Reactive Oxygen Species: Roles in Blood Pressure and Kidney Function

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Introduction
Reactive oxygen species (ROS) are a family of short-lived, highly reactive byproducts of oxygen (O2) metabolism. They include superoxide anion (O2•-), hydroxyl anion (OH•), and hydrogen peroxide (H2O2). O2•- bioinactivates nitric oxide (NO), thereby diminishing its half-life, but leads to the generation of the highly pro-oxidant molecule, peroxynitrite (ONOO•). ROS are generated by O2 metabolism in mitochondria and by specific oxidases, including NADPH oxidase, xanthene oxidase (XO), and arachidonic acid (AA)-metabolizing enzymes [1]. Nitric oxide synthase (NOS) also generates O2•-, especially during suboptimal availability of its substrate, L-arginine, or its cofactor, tetrahydrobiopterin (BH4) [2]. Some established mechanisms whereby ROS may promote vascular smooth muscle cell (VSMC) contraction and proliferation, together with new information published in the past year, are reviewed in this manuscript and summarized in Figure 1. These established mechanisms include the stimulation of cyclooxygenase by ONOO•. The ensuing metabolism of AA to endoperoxides including prostaglandin (PG) H2, the stimulation of thromboxane synthase (TxA2-S) to generate TxA2, and the generation of isoprostanes from AA that act on thromboxane receptors (TP-R) in VSMCs induce contraction and proliferation. O2•- inactivates prostacyclin synthase (PGI2-S) to reduce the vasodilator (PGI2). O2•- enhances generation of endothelin 1 (ET1) that acts on type A receptors (ETA-R). Endothelium-derived contraction factors (EDCFs) include cyclooxygenase-dependent products that activate TP-R, ET1 that activates ETA-R, and ROS themselves, including O2•-H2O2 [1]. Importantly, O2•- can enhance contractions by diminishing endothelium-derived relaxing factor (EDRF)-NO. This review focuses on studies published in the past year on the role of ROS in the regulation of blood pressure and kidney function in experimental models of hypertension.

Assessment of Reactive Oxygen Species
O2•- interacts nonenzymically with free AA to form a family of isoprostanes including 8-epi prostaglandin (PG)F2α (8-epi), which have been used widely to assess oxidative stress. However, 8-epi also can be formed enzymically by cyclooxygenase. In a study of isolated glomeruli, Klein et al. [3•] induced oxidative stress and detected only a minor increase in isoprostanes, whereas induction of cyclooxygenase-2 led to a large increase in 8-epi and isoprostanes. Thus, caution is required in using renal generation or excretion of 8-epi or isoprostanes as faithful indices of oxidative stress.

Vascular Mechanisms
Schnackenberg et al. [4•] used the nitroxide, tempol, which is a permeant superoxide dismutase mimetic, to study the role of O2•- in mediating contractile responses of the rabbit isolated perfused afferent arteriole to the TxA2 mimetic, U-46,619. The contractile responses were enhanced by blockade of NOS with L-nitroarginine methyl ester (L-NAME) and blunted by metabolism of O2•- to H2O2 by tempol [5]. Thus, agonist-induced generation of...
O$_2^•$ and NO can provide potent regulation of contractile responses in renal vessels.

Usui et al. [6] reported that rats given L-NAME develop oxidative stress and increased angiotensin converting enzyme (ACE) activity in the aorta. Administration of antioxidants for 7 days obviated the L-NAME-induced oxidative stress and blocked the increase in ACE activity. This implicates O$_2^•$ in the activation of ACE. Kitamoto