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abstract

Hypertension in the 21st century - molecular mechanisms to novel therapies

Despite the enormous advances in antihypertensive-drug therapy in the 21st century, the number of people with uncontrolled hypertension has continued to rise. Hypertension affects 30% of N. Americans and up to 60% of adults in other countries. Reasons underlying this paradoxical situation relate, in part, to the fact that exact molecular mechanisms underlying the pathophysiology of hypertension still remain elusive. Factors that have been implicated include altered signaling through G protein-coupled receptors, the renin-angiotensin system, innate immunity, vascular inflammation and remodeling, vascular senescence and aging and developmental programming. Common to these systems is NADPH oxidase-derived reactive oxygen species (ROS). ROS play a major role as intracellular signaling molecules to regulate normal biological cellular responses. In pathological conditions, loss of redox homeostasis contributes to vascular oxidative damage. Recent evidence indicates that specific enzymes, the Nox family of NADPH oxidases, have the sole function of generating ROS in a highly regulated fashion in physiological conditions, and that in disease states, hyperactivation of Noxes contributes to oxidative stress and consequent cardiovascular and renal injury. The Nox family comprises seven members, Nox1-Nox7. Nox1, Nox2 (gp91phox-containing NADPH oxidase), Nox4 and Nox5 have been identified in the cardiovascular-renal systems and have been implicated in the pathophysiology of cardiovascular and renal disease. This has evoked considerable interest because of the possibilities that therapies targeted against specific Nox isoforms to decrease ROS generation or to increase nitric oxide availability or both may be useful in minimizing vascular injury and renal dysfunction, and thereby prevent or regress target organ damage associated with hypertension. Here we will focus on some of these strategies as potential new therapies to manage hypertension in the 21st century.