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Forum Review

NADPH Oxidases in the Kidney

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ABSTRACT

NADPH oxidases have a distinct cellular localization in the kidney. Reactive oxygen species (ROS) are produced in the kidney by fibroblasts, endothelial cells (EC), vascular smooth muscle cells (VSMC), mesangial cells (MCs), tubular cells, and podocyte cells. All components of the phagocytic NADPH oxidase, as well as the Nox-1 and -4, are expressed in the kidney, with a prominent expression in renal vessels, glomeruli, and podocytes, and cells of the thick ascending limb of the loop of Henle (TAL), macula densa, distal tubules, collecting ducts, and cortical interstitial fibroblasts. NADPH oxidase activity is upregulated by prolonged infusion of angiotensin II (Ang II) or a high salt diet. Since these are major factors underlying the development of hypertension, renal NADPH oxidase may have an important pathophysiological role. Indeed, recent studies with small interference RNAs (siRNAs) targeted to p22^{phox} implicate p22^{phox} in Ang II-induced activation of renal NADPH oxidase and the development of oxidative stress and hypertension, while studies with apocynin implicate activation of p47^{phox} in the development of nephropathy in a rat model of type 1 diabetes mellitus (DM). Experimental studies of the distribution, signaling, and function of NADPH oxidases in the kidney are described. *Antioxid. Redox Signal.* 8, 1597–1607.

OVERVIEW OF NADPH OXIDASES

NADPH OXIDASES have been studied extensively in phagocytes (4, 5, 35, 71). Analogous enzymes are found in endothelial cells (ECs) and vascular smooth muscle cells (VSMCs). The phagocytic enzyme includes the membrane-associated flavocytochrome subunits Nox-2 (originally termed gp91^{phox}) and p22^{phox} and cytosolic regulatory proteins p47^{phox}, p67^{phox}, p40^{phox}, and the GTPase, Rac1 (35, 61). The cytosolic elements assemble and bind to the flavocytochrome and p22^{phox} to form an active enzyme. There are now recognized to be distinct components of the NADPH oxidase (Nox) family of superoxide ($O_2^{\bullet -}$)-generating enzymes. However, all the NADPH oxidase enzymes described presently contain heme-binding sites on a membrane-spanning region in the N-terminal half and NADPH- and FAD-binding domains in the C-terminal half (35, 61). The regulation of NADPH oxidases has been comprehensively reviewed (4, 5, 28, 35, 38, 71).

Studies of homogenates of rabbit kidney have shown that the predominant source of $O_2^{\bullet -}$ generation in the renal cortex is NADPH oxidase. NADPH-and xanthine-oxidase make equivalent contributions to $O_2^{\bullet -}$ generation in the outer medulla (73).

NADPH OXIDASE COMPONENTS

There are to date descriptions of six homologues of phagocytic Nox-2 proteins that have distinct major sites of expression: Nox-1 (colon), Nox-3 (fetal kidney), Nox-4 (renal cortex), Nox-5 (spleen), Duox-1 (thyroid), and Duox-2 (thyroid). Novel homologues of p47^{phox} and p67^{phox} have been cloned and are designated as p41^{phox} or Nox organizer 1 (NoxO1) and p51^{phox} or Nox activator 1(NoxA1) (6, 63). The catalytic core of the phagocytic NADPH oxidase contains a flavin nucleotide oxidase bound to p22^{phox}. The p22^{phox} also directly interacts with Nox-1 and Nox-4 to induce $O_2^{\bullet -}$ generation (2).

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Nox-1 was originally referred as Mox-1(60). It is expressed in colon epithelium, prostate, uterus, VSMC (7, 37, 60), and kidney cortex (8, 9). Activation of Nox-1 can occur in the presence of NoxO1 and p67^{phox} or p47^{phox} and NoxA1 (6, 63) and requires p22^{phox}.

Nox-3 is expressed in fetal kidney and the inner ear (11). It generates superoxide with p47^{phox} and p67^{phox} and requires p22^{phox}.

Nox-4 was first termed renox since it is expressed heavily in the kidney cortex (21, 59). It is an important oxidase in mouse osteclasts, myocytes (59), rat mesangial cells (23, 59), human embryonic and adult rat kidney cells (21), endothelial cells (1), and mouse VSMCs (18).

DISTRIBUTION OF THE NADPH OXIDASE SUBUNITS IN THE KIDNEY

The kidney has a wide distribution of various NADPH oxidase subunits in its blood vessels, interstitial cells, glomeruli, and tubules (9). Table 1 summarizes reports of the distribution of NADPH oxidase subunits in the kidney.

