Angiotensin II and Oxidative Stress: An Unholy Alliance

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Angiotensin II (AngII) is a vasopressor agent, but is acute vasoconstriction all there is to the hypertensinogenic action of AngII? In a seminal study from decades ago Dickinson et al. (1) demonstrated the slow pressor action of AngII; the rabbit infusions of AngII that initially were pressor induced progressively larger rises in BP. What are the implications of this observation? In many forms of hypertension, plasma renin activity or AngII concentrations are within the normal range, yet BP is normalized by administration of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers. As a sensible explanation for this paradox (2), he proposed that although AngII concentrations are within the normal range, they may still be inappropriately high if the response to AngII is increased. He also reported that the slow pressor response to a low dose of AngII by intravenous infusion is accompanied by signs of oxidative stress, as suggested by increased $F_2$ isoprostane levels.

In this journal Kawada et al. (3) reported last year that subpressor doses of AngII initially increased GFR and FF (consistent with increased postglomerular resistance), but later caused a rise in RVR with a fall in GFR (consistent with increased preglomerular resistance). These findings pointed to the preglomerular vessel as the smoking gun.

Why is the preglomerular vessel such a hot candidate for a hypertensinogenic action? In a series of elegant studies, Danish investigators had shown that luminal narrowing of the afferent arteriole by eutrophic remodeling was correlated with (4) and even predictive of (5) hypertension in the SHR rat, possibly causing missensing by the baroreceptor and providing an inappropriate signal for renin release. Thus preglomerular arterioles may potentially play a crucial role, and this notion is further supported by the observation that AngII causes vasoconstriction of these vessels before the vascular resistance in other vascular beds increases and before systemic BP begins to rise (3,6).

These considerations prompted Wang et al. (7) to perform the present study that is reported in this issue of JASN. The results document that the slow pressor response to AngII is accompanied by increased cortial NADPH– and NADH oxidase–dependent generation of superoxide anions and by mRNA expression of p22$^{phox}$, and a constituent of NADPH oxidase nitric oxide synthase–dependent vasorelaxation was decreased, presumably by scavenging of NO, i.e., reduction of the bioavailability of NO as a result of its transformation into peroxynitrite. Conversely, AngII-induced contraction was increased, despite diminished expression of mRNA for the AT$_1$ receptor. The functional relevance of these findings was indicated by the finding that the superoxide dismutase mimetic tempol diminished the above abnormalities, similar to what had been shown in afferent arterioles in another model of increased oxidative stress, i.e., diabetes mellitus (8). Furthermore, another study (9) had previously shown that tempol reduced overall vascular resistance in the kidney of AngII-infused rats, which had caused a striking increase in superoxide production.

Is the link between AngII and oxidative stress unique to the preglomerular arteriole, or can the findings be generalized to other organs and other forms of hypertension? Is chronic AngII-induced vasoconstriction generally linked to ROS?

Increased oxidative stress had convincingly been shown in a paradigm of a high-renin/high-angiotensin state, i.e., renovascular hypertension in animals (10) or humans (11,12). The study by Higashi et al. (12) is of particular interest. They compared patients with renal artery stenosis before and after angioplasty. Impaired endothelium-dependent vasodilatation as well as increased markers of oxidative stress (urinary 8-hydroxy-2'-deoxyguanosine, malondialdehyde-modified LDL) were found before angioplasty and were abrogated by the intervention. This finding is in line with experimental studies in vascular smooth muscle cell (VSMC) cultures (13), including human VSMC (14), and studies in the kidney of ren2 rats, which overexpress human renin and overexpress the NADPH oxidase constituents Nox 1 and Nox 4 (15).

The hypertensinogenic effect of reactive oxygen species (ROS) extends beyond the AngII infusion model. For instance in the kidney of the SHR rat, all the main components of the NADPH oxidase are overexpressed even before the onset of hypertension, particularly in the vasculature, the macula densa, and the distal nephron (16). Furthermore, hypertension in the subtotally nephrectomized rat was markedly attenuated by the superoxide dismutase mimetic tempol, pointing to an important causal role of endothelial cell dysfunction as a consequence of oxidative stress (17,18).

