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Oxidative stress and hypertension

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Abstract

Mammalian cells are capable of generating metabolites of oxygen, referred to as reactive oxygen species (ROS) via the action of several enzymes. In vascular cells, ROS are predominantly produced by the NADPH oxidases, uncoupled nitric oxide synthase, xanthine oxidase and by mitochondrial sources. In hypertension, ROS production by these sources is increased, and this not only contributes to hypertension, but also causes vascular disease and dysfunction. ROS production in other organs, particularly the kidney and the centers within the brain, likely participate in blood pressure regulation. Despite the wealth of data supporting a role of ROS in hypertension and other cardiovascular diseases, treatment with commonly employed antioxidants have failed, and in some cases have proven harmful, prompting a reconsideration of the concept of oxidative stress. Within the cell, ROS are produced locally and have important signaling roles, such that scavenging of these species by exogenous antioxidants is difficult and could produce untoward effects. In this article, we consider these tissues and discuss potential new approaches to treatment of "oxidative stress". © 2007 American Society of Hypertension. All rights reserved.
Keywords: NADPH oxidase; tetrahydrobiopterin; nitric oxide; superoxide; Nox enzymes; multidrug resistance protein 1.

A Brief Primer on Reactive Oxygen Species (ROS)

During normal cellular metabolism, several enzymes are capable of transferring electrons from an electron donor to molecular oxygen. These include the nicotinamide adenine dinucleotide phosphate (reduced form) [NADPH] oxidase, xanthine oxidase, mitochondrial electron transport, and, under certain circumstances, nitric oxide (NO) synthase (Figure 1A). The 1-electron oxidation product of oxygen yields superoxide (O_2^-), while a 2-electron reduction of oxygen results in formation of hydrogen peroxide (H_2O_2). These are referred to as ROS, and they can undergo numerous subsequent reactions leading to production of many other ROS. Some of these contain unpaired electrons in their outer electron orbital and are, therefore, considered radicals, while others like H_2O_2, peroxynitrite ($ONOO^-$), and hypochlorous acid do not have unpaired electrons but are oxidizing agents and are, therefore, considered "reactive." The chemistry of these reactions as they pertain to vascular biology and hypertension has recently been reviewed in depth.[1]

Importantly, atherosclerotic risk factors such as hypertension, hypercholesterolemia, diabetes, insulin resistance, aging, and cigarette smoking increase vascular ROS production.[2] This is important because virtually every aspect of atherosclerotic lesion formation is influenced by oxidative events.[3] As examples, ROS cause lipid oxidation, an early event in lesion formation. ROS stimulate expression of adhesion and chemotactic molecules, which promote uptake of inflammatory cells into the vessel wall. ROS also enhance vascular smooth muscle proliferation and hyper-

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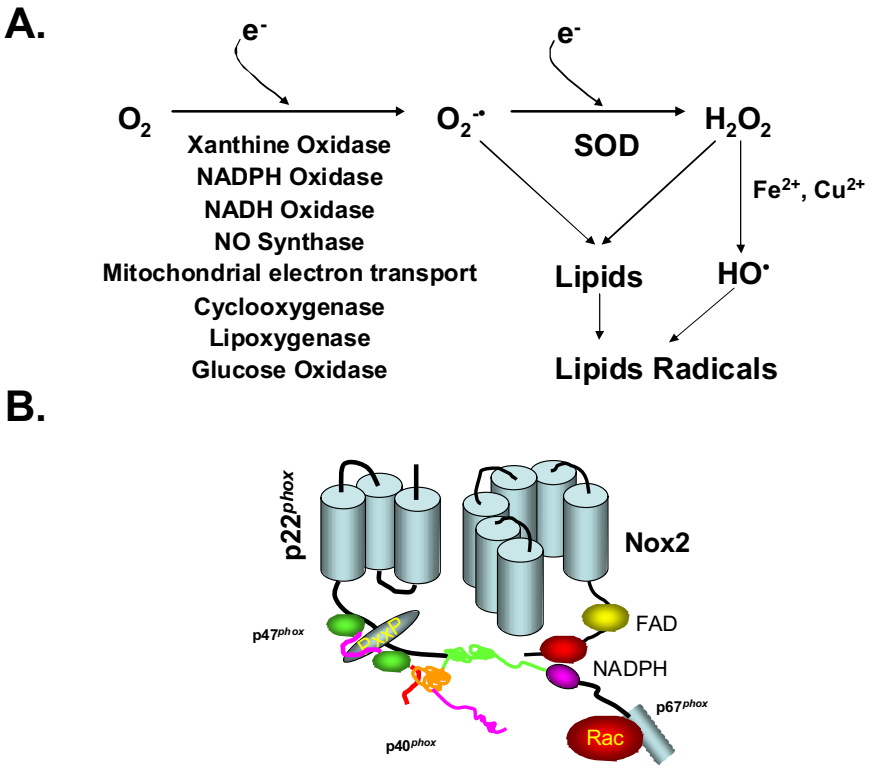