An early study identified NADPH oxidase components (alpha- and beta- subunits of cytochrome b558 and 54 kDa flavoprotein) in mesangial cells (52). Human glomerular mesangial cells produce ROS and express p22^{phox}, p67^{phox}, and p47^{phox} components of NADPH oxidase (29) and Nox-4 (22, 23). The outer medullary thick ascending limb (TAL) of the loop of Henle of rats expresses p40^{phox}, p47^{phox}, p22^{phox}, and Nox-2 (39). Northern analysis of renal tubular cells in the mouse and pig show expression of p22^{phox} (26). The renal cortex of Wistar and spontaneously hypertensive rats (SHR) have mRNA and protein expression for Nox-2, p22^{phox}, p67^{phox}, and p47^{phox} (8, 9, 34, 79).

Human cultured podocytes generate ROS via NADPH oxidase, and express mRNA for p67^{phox}, p47^{phox}, Nox-2, and p22^{phox} (25). Streptozotocin-induced diabetes in the rat upregulates the mRNA expression for p47^{phox}, p22^{phox}, and Nox-4 in the kidney. Immunohistochemistry localizes these subunits to distal tubular cells and glomerular podocytes (19, 46).

Nox-4 is the predominant Nox isoform expressed in the kidney epithelium (21, 59), where it is distributed to vasculature, glomeruli, mesangial cells, and nephron segments (Table 1). Nox-4 is detected in the renal cortex by *in situ* hybridization and immunohistochemistry (21). It is expressed in proximal convoluted tubule epithelial cells and may be involved in erythropoietin secretion (21). It is expressed in mesangial cells where it mediates Akt/protein kinase B (PKB) expression (23). It is a major Nox isoform expressed in blood vessels (77).

Recently, studies of the renal cortex by RT–PCR and Western blot analysis show the expression of Nox-1, Nox-2, Nox-4 (8, 34), p22^{phox}, p47^{phox}, and p67^{phox} (8, 9). Immunohisto-

TABLE 1. SUMMARY OF REPORTS OF THE CONSTITUTIVE DISTRIBUTION OF NADPH OXIDASE COMPONENTS IN RAT KIDNEY

Site	*Component*	*mRNA*	*Protein*	*Ref #*
Renal cortex*	Nox-1		+	(41)
	p22^{phox}	+	+	(41)
	p47^{phox}, p67^{phox}		+	(41)
	Nox-2, Nox-4		+	(41)
Renal vessels	Nox-2, p22^{phox}		+	(21)
Microvascular	Nox-4	+	+	(21)
endothelium	Nox-4	+	+	(21)
Glomeruli:	p22^{phox}, Nox-4	+	+	(19)
	Nox-2, p22^{phox}, p67^{phox}, p47^{phox}		+	(79)
	Nox-2		+	(3)
• Mesangial	p22^{phox}, p47^{phox}, p67^{phox}	+	+	(29)
	Nox-4	+	+	(23)
• Podocytes	Nox2, p22^{phox}		+	(25)
	p47^{phox}, p67^{phox}		+	(25)
	p67^{phox}		+	(8)
	p47^{phox}		+	(3;9)
Endothelial	p47^{phox}		+	(9)
Interstitial fibroblast	p22^{phox}		+	(3)
Proximal tubule	p22^{phox}	+		(26)
TAL	p40^{phox}, p47^{phox}, p22^{phox}	+		(39)
	Nox-2	+	+	(39)
	p22^{phox}, p47^{phox}, p67^{phox}	+		(9)
Macula densa	p22^{phox}, p47^{phox}, p67^{phox}	+		(9)
DCT	p22^{phox}, p47^{phox}, p67^{phox}	+		(9)
CCD	p22^{phox}, p47^{phox}, p67^{phox}	+		(9)
MCD	p22^{phox}, p47^{phox}, p67^{phox}	±		(9)

+, present; ±, weak; TAL, thick ascending limb; DCT, distal convoluted tubule; CCD, cortical collecting duct ; MCD, medullary collecting duct; *, homogenates of renal cortex.

chemistry localizes these subunits in the renal cortex to specific nephron segments in the TAL, macula densa, apical areas of the distal convoluted tubule, and the cortical and medullary collecting ducts, as well as the renal vasculature and glomeruli (8, 9). p47^{phox} is also localized in the glomerular podocytes and endothelial cells (9), and p22^{phox} in renal interstitial fibroblasts (9).

