is associated with impaired endothelial function, enhanced reactivity, and vascular inflammation. All of these processes can be influenced by oxidant stress.

Vascular remodeling

In hypertension, oxidative stress promotes vascular smooth muscle cell proliferation and hypertrophy, collagen deposition, and alterations in activity of MMPs, which lead to thickening of the vascular media and arterial remodeling (Fig. 6). Superoxide anion and H_2O_2 stimulate several growth factor-like cellular responses, such as intracellular alkalinization, MAP kinase phosphorylation, and tyrosine kinase activation [16••]. H_2O_2 induces vascular smooth muscle cell DNA synthesis, increases expression of protooncogenes, and promote cell growth [4]. During vascular damage in hypertension, when oxidative stress is increased, H_2O_2 actions may lead to accelerated vascular smooth muscle cell proliferation and hypertrophy. Reactive oxygen species also modulate vascular remodeling in hypertension by increasing deposition of connective tissue. Superoxide anion and H_2O_2 influence activity of vascular MMP-2 and MMP-9 and promote production and deposition of collagen [33]. The role of oxidative stress in remodeling was also suggested in studies that demonstrated antioxidant vitamins increased lumen diameter and regressed arterial remodeling in damaged pig coronary arteries [45]. Furthermore, intravenous injection of a fusion protein of SOD linked to a C-terminal basic domain, which has high affinity for heparin-like proteoglycans on vascular endothelial cells, lowered blood pressure in SHRs [46].

In addition to oxidative stress influencing arterial structure in hypertension, media thickening affects vessel redox state. Vascular wall thickening increases the distance required for diffusion of oxygen from the lumen. A reduced pO_2, in turn, results in incomplete oxidation and increased concentrations of free radicals and abnormalities of the oxidant state. This $\bullet\ {}_2^-$ formation further contributes to vascular smooth muscle cell growth, endothelial dysfunction, and vascular damage in hypertension.

Endothelial dysfunction

Increased $\bullet O_2^-$ in hypertension impairs endothelium-dependent vascular relaxation and increases vascular contractile reactivity (Fig. 6) [25••]. These effects may be mediated directly by increasing $[Ca^{2+}]_i$ or indirectly by reducing concentrations of the vasodilator NO•. In aortic vessels from stroke-prone SHRs, decreased NO• availability and associated endothelial dysfunction have been

attributable to excess • $_2^-$ [9], whereas in resistance arteries NO• production was found to be normal, but •O_2^- decomposition was augmented [47]. Oxygen radicals also induce endothelial permeability, with extravasation of plasma proteins and other macromolecules, and recruitment of inflammatory proteins and cells, which could further impair endothelial function and aggravate vascular damage. In SHRs that have increased production of vascular •O_2^-, albumin leakage response, mediated via an interaction betwee β2 (CD18) integrins on leukocytes and ICAM-1 in endothelial cells, is exaggerated [48]. It has recently been shown that peripheral polymorphonuclear leukocytes, which generate •O_2^-, participate in oxidative stress and inflammation in patients with essential hypertension [49]. The coexistence of an inflammatory reaction with oxidative stress induces endothelial dysfunction. Many of the redox-sensitive vascular changes that occur in hypertension also exist in atherosclerotic vessels [16••]. In fact, oxidative stress-mediated vascular damage may be a link between hypertension and atherosclerosis [50].

Antioxidants and Vascular Damage in Hypertension

The prospect that vascular injury can be avoided or minimized by reducing oxidative stress through increased intake of antioxidants is appealing. A few studies reported that antioxidant vitamins, SOD mimetics, and liposome-entrapped SOD can normalize endothelial dysfunction and improve vascular remodeling in experimental hypertension [8•,11,44]. Data from a recent meta-analysis demonstrated that chronic intake of antioxidants improves endothelial function in conduit arteries but not in resistance arteries [51]. This heterogeneity may relate to the coexistence of atherosclerosis in large, but not small, arteries. Other studies reported that antioxidants reduce blood pressure and improve antioxidant status in patients with essential hypertension [42,43,52], suggesting that oxidative stress plays a pathophysiologic role, at least in part, in human hypertension. It is not clear whether antioxidants regress vascula remodeling and whether vascular damage can be reversed in human hypertension. Although the experimental data and preliminary clinical results are encouraging, it is premature at this time to advocate antioxidants as therapeutic modalities in the management of hypertension. Recent evidence suggests that some of the beneficial effects of antihypertensive drugs such as angiotensin-converting enzyme inhibitors AT_1, receptor blockers, and Ca^{2+} channel blockers may be mediated, in part, by modulating oxidative stress

Conclusions

This review has focused on the physiologic role of reactive oxygen species in the regulation of vascular structure and function and on the pathophysiologic importance of oxidative stress in vascular damage in hypertension. Until recently, it was thought that reactive oxygen species were toxic byproducts of cellular metabolism, which induced DNA damage, lipid peroxidation, and cell death. However, it has become clear that reactive oxygen species are produced in the vessel wall in a controlled and tightly regulated manner and that they have critical signalin functions that maintain vascular functional and structural integrity. In hypertension, dysregulation of enzyme systems such as NADH/NADPH oxidase or SOD that generate •O_2^-, H_2O_2, and •OH, or reduced scavenging by endogenous antioxidants, results in increased formation of reactive oxygen species, which has detrimental effects on vascular structure and function. Oxidative stress in hypertension contributes to vascular damage by promoting vascular smooth muscle cell proliferation, endothelial dysfunction, vascular tone alteration, and MMPs activation. These processes induce vascular remodeling and contraction-relaxation abnormalities, which characterize vascular injury in hypertension. However, preliminary data suggest that antioxidant vitamins may improve vascular damage and reduce blood pressure in patients with essential hypertension. With a greater understanding of molecular, biochemical, and physiologic mechanisms that regulate vascular reactive oxygen species metabolism, and identification of processes that tip the balance to states of oxidative stress that cause vascular damage, it should be possible to target therapies more effectively so that detrimental actions of vascular oxygen free radicals can be reduced and beneficial effects of NO• be enhanced. Such therapies would be useful in the prevention and treatment of many disease processes associated with vascular damage, including hypertension, atherosclerosis, and diabetes.

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