Oxidative Stress and Hypertensive Diseases

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KEYWORDS

• Superoxide • Hydrogen peroxide • NADPH oxidase • Vascular • Renal
• Sympathetic nerves • Dendritic cells

KEY POINTS

- Oxidative stress is considered a major mechanism in hypertension.
- Formation of reactive oxygen species contributes to dysfunction in the vasculature, the kidney, and the central nervous system.
- Recent evidence supports a role of reactive oxygen species in inflammation in hypertension.

INTRODUCTION

It has become clear that reactive oxygen species (ROS) contribute to the development of hypertension via myriad effects. ROS are essential for normal cell function; however, they mediate pathologic changes in the brain, the kidney, and blood vessels that contribute to the genesis of chronic hypertension. There is also emerging evidence that ROS contribute to immune activation in hypertension. In this review, we discuss these events and how they coordinate to contribute to hypertension and its consequent end-organ damage.

REACTIVE OXYGEN SPECIES

ROS are formed by oxidation-reduction reactions in which one molecule is reduced by removal of an electron, which is then transferred to a recipient molecule. ROS can be divided into 2 major groups: free radicals and nonradical derivatives. Free radicals possess an unpaired electron in their outer orbital, which makes them highly reactive. These include superoxide ($O_2^{\cdot -}$), the hydroxyl radical ($OH^{\cdot}$), lipid peroxy-radicals

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($LOO^{\cdot}$) and alkoxy-radicals ($LO^{\cdot}$). Nitric oxide (NO) is also a free radical, and often is referred to as a reactive nitrogen species. Nonradical ROS include hydrogen peroxide (H_2O_2), peroxynitrite ($ONOO^-$), hypochlorous acid ($HOCl^-$), and reactive carbonyls. These do not possess unpaired electrons, and are more stable with a longer half-life but have strong oxidant properties.

PHYSIOLOGIC ROLES OF REACTIVE OXYGEN SPECIES

Although originally considered toxic by-products of cellular metabolism, ROS are now recognized to have signaling roles that are critical for normal cell function, including proliferation, differentiation, aging, host defense, and repair processes. Recent studies show that ROS, including H_2O_2, may drive prosurvival signaling and protect from the aging process.[1] As a part of innate immunity, ROS not only contribute to host defense via respiratory bursts in phagocytes, but also by signaling chemotaxis of inflammatory cells to sites of infection or injury. Related to this, ROS also participate in tissue repair and remodeling by inducing expression of matrix metalloproteinases (MMPs).[2] These responses, which are vital for normal cell function, become exaggerated in disease states and promote pathologic processes.

OXIDATIVE STRESS

The term oxidative or oxidant stress traditionally refers to an imbalance between the production of ROS and antioxidant defenses. This can lead to an increase in ambient levels of ROS that can damage various cellular components, including DNA, proteins, and lipids. This traditional definition of oxidant stress has been modified, because it is now clear that such an imbalance might be localized to subcellular compartments, such the mitochondria, the nucleus, or localized at the cellular membrane. Localized alterations of ROS production in the mitochondria can affect energy homeostasis, whereas localized ROS production in the nucleus can affect transcriptional events and epigenetic control. Extracellular ROS can participate in outside in signaling and affect cellular function.

MAJOR REACTIVE OXYGEN SPECIES MOLECULES

Superoxide Radical

Superoxide, produced by 1-electron reduction of molecular oxygen, can act both as an oxidant and as a reductant in biological systems, depending on the redox potential of the molecule with which it is reacting. Superoxide is important, as it serves as the progenitor for many other biologically relevant ROS, including hydrogen peroxide (H_2O_2), the hydroxyl radical ($HO^{\cdot}$), and peroxynitrite ($OONO^-$), which forms on reaction of $O_2^{\cdot -}$ with NO.

Hydrogen Peroxide

Hydrogen peroxide is formed by dismutation of $O_2^{\cdot -}$, which can occur either spontaneously or can be catalyzed by the superoxide dismutases (SODs). In contrast to $O_2^{\cdot -}$, H_2O_2 is relatively stable under physiologic conditions. Because it is uncharged and lipophilic, H_2O_2 can readily diffuse across membranes and thus can react with targets in organelles and cells apart from where it is formed. In this regard, H_2O_2 has been implicated as a signaling molecule that can, among other actions, promote vasodilatation, activate gene transcription, modify phosphatase activity, and activate other sources of ROS. As part of the antioxidant defense mechanisms, catalase and glutathione peroxidase (Gpx) can further reduce H_2O_2 to H_2O. Myeloperoxidase catalyzes