The p22^{phox} is required for ROS generation from Nox-1, Nox-2, and Nox-4 *in vitro* (2). Mutagenesis studies have identified a proline-rich region at the C terminus on p22^{phox} that is required for its interaction with, and activation of, Nox proteins (33). The p47^{phox} protein acts as a cytoplasmic Nox-2 organizer, and the p67^{phox} as a cytoplasmic Nox-2 activator. The Nox organizer for Nox-1(Nox O1 or p41^{Nox}) and the Nox activator for Nox-1(Nox A1 or p51^{Nox}) are homologous proteins that apparently can fulfill these functions for Nox-1(6, 49, 62, 63). The Nox-4 can function without these cytoplasmic regulators (1, 14, 33, 62). NoxO1 is expressed as four splice variants (12). Activation of p47^{phox} after cell stimulation is inhibited by apocynin. This is followed by a conformational change that exposes an SH3-domain that interacts with p22^{phox} that, in the presence of the small GTPase, rac1, activates Nox-2 (62). In contrast, *in vitro* studies imply that Nox-1 can be constitutively activated by NoxO1 and NoxA1 (62). These concepts derive from cell biology and have yet to be investigated in the kidney.

REGULATION OF NADPH OXIDASE EXPRESSION AND ACTIVITY

NADPH oxidase in the kidney is activated by prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), phorbol 12-myristate 13-acetate (PMA), low density lipoprotein (LDL), arachidonic acid (AA), angiotensin II (Ang II) acting on type I receptors (AT_1-Rs), serum, and platelet-derived growth factor (PDGF) (8, 34, 38, 61, 73, 74).

Cultured human podocytes produce ROS by NADPH oxidases after stimulation with vasoactive hormones and adenosine triphosphate (25). NADPH oxidase activity in the kidney cortex is upregulated by infusion of Ang II (73)and by a high salt diet (34). Nox-1 and p22^{phox} are upregulated by AT_1-Rs, and counteracted by angiotensin type 2 receptors (AT_2-R) (8). Nox-1 is upregulated in rat cultured VSMCs by Ang II, PDGF, and serum (37).

There is extensive regulation of NADPH oxidase in blood vessels. The expression of Nox-4 in VSMC is inhibited by PDGF (18). About 40% of $O_2^{\bullet-}$ generated in mouse VSMCs is blocked by antisense to Nox-4 (18). Nox-4 is downregulated in the kidney cortex by 2 weeks of Ang II infusion at a slow pressor rate via AT_1-R (8). It is also downregulated in rat VSMCs by Ang II, PDGF, and serum (37), but is upregulated by Ang II in VSMCs of rats that are transgenic for human renin genes (77). Some of these discrepancies may relate to the time of exposure since Ang II stimulates Nox-4 expression in VSMCs only for the first 24 h of exposure (42). Nox-4 is the major oxidase in rat aortic ECs. Its activity is comparable to that of activated phagocytes, but can be independent of p47^{phox} and p67^{phox} (1). Rat ECs contain 2,000-fold more mRNA copies for Nox-4 than Nox-2, and no detectable copies for Nox-1, Nox-3, or Nox-5 (1). Antisense to Nox-4 or p22^{phox} reduces $O_2^{\bullet-}$ generation by ECs by 40%, in parallel with a reduction in mRNA for these two genes (1). Ang II upregulates p67^{phox} expression in rabbit aortic periadvential fibroblasts (48) and the mouse aorta (13).

SIGNALING

ROS can act as second messengers for several transcription factors that are implicated in renal disease and hypertension (75), such as nuclear factor-κB (NF-κB), activator protein-1 (AP-1) (54, 64), serine-threonine kinase Akt/PKB (23), and extracellular-signal-related kinases 1 and 2 (ERK1/2) (22, 24). Low concentrations of ROS within the cell can serve as signaling molecules (22, 23, 64). Three pathways that are implicated in the assembly of NADPH subunits are protein kinases, lipid metabolizing enzymes, and nucleotide-exchange proteins that activate the GTPase Rac (35).

NADPH oxidase can be activated by protein kinase C (PKC), which activates p47^{phox} (38). Ang II-induced hypertrophy in VSMCs is mediated by ROS generated by NADPH oxidase (67). ROS generation in VSMCs is biphasic. A rapid first phase is PKC dependent. This is followed by a second phase of activation of c-src, which, in turn, transactivates the epidermal growth factor receptor (EGFR), stimulates phosphatidylinositol-3-kinase (PI3-K), and is mediated by Rac (58). Mice lacking PI3-K gamma have a blunted increase in BP and ROS production with Ang II (70).

Peroxisome proliferator activated receptor (PPAR) alpha gene knockout mice have hypertension, oxidative stress, and enhanced renal NADPH oxidase activity (45). Activation of PPARalpha with clofibrate in DOCA-salt hypertensive mice reduces their BP and renal NADPH oxidase activity. This demonstrates that renal NADPH oxidase is strongly inhibited by PPARalpha.

The mRNA for p47^{phox} in the rat kidney is strongly upregulated by a high dietary salt intake (34). It is modestly reduced by Ang II acting on AT_2-Rs (8, 9). p47^{phox} is required for NADPH oxidase activation during phagocytosis (15) and, in VSMCs, is linked to Ang II-dependent JAK/STAT signaling that underlies proliferation (55).

