Oxidative stress has been associated with cardiovascular disease and the development of hypertension in both humans and in animal models. Antioxidant therapy has been successful in ameliorating disease in animals, but the results from human studies have been largely disappointing. Despite these negative results, a wealth of evidence suggests that oxidative stress is involved in the development of cardiovascular disease both in humans and animal models. Because global attenuation of cellular reactive oxygen species (ROS) may not be advantageous, more recent therapeutic strategies target specific subcellular sources of oxidative stress. Most studies implicate plasmalemmal membrane-bound NADPH oxidase as a key mediator of ROS generation in cardiovascular disease. However, in the current issue of Circulation Research, Dikalova et al demonstrate that specific attenuation of mitochondrial derived oxidants prevents the development of angiotensin II–induced hypertension in the mouse. Perhaps more interesting is the mechanism: inhibition of a mitochondrial ROS-triggered activation of NADPH oxidase, interrupting a vicious cycle of ROS production. The novel approach of targeting the initiating source of ROS (mitochondria) to prevent accelerated oxidant production may hold more promise for humans by eliminating pathological but not homeostatic sources of ROS.

Oxidative Stress and Antioxidant Therapy in Hypertension

Seminal observations by Harrison et al showed evidence of increased oxidative stress within the systemic vasculature in an Angiotensin II–induced rat model of hypertension, piquing interest in a possible etiologic role for ROS in this condition. In animal models, stimulating ROS production can induce hypertension, whereas treatment with a variety of antioxidants including vitamin C and E, or targeted inhibition of enzymatic oxidant production, can reduce blood pressure. Hypertensive patients demonstrate increased NAD(P)H oxidase activity with elevated levels of hydrogen peroxide in plasma. Antioxidant treatment leads to enhanced vasodilation in both forearm and coronary arteries of human hypertensive subjects, indicating a functional vasomotor effect of oxidants. Despite a compelling rationale and supportive animal studies, clinical studies testing the effects of antioxidant treatments for hypertension have been disappointing. Chronic treatment of individuals at high risk for cardiovascular disease with varying doses of vitamin C, E, and β-carotene, either alone or in combination, have failed to reduce blood pressure, improve cardiovascular risk, or reduce mortality rates. Although the reasons for this ineffectiveness in humans are not known, it could relate to abrogation of both pathological and beneficial (physiological) ROS. This provides rationale for the theoretical benefit of targeted antioxidant therapies.

Mitochondria as the Source of Free Radicals in Hypertension

The present study suggests a novel role for mitochondria as the initiating source of free radicals in response to angiotensin II, with NAD(P)H oxidase secondarily activated by mitochondrial ROS. Pathways have been established through which NADPH oxidase generation of ROS can stimulate mitochondrial ROS, but now the reverse must be entertained as a key pathological process creating a potential loop for feed-forward ROS generation. Interestingly, the Framingham Heart Study demonstrated a maternal influence on blood pressure, suggesting that hypertension may be transferred to offspring via inheritance of maternal mitochondrial DNA. The mitochondrial genome is highly conserved, reflecting its critical role in cell survival; however, Dikalova et al now provide a potential explanation for this maternal heritability of blood pressure by linking it to systemic oxidative stress and inappropriate activation of NAD(P)H oxidase in hypertension.
Organ Systems: What Is the Site of Action for Mitochondria-Derived ROS? 

Both the current study and prior work indicate that systemic scavenging of mitochondrial ROS attenuates hypertension. However, these approaches provide no insight into the organ system(s) responsible for mitochondrial ROS-induced pathology. The current study focuses on vascular endothelial cell mitochondria as the source of pathological levels of superoxide, which in turn inactivate nitric oxide, resulting in arterial vasoconstriction and hypertension. However, ROS-induced hypertension may involve mitochondria from other organ systems including the brain, the kidney, and the immune system.

In Guyton's classic model, development of hypertension requires that the renal pressure natriuresis mechanism be reset to a higher level of arterial pressure. In keeping with the data of Dikalova et al., such a change could occur in response to oxidative stress within the renal vasculature. In this scenario, inactivation of nitric oxide and vasoconstriction within the kidney afferent arterial system would reduce distal renal arteriolar pressure, thereby invoking reflex mechanisms to elevate systemic arterial pressure to stimulate the same level of renal Na^+ excretion. In addition to renal vasomotor alterations, Dikalova's model might also operate via a direct renal parenchymal effect. In the resting state, the kidney is second only to the heart in terms of oxygen consumption per gram of tissue. Tubular epithelia of the medullary thick ascending limb nephron segment have a mitochondrial density similar to that of cardiac myocytes (40% to 50% of cell volume). Tubular ROS are elevated in hypertensive rat models and enhance Na^+ reabsorption via both inactivation of nitric oxide and direct effects on membrane Na^+ transporters. Thus, alterations in mitochondrial ROS production could plausibly alter renal pressure natriuresis and promote the development or maintenance of hypertension.