Figure 1. (A) A brief primer on reactive oxygen species. In mammalian cells, numerous enzymes can generate electrons that reduce molecular oxygen to form superoxide ($O_2^{\cdot -}$). A 2-electron reduction of oxygen leads to formation of hydrogen peroxide (H_2O_2). The dismutation of $O_2^{\cdot -}$ by superoxide dismutase (SOD) can also yield H_2O_2. Transition metals are capable of reacting with H_2O_2 to yield the hydroxyl radical ($^{\cdot}OH$). Reactions with lipid form lipid peroxides that are biologically active. These reactive oxygen species, in turn, react with other species to yield numerous other reactive products. (B) Organization of the Nox2-based NADPH oxidase. Nox2, also known as $gp91^{phox}$ and $p22^{phox}$ are membrane-associated subunits. In this figure, $p22^{phox}$ is shown having 3 transmembrane domains. However, other models have predicted that it has from 2 to 4 such domains. In the case of Nox1, other cytosolic subunits, referred to as NoxO1 and NoxA1, can substitute for $p47^{phox}$ and p67*phox*. Nox4 does not require cytosolic subunits, and is constitutively active. NO, nitric oxide.

trophy, key processes in lesion formation and hypertension. ROS increase expression and activity of matrix metalloproteinases, which cause vessel remodeling and plaque rupture in acute coronary syndromes. Importantly, $O_2^{\cdot -}$ reacts rapidly with endothelium-derived NO, leading to formation of the strong oxidant peroxynitrite ($ONOO^-$) and loss of NO "bioactivity." This is, at least in part, responsible for alterations in endothelium-dependent vasodilatation observed in the various disorders mentioned above. The rate constant for the reaction between NO and $O_2^{\cdot -}$ has been estimated to be $6.7 \times 10^9\ M^{-1} \times sec^{-1}$.[4] This is higher than the reaction between $O_2^{\cdot -}$ and the superoxide dismutases (SODs) ($2 \times 10^9\ M^{-1} \times sec^{-1}$), and several orders of magnitude higher than the reaction between $O_2^{\cdot -}$ and the commonly employed antioxidant vitamins including vitamins E and C.[5]

ROS and Hypertension — Role of the NADPH Oxidase

In the past decade, it has become widely recognized that ROS contribute to hypertension. In an initial study, Nakazono et al[6] showed that bolus administration of a heparin binding form of SOD acutely lowered blood pressure in hypertensive rats. We have shown that membrane-targeted forms of SOD lower blood pressure in angiotensin-II-induced hypertension.[7–10] Studies by Schnackenberg and coworkers[11,12] have shown that the SOD mimetic tempol lowers blood pressure and decreases renovascular resistance in hypertensive rats. Tempol also lowers blood pressure and improves acetylcholine-induced vasodilatation in rats with reduced renal mass hypertension.[13]

It appears that the NADPH oxidases are critical sources of ROS in hypertension. These enzymes, also known as the Nox enzymes, are a predominant vascular source of ROS not only because they directly produce ROS, but also because they stimulate other ROS-generating enzymes.[14] The Nox proteins represent the catalytic subunits of the NADPH oxidases, and vary in terms of their mode of activation and need for co-factors.[15] In vascular cells, Nox1 is minimally expressed under basal conditions, but stimuli such as platelet de-

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