Oxidases present in VSMCs have a basal activity supported by both NADH and NADPH (38). Overexpression of Nox-1 increases cell growth, hypertrophy, and angiogenesis (60). ROS derived from Nox-4 contribute to oxidative stress in animal models of insulinopenic diabetes mellitus, where they may contribute to renal hypertrophy and fibronectin expression (22). Nox-4 in mesangial cells mediates Ang II-induced protein and extracellular matrix synthesis through activation of Akt and ERK1/ERK2 (22). Oxidative stress increases NADPH oxidase expression and inflammation via activation of NF-κB in renal interstitial cells (44). Ang II induces ROS production and activation of Ras and NF-κB in murine proximal tubular cells. These are major pathways for expression of monocyte chemoattractant protein-1 (MCP-1), whereas in mesangial cells Ang II-induced MCP-1 expression is more dependent upon PKC and the p38 mitogen-activated protein kinase (p38MAPK) pathway (64). Studies in the kidneys of Dahl

salt-sensitive rats show increased phosphorylation of p38 MAPK. Blockade of p38 MAPK phosphorylation with a specific inhibitor, FR-167,653, reduces NADPH oxidase activity, $O_2^{\bullet-}$ generation, and also reduces the proteinuria, glomerulosclerosis, and interstitial macrophage migration (65). Thus, phosphorylation of p38 MAPK is an important signal to NADPH oxidase activity in the hypertensive kidney.

ROLE IN RENAL TUBULAR TRANSPORT, RENAL VASOCONSTRICTION, NEPHROPATHY, AND HYPERTENSION

Studies using dihydroethidium fluorescence microscopy of isolated nephron segments have shown that the thick ascending limb of the loop of Henle (TAL) from the cortex or outer medulla (M) of the rat is the most prominent site for $O_2^{\bullet-}$ generation from NADH (39). Incubation of MTALs with L-arginine decreases Cl^- reabsorption. This is enhanced by tempol but prevented by inhibition of SOD with diethyl- dithiocarbamate. The authors concluded that NO bioavailability in the MTAL is reduced by $O_2^{\bullet-}$, which acts as a physiologic regulator of NaCl transport (47). Further studies by Garvin and colleagues defined the mechanism. $O_2^{\bullet-}$ interacts with high concentrations of NO in MTALs to form $ONOO^-$, which bioinactivates Na^+/K^+ ATPase (68). A critical finding is that increases in $O_2^{\bullet-}$ in the bath of perfused MTALs enhances the luminal $Na^+/K^+/2Cl^-$ transporter that is the major route for NaCl entry into the tubules in the TAL segment (31). Additionally, $O_2^{\bullet-}$ leads to modest inhibition of the luminal K^+ conductance (31). $O_2^{\bullet-}$ in MTALs also stimulates luminal Na^+/H^+ exchange via sodium/hydrogen exchanger 3 (NHE3). This should enhance Na^+ and HCO_3^- absorption (32). Thus, $O_2^{\bullet-}$ in the renal medulla enhances NaCl reabsorption by stimulating Na^+ transport via the luminol $Na^+/K^+/2Cl^-$ co-transporter and the luminal Na^+/H^+ exchanger. This effect may be offset by inhibition of K^+ section in the TAL (which can secondarily limit the activity of the $Na^+/K^+/2Cl^-$ co-transporter) and by inhibition of the Na^+/K^+/ATPase. Further work is required to define the significance of these single nephron studies, and the sources and regulation of $O_2^{\bullet-}$ in the TAL and other nephron segments. In so far as $O_2^{\bullet-}$ enhances NaCl reabsorption in TAL, this could be an important prohypertensive action of $O_2^{\bullet-}$ within the kidney. This tubular action may synergize with the effect of $O_2^{\bullet-}$ to enhance afferent arteriolar reactivity (73) and the tubuloglomerular feedback response to limit NaCl elimination, and thereby contribute to salt-sensitivity and hypertension (75).

The hypertension in various animal models such as the SHR, Ang II slow pressor infusion model, obesity-induced, and deoxycorticosterone acetate (DOCA)/salt-hypertension is dependent on an increased oxidative stress (56, 75, 76). Compared to normotensive WKY, the blood vessels of SHR have a 10-fold increase in the mRNA expression for Nox-2, a diminished response to acetylcholine, and threefold increase in superoxide generation (43).