Mitochondria-targeted antioxidants might also act centrally at sites important for blood pressure regulation, especially circumventricular organs. In a recent study, Chan et al. demonstrated that the activity of various components of the electron transport chain are reduced in the spontaneously hypertensive rat, resulting in elevated mitochondrial ROS production within the rostral ventrolateral medulla (RVLM). Importantly, direct administration of the mitochondrial antioxidant coenzyme Q10 into the RVLM significantly reduced mitochondrial ROS production and blunted hypertension in the spontaneously hypertensive rat. Direct RVLM administration of the ETC inhibitors rotenone or antimycin A stimulated mitochondrial ROS production and produced hypertension.

Intrakraniobaseventricular administration of angiotensin II produces hypertension in part by stimulating central mitochondrial ROS production. An interesting mechanistic difference exists between the present study and that by Chan et al. Chan observed that NAD(P)H oxidase stimulated mitochondrial ROS production through a ROS-induced-ROS release mechanism. This conclusion was based on indirect evidence that within the RVLM of spontaneously hypertensive rats, overexpression of both superoxide dismutase 1 and catalase, which are primarily localized to the cytoplasmic compartment, restored mitochondrial ETC activity and prevented hypertension in the spontaneously hypertensive rat. In contrast, Dikalova reports mitochondrial ROS as the initiating stimulus. Both observations might be explained by the bidirectional nature of the ROS amplification system that initiates the vicious cycle described in the present study.

In addition to neurogenic and renal pathways of hypertension, the immune system has also been implicated in the development of hypertension, possibly as a common mechanism for end-organ involvement. T cells have been shown to be required for full development of hypertension to angiotensin II in mice. Although it has been suggested that infiltration of T cells into the kidney or systemic vasculature with release of cytokines or other paracrine factors such as angiotensin II may be of importance, how T cells modulate the hypertensive phenotype remains incompletely understood.

The current study provides strong evidence that whatever the mechanism, a mitochondrial element is of critical importance in multiple animal models of hypertension (angiotensin II and DOCA salt). Further studies are warranted to determine the critical organ(s) in which mitochondrial ROS generation leads to the development of human hypertension. Involvement of multiple sites could reveal systemic mitochondrial antioxidants as a powerful multipronged yet subcellularly focused approach to treating hypertension.

Role of Hydrogen Peroxide as a Mediator of Hypertension

In the present study, treatment with superoxide dismutase 2 or 1-Oxyl-2,2,6,6-tetramethyl-4-hydroxypiperidine (TEMPOL) reduced the ambient levels of H_2O_2, the presumed mediator of NADPH oxidase activation via c-Src. This finding is unexpected because the direct effect of either treatment should be an elevation in H_2O_2 production. Although no explanation is provided, it is possible that damage to mitochondrial ETC elements by superoxide is responsible for the majority of H_2O_2 produced. In this case, rapid conversion to hydrogen peroxide reduces the superoxide-induced damage and attenuates overall mitochondrial ROS production.

Conclusion

The study by Dikalova et al provides evidence that mitochondrial dysfunction and ROS production are critical to the development hypertension in both the angiotensin II and DOCA salt mouse models. Mitochondrial targeted antioxidants such as mitoTEMPOL are effective in treating hypertension in animals and provide renewed hope that through their focused site of action, this class of chemical agents may be more effective than traditional global antioxidants in treating hypertension in humans.
Sources of Funding
The authors acknowledge support from NHLBI (HL094971, HL080704, HL29587).

Disclosures
None.

References

Key Words: vascular | superoxide | therapy | hydrogen peroxide | mouse | editorial
Resurrecting Hope for Antioxidant Treatment of Cardiovascular Disease: Focus on Mitochondria
Paul M. O'Connor and David D. Gutterman

Circ Res. 2010;107:9-11
doi: 10.1161/CIRCRESAHA.110.223321

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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