A particularly elegant demonstration of the role of the ROS in the BP response to AngII was provided by studies in p47$^{phox}$ knockout mice (i.e., animals with deficient synthesis of NAD(P)H [19]) and in mice overexpressing human superoxide dismutase, (i.e., animals with excessive breakdown of ROS...
It is therefore of note that AngII infusion increased heme oxygenase (HO) expression on the mRNA and protein level in the kidney, possibly as a negative feedback exerting a renoprotective effect (22). The overexpression of the isoenzyme HO-1 occurred in the proximal tubule (23).

The effect of AngII on ROS in the kidney is mediated via AT1 receptors, while AT2 receptors mediate strong protective effects with decreased expression of p22phox (24) reminiscent of the divergent effects of AT1 and AT2 receptors in the coronary microcirculation (25).

Apart from mediating the vasomotor effects of AngII, ROS are also involved in nonhemodynamic effects of AngII. Upon stimulation with AngII, a peroxide scavenging deficit and susceptibility to cell death was recently shown in proximal tubular cells overexpressing glia maturation factor beta and activated by proteinuria (26). AngII-induced apoptosis of mesangial and proximal tubular cells (27,28) is also associated with increased generation of ROS.

In view of the recent interest in the AngII-independent role of aldosterone on progression (29), it should also be mentioned that the aldosterone receptor antagonist spironolactone partially corrected AngII-induced structural and functional abnormalities in resistance vessels and, at least partially, abrogated activation of the NADPH oxidase (30).

Conversely, estrogens that are thought to be vasoprotective and renoprotective diminish AngII-induced ROS production and stimulate superoxide dismutase isoenzyme activity in VSMC (31). In endothelial cells, they also increase the expression of NADPH oxidase and NOS (32).

Although the interest of the nephrologists is focused on the kidney, it is worth mentioning that AngII exerts similar effects in nonrenal tissues as diverse as cerebral arterioles (33), heart (particularly in the genesis of left ventricular hypertrophy [34]), or liver (35). Of considerable clinical relevance is the role of AngII-induced ROS in atherogenesis (36). This possibly explains the BP-independent beneficial effect of ACE inhibitors and angiotensin receptor blockers on cardiovascular events.

From a clinical perspective, the potentially most exciting aspect in the study of Wang (7) is the observation that these adverse effects of AngII could be abrogated (at least partially) by the superoxide dismutase mimetic tempol. Although tempol is currently not available for therapeutic use, this observation raises the more general issue of the extent to which the adverse effects of ROS, whether provoked by AngII or otherwise, are susceptible to therapeutic intervention. Vasoconstriction induced by infusion of AngII could be attenuated by co-infusion of ascorbic acid (37). In experimental studies, ascorbic acid (vitamin C) and alpha-tocopherol (vitamin E) improved vascular structure and function and also prevented the progression of hypertension in the stroke-prone SHR rat. This effect was associated with decreased activation of vascular NADPH oxidase (38). Comparable observations with high-dose vitamin E were also made in the subtotally nephrectomized rat (39). Furthermore, in the AngII-infused Sprague-Dawley rat, docosahexaenoic acid, which activates the PPARα receptor (peroxisome proliferator–activated receptor), reduced BP and improved endothelial dysfunction (40). An antioxidant-enriched diet improved hypertension and inflammatory changes in the renal interstitium of the SHR rat (41). Even the well-known beneficial effects of ACE inhibitors or angiotensin receptor blockers on arterial endothelial cell dysfunction in patients with coronary heart disease are associated with reversal of oxidative stress, mediated in part by EC superoxide dismutase (42). Finally an intervention well known to the nephrologists, low-salt diet, was shown to abrogate increased superoxide and hydrogen peroxide production in AngII-infused rats (43).

We hope that in due time all these advances in the understanding of ROS as a signal substance, but also as a culprit in the genesis of target organ damage, will lead to novel therapeutic approaches.

References
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See related article, “Role of Oxidative Stress in Endothelial Dysfunction and Enhanced Responses to Angiotensin II of Afferent Arterioles from Rabbits Infused with Angiotensin II,” on pages 2783–2789.