Several studies have implicated distinct subunits of the NADPH oxidase in hypertension. The rise in systolic blood pressure (SBP) in mice infused with pressor doses of Ang II at 4 and 7 days is reduced by about 50% in p47*phox* knockout (−/−) mice (36). Cultured ECs from p47*phox* −/− mice have no increase in $O_2^{\bullet-}$ when stimulated with Ang II, but retain expression of endothelial AT_1 receptors (36). The basal SBP and vascular $O_2^{\bullet-}$ generation does not differ between p47*phox* +/+ and −/− mice. Thus, p47*phox* appears to be a requirement for ROS generation with Ang II in ECs and VSMCs of the aorta of the mouse but not for basal ROS levels. This is not anticipated from the finding that Nox-4 is by far the predominant Nox isoform expressed in rat ECs (1) and Nox-4 does not require activation by p47phox (1).

Mice made hypertensive by infusion of Ang II have an increase in $O_2^{\bullet-}$ and in protein expression for p67*phox* and Nox-2 in the thoracic aorta (13). A chimeric peptide, gp91ds-tat, which inhibits p47*phox* association with Nox-2, attenuates the hypertensive response and aortic $O_2^{\bullet-}$ generation in rats infused with Ang II (53). The Nox-2 −/− mouse has a normal basal BP but a reduced renal vasoconstriction with Ang II (27). Lead-induced hypertension in rats is accompanied by oxidative stress and upregulation of Nox-2 (69). Thus, Nox-2, and its interaction with p47*phox* and p67*phox*, are implicated in the vascular ROS response and associated hypertension in several models, including Ang II infusion. However, renal cortical expression of Nox-2, p47*phox*, and p67*phox* in the rat are not upregulated by a prolonged infusion of Ang II (8). Thus, the role of these components in renal responses to Ang II is not clear. On the other hand, renal cortical expression of Nox-2 and/or p47*phox*are increased by salt intake (34) and DM (3). These subunits are implicated in renal ROS generation in the diabetic rat (3).

Overexpression of Nox-1 in mouse VSMCs does not affect basal SBP, but enhances the early rise in SBP with Ang II. This is accompanied by increased aortic $O_2^{\bullet-}$ generation and medial hypertrophy (16). There is upregulation of catalase and manganese superoxide dismutase (Mn-SOD), but downregulation of extracellular superoxide dismutase (EC-SOD) and no change in Cu/Zn, or intracellular superoxide dismutase (IC-SOD) in this Nox-1 overexpressing mouse model. Nox-1 −/− mice have normal basal BP (40). The BP rises normally for the first 5 days of infusion of Ang II, but, by day 14, is lower in the Nox-1 −/− mice. This is accompanied by a 40% reduction in aortic $O_2^{\bullet-}$ production and an improvement in aortic acetylcholine-induced cyclic guanosine monophosphate (cGMP) generation and relaxation responses. This suggests that Nox-1 impairs the endothelium-dependent relaxation factor/nitric oxide (EDRF/NO) response during Ang II (40). This effect of Nox-1 is surprising in view of the finding that Nox-1 is expressed to a negligible degree in ECs (1, 30). Perhaps Nox-1 expressed in VSMCs generates sufficient $O_2^{\bullet-}$ from NADPH oxidase to bioinactivate NO released from ECs.

A high salt diet and Ang II infusion have distinct effects on the regulation of renal cortical gene products for NADPH oxidase or SOD (Fig. 1). Two weeks of high salt diet in the rat increases the renal cortical expression of Nox-2 and p47*phox*, and lowers the expression of intracellular (IC)- or Cu/Zn-SOD and manganese (Mn)-SOD (34). In contrast, 2 weeks of infusion of Ang II activates the AT_1R, which upregulates the expression of p22*phox* and Nox-1, and downregulates extracellular (EC)-SOD (75). Thus, both a high salt diet and an Ang II infusion increase NADPH-dependent $O_2^{\bullet-}$ production and decrease SOD expression in kidney cortex (34, 75). However, these two stimuli regulate distinct components of NADPH oxidase or distinct SOD isoforms. This may explain why oxi-

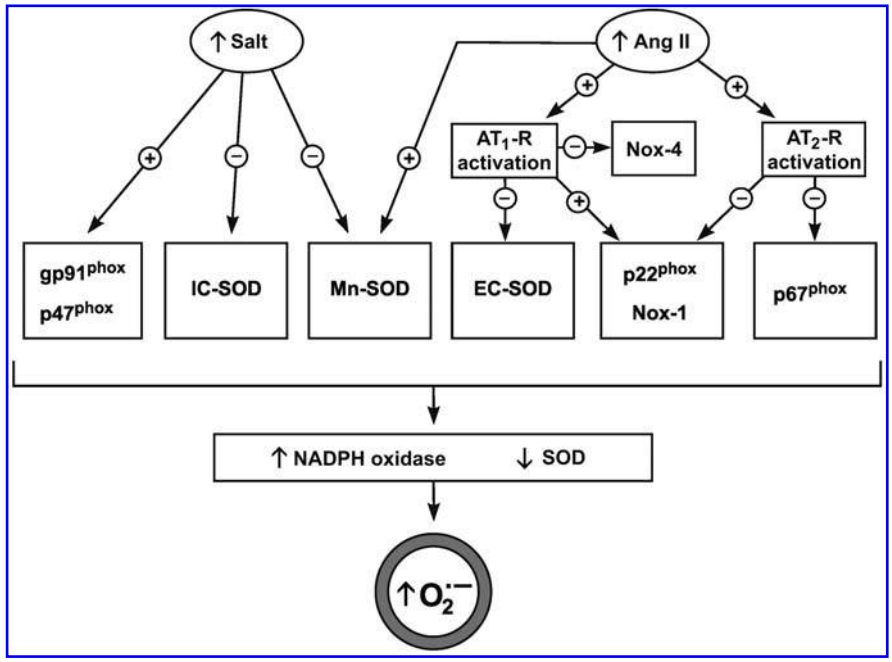

FIG. 1. Flow diagram of the effects of 2 weeks of high salt diet (salt) or of angiotensin II infusion (Ang II) on the expression of NADPH oxidase components and SOD-isoforms in the rat kidney cortex. Redrawn from Ref. 75, with permission.

dative stress accompanies a high salt diet despite a reduction in renin secretion and Ang II levels. This may be quite important since the kidney is implicated in setting the long-term level of BP. An inappropriate salt intake or salt retention, and/or an inappropriate Ang II secretion or Ang II response are the cardinal features of hypertensive states in human and animal models.

An increase in renal cortical $O_2^{\bullet-}$ (*e.g.*, during infusion of Ang II) could decrease the bioavailability of nitric oxide (NO), which should increase the renal cortical vascular resistance (RVR) and mitochondrial respiration. The renal afferent arterioles from rabbits infused with Ang II have oxidative stress, endothelial dysfunction, and enhanced contractility to Ang II, endothelin-1, and thromboxane A_2, which may contribute to the evalated levels of renal vascular resistance (72, 73). Moreover, Sprague–Dawley rats infused with Ang II for 2 weeks have a decreased efficiency of O_2 usage for Na^+ transport in the kidney and an increased NADPH activity and p22*phox* expression in the kidney cortex (74). These effects depend on $O_2^{\bullet-}$ since they are prevented by co-infusion of the permeant SOD mimetic drug, tempol. Interestingly, the rat renal cortex has a decrease in NADPH-dependent $O_2^{\bullet-}$ production at low values of pO_2 (10) (Fig. 2). Thus, the generation of $O_2^{\bullet-}$ by NADPH oxidase in the kidney cortex may be limited by the availability of O_2. Since Ang II infusion reduces the renal cortical pO_2, this may limit further $O_2^{\bullet-}$ generation by NADPH oxidase and thereby protect the kidney cortex from the effects of severe oxidative stress in hypertension. It is likely that the very low level of pO_2 in the renal medulla (~10 mm Hg) places a major constraint on NADPH-dependent $O_2^{\bullet-}$ generation at this site. However, in the outer medulla, xanthine oxidase also contributes significantly to $O_2^{\bullet-}$ generation, and the effects of pO_2 on the activity of this enzyme are not yet clear.

Immortalized lymphoblasts from hypertensive patients have an increased production of ROS and an increased expression of p22*phox* but a maintained expression of Rac2, p47*phox*, p67*phox*, and Nox-2 (50). SHR have increased renal expression of Nox-2 and p22*phox* (23). The BP and p22*phox* expression in the renal cortex of SHR are both reduced by antioxidant treatment (79). The expression of p22*phox* in the aorta (20) and the kidney cortex (8) of rats are both upregulated by Ang II infusion. Prolonged Ang II activates renal cortical p22*phox* via AT_1-R, but downregulates it by AT_2-R (8). Thus, p22*phox* is emerging as an important determinant of increased ROS generation in the blood vessels and kidneys of hypertensive models.

Several polymorphisms have been reported in the promoter and the coding region of *CYBA*, the gene that encodes NADPH oxidase subunit p22*phox*. More recently, a polymorphism in the promoter region of *CYBA* gene ($-930^{A/G}$) has been shown to determine the genetic susceptibility of hypertensive patients to oxidative stress (78).

During Ang II infusion into rats, p22*phox* increases in parallel with Nox-1. Recent studies have examined the specific role of p22phox in the activation of NADPH oxidase in this model. The intravenous injection of a small interference (Si)RNA targeted to p22*phox* (sip22*phox*) into Ang II-infused rats reduces the renal NADPH oxidase activity and reduces the expression

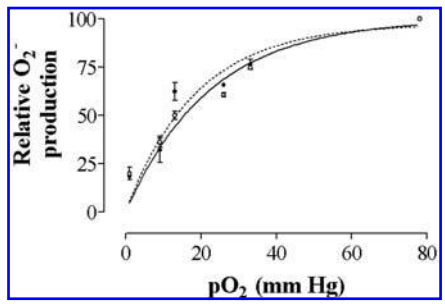

FIG. 2. Regression analysis of NADPH-dependent $O_2^{\bullet-}$ production in kidney homogenates as a function of pO_2. Data are from normotensive WKY rats ($r^2 = 0.90$; *open circles* and *solid lines*) and spontaneously hypertensive rats ($r^2 = 0.87$; *closed circles* and *dotted lines*). Redrawn from Ref. 10, with permission.

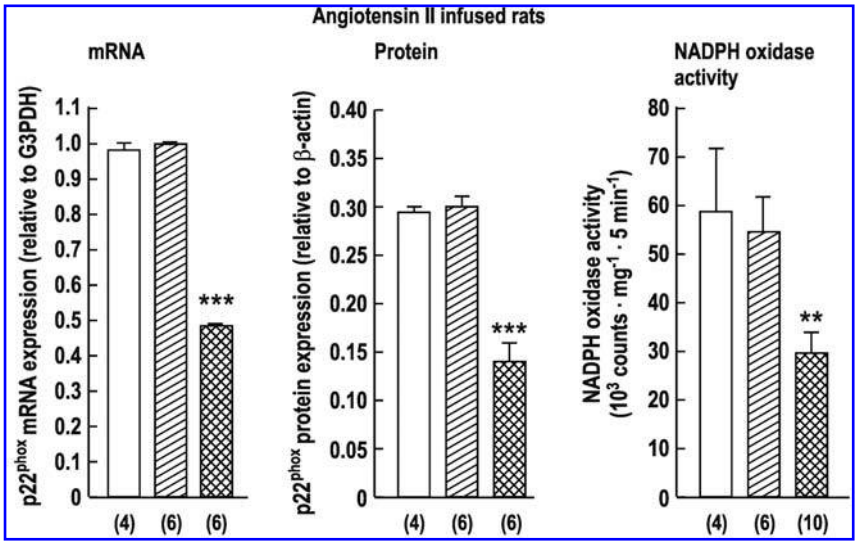

FIG. 3. Mean + SEM values (number of rats) for mRNA and protein expression for p22*phox* and NADPH oxidase activity in the renal cortex of angiotensin II infused rats 72 h after iv injections of vehicle (*open bars*), a control, nontargeted small interference RNA (siCont *diagonal shading*), or an siRNA targeted to p22*phox* (*doubling cross-hatched shading*). Compared to siCont $^{**}p < 0.01$; $^{***}p < 0.005$. Redrawn from Ref. 41, with permission.

of Nox-1, Nox-2, and Nox-4 in the kidney cortex (41). The p22*phox* is required for Ang II-induced $O_2^{\bullet-}$ and H_2O_2 generation and proliferation in VSMCs since these are all blocked by transfection of antisense to p22*phox* (2, 67). An interesting finding is that not only is the expression of p22*phox* apparently required for $O_2^{\bullet-}$ generation in these models, but also p22phox is responsive to ROS generation. Thus, cultured ECs stimulated with thrombin generate $O_2^{\bullet-}$ and have an upregulated p22*phox* mRNA and protein. The expression of p22*phox* is abrogated by diphenyleneiodonium (DPI), which blocks NADPH oxidase or by the antioxidant vitamin C, but is induced by H_2O_2 (17). Likewise, p22*phox* mRNA and protein expression is increased in the kidney cortex of rats infused with Ang II, but the expression is reduced to baseline or below after prevention of oxidative stress by co-infusion of tempol with Ang II (74). Thus, p22*phox* in ECs and the kidney cortex forms a positive feedback loop to sustain or enhance ROS generation.

The intravenous injection of siRNA targeted to p22*phox* in the Ang II-induced rat model of hypertension lowers the MAP, renal cortical NADPH activity, 8-isoprostane excretion, and p22*phox* expression (Figs. 3 and 4) (41). These studies of siRNA to p22*phox* show further that, during infusion of Ang II, renal cortical expression of Nox-1, -2, and -4 all depend on p22*phox*. A summary of some of the effects of Ang II on the ex-

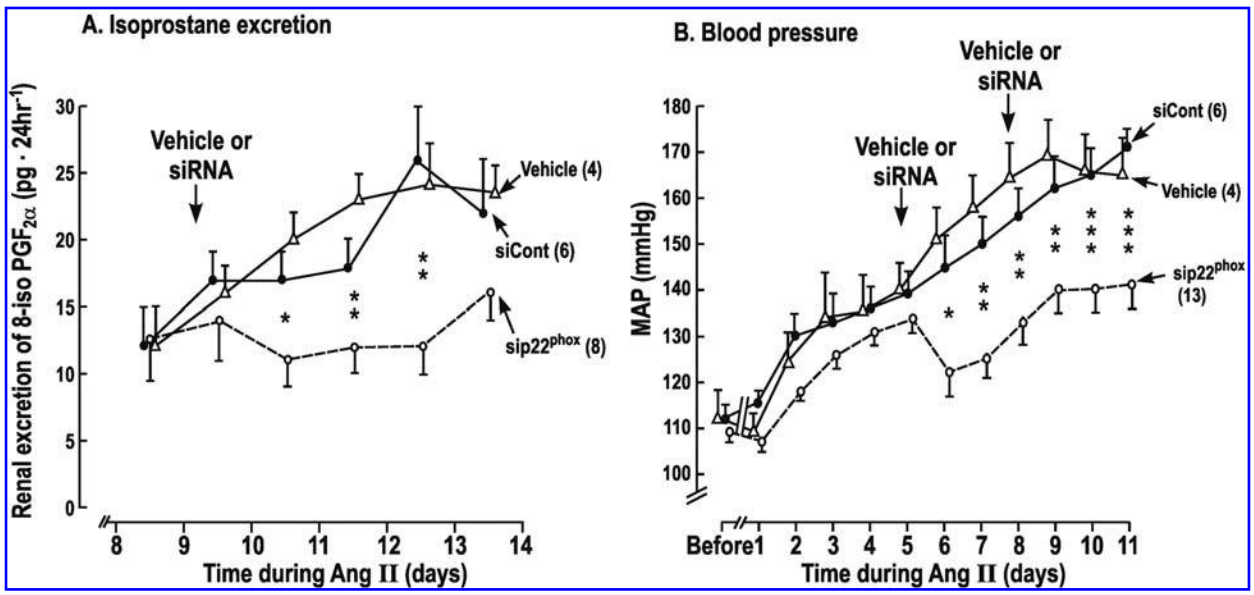

FIG. 4. Mean and SEM values (number of rats) for 24 h excretion of 8-isoprostane PGF_{2alpha} and mean arterial pressure in groups of conscious rats before, or at time points during, the infusion of Ang II. Data are shown for rats that received one (**A**) or two (**B**) intravenous injections of vehicle (*open triangles* and *continuous lines*), control, nontargeted siRNA (siCont; *solid circles* and *continuous lines*), or an siRNA to p22*phox* (sip22*phox*; *open circles* and *broken lines*). Compared to siCont: $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.005$. Redrawn from Ref. 41, with permission.

pression of the components of NADPH oxidase are shown in Fig. 5. Collectively, these reports implicate p22*phox* in the renal oxidative stress that develops with Ang II-induced hypertension.

The peptide endothelin-1 (ET-1) is produced in the kidney. It is implicated in NADPH-dependent production of ROS and hypertension. ET-1 infusion in Sprague–Dawley rats increases the BP, lipid peroxidation, and urinary excretion of 8-iso PGF_{2alpha} (57). The increase in BP can be abolished by the SOD mimetic, tempol (57). Moreover, ET_A receptor blockade in rats with aldosterone- and salt-induced hypertension prevents vascular remodeling, hypertension, oxidative stress, and NADPH oxidase activity (51). ET-1 and Ang II have separate pathways to ROS generation in human VSMCs (66). Ang II activates kinases such as p38MAPK, JNK, and ERKs primarily through NAD(P)H oxidase-generated ROS, whereas ET-1 stimulates these kinases via redox-sensitive processes that involve mitochondrial-derived ROS (66). In general, ET-1 has complex, and incompletely understood, actions on ROS generation and vascular reactivity.

The protein expression for p47*phox* is increased in the kidneys of rats with 6 weeks of insulinopenic diabetes mellitus(DM) induced by stretozotocin (46). Two weeks of administration of an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB), or apocynin, which inhibits the membrane assembly of p47phox, prevent the increase in plasma lipid peroxidation products(LPO), renal H_2O_2 production, nitrotyrosine deposition, and albumin excretion in this rat model of insulinopenic DM (Figs. 6 and 7). Rats with streptozotocin-induced DM have an upregulated expression of p47*phox* in the distal nephron and glomerular podocytes (3). Apocynin administration to this rat model of DM prevents the increase in p47*phox* partitioning from cytosol to plasma membranes of the kidney (Fig. 8). This may explain the prevention by apocynin of the increase in H_2O_2, LPO, albumin excretion, and mesangial matrix expansion (Figs. 6 and 7).

The individual NADPH oxidase subunits have a discreet renal distribution. Future challenges to understanding their function include the generation of inducible tissue- or nephron site-specific knockout and/or gene silencing models to assess the physiological roles of the NADPH oxidase subunits in the kidneys. These studies are required to establish whether NADPH oxidase has direct effects on renal vascular resistance or tubular function.

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