Editorial Commentary

Linking Oxidative Stress, the Renin-Angiotensin System, and Hypertension

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The involvement of oxidative stress in hypertension and in renal and cardiovascular diseases has been intensely studied since the early 1990s. Oxidative stress has been implicated in chronic kidney disease, endothelial damage, atherosclerosis, and myocardial disease, whereas the administration of antioxidants, such as Tempol and N-acetyl cysteine, has been shown to exert a protective effect against these conditions. Nevertheless, the molecular mechanisms and intracellular pathways involved in the pathogenic effects of oxidative stress are still far from established.

Several studies suggest that one of the mechanisms linking oxidative stress and hypertension is represented by activation of the renin-angiotensin-aldosterone system (RAAS). The relationship between the RAAS and the pathogenesis of hypertension is well known. Activation of the RAAS takes place through the angiotensin (Ang) II type 1 (AT1) receptor, which promotes renal and systemic vasoconstriction and enhances tubular sodium reabsorption directly at the proximal tubule and indirectly through the action of aldosterone at the distal nephron. These actions minimize contraction of the extracellular volume and hypotension in a context of fluid loss and dehydration but may lead to the development of hypertension when set in motion under pathophysiologic conditions.

A number of recent observations have revealed a very close relationship between oxidative stress and RAAS over-activation. In vitro experiments have shown that Ang II stimulates mesangial cells to produce superoxide anions, whereas inhibition of the RAAS was shown to diminish oxidative stress in several pathological conditions. In addition, the nuclear factor-κB transcription factor, a key player in inflammation, can be activated by either oxidative stress or binding of Ang II to the AT1 receptor, further suggesting the existence of a link between these processes.

Recent studies by Banday and Lokhandwala contributed to extend our knowledge of the intracellular mechanisms by which oxidative stress and the RAAS can interact to promote sustained blood pressure elevation. In the first of these studies, these investigators showed that rats treated chronically with L-buthionine sulfoximine (BSO), an oxidant agent, developed hypertension and showed increased abundance of the AT1 receptor at the proximal tubules. Moreover, Ang II binding to the AT1 receptor not only was enhanced in BSO-treated rats but also evoked more intense activation of phospholipase C and intracellular accumulation of inositol trisphosphate. Most interestingly, activation of AT1-mediated mitogen-activated protein kinase, Na-KATPase, and Na/H exchanger 3 (NHE3) was enhanced in proximal tubular cells of rats that had been pretreated with BSO. These observations suggested that oxidative stress sensitized proximal tubular cells to the effects of Ang II, exacerbating the sodium-retaining effect evoked by the peptide. Because the expression of the AT1 receptor itself was also increased, these studies suggested the existence of a positive feedback loop, which would further intensify the effect of oxidative stress on blood pressure.

In a study published in the present issue of Hypertension, Banday and Lokhandwala extended their previous observations by investigating more directly the intracellular pathways through which oxidative stress might interact with Ang II to promote exaggerated sodium transport at the proximal tubule. They showed once again that oxidative stress induced by chronic BSO administration leads to increased abundance of the AT1 receptor and of the NHE3 exchanger in proximal tubular cells and that these changes no longer occur when rats are pretreated with the antioxidant Tempol. They showed, in addition, that these phenomena can be prevented by treatment with the AT1 receptor blocker candesartan, suggesting that Ang II binding to its receptor is required for the effects of oxidative stress to become manifest. They proceeded by demonstrating that the cellular effects of oxidative stress involved an increase of intracellular calcium concentration, because they were mimicked by exposure of these cells to a calcium ionophore, A23187. Accordingly, the stimulatory effect of BSO treatment on NHE3 abundance was no longer detected when proximal cells were previously exposed to A23187, thus becoming saturated with calcium. Conversely, exposure of these cells to a calcium chelator drastically decreased NHE3 abundance, indicating that the effect of oxidative stress on this transporter was indeed mediated by changes in cytosolic calcium concentration. Banday and Lokhandwala went on to show that the effect of BSO on NHE3 requires phosphorylation of calmodulin, which, in turn, depends on AT1-induced phosphorylation of the Janus kinase 2, and that calmodulin and Janus kinase 2 then form a molecular complex that interacts with NHE3 and increases the availability of this transporter at the luminal membrane. The intricate sequence of events proposed by Banday and Lokhandwala to explain their findings is...
illustrated in a schematic and simplified manner in the bottom part of Figure.

The pathophysiologic and clinical implications of these studies may transcend the important effects of oxidative stress on proximal sodium reabsorption and blood pressure levels. The consequences of activating the RAAS and the intracellular mechanisms described in these studies, notably the Janus kinase 2 and mitogen-activated protein kinase pathways, are not limited to stimulation of sodium transport. These systems, along with several other signaling pathways, such as the nuclear factor-κB cascade, are deeply involved in the pathogenesis of chronic inflammation, which, in turn, plays an essential role in the development of atherosclerosis, myocardial fibrosis, and chronic kidney disease (Figure). Because the RAAS can be locally activated in all of these tissues, a single set of mechanisms (the interaction between Ang II and oxidative stress) could at one time promote hypertension and the development of cardiovascular and renal damage, which provide a plausible explanation as to why all of these abnormalities so often coexist.

An obvious corollary of the pathogenic mechanisms unraveled by these studies is that, as these findings are confirmed, effective antioxidant therapy, by pharmacological means and/or by substantial changes of nutritional habits, can definitively become part of our arsenal against cardiovascular and renal disease, thus contributing to fight one of the main causes of morbidity and mortality of our time.

Figure. Schematic and simplified representation of the interactions between oxidative stress and the renin-angiotensin system to generate hypertension (bottom) and inflammation (top), which, in turn, interact to promote cardiovascular and kidney disease.

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Disclosures
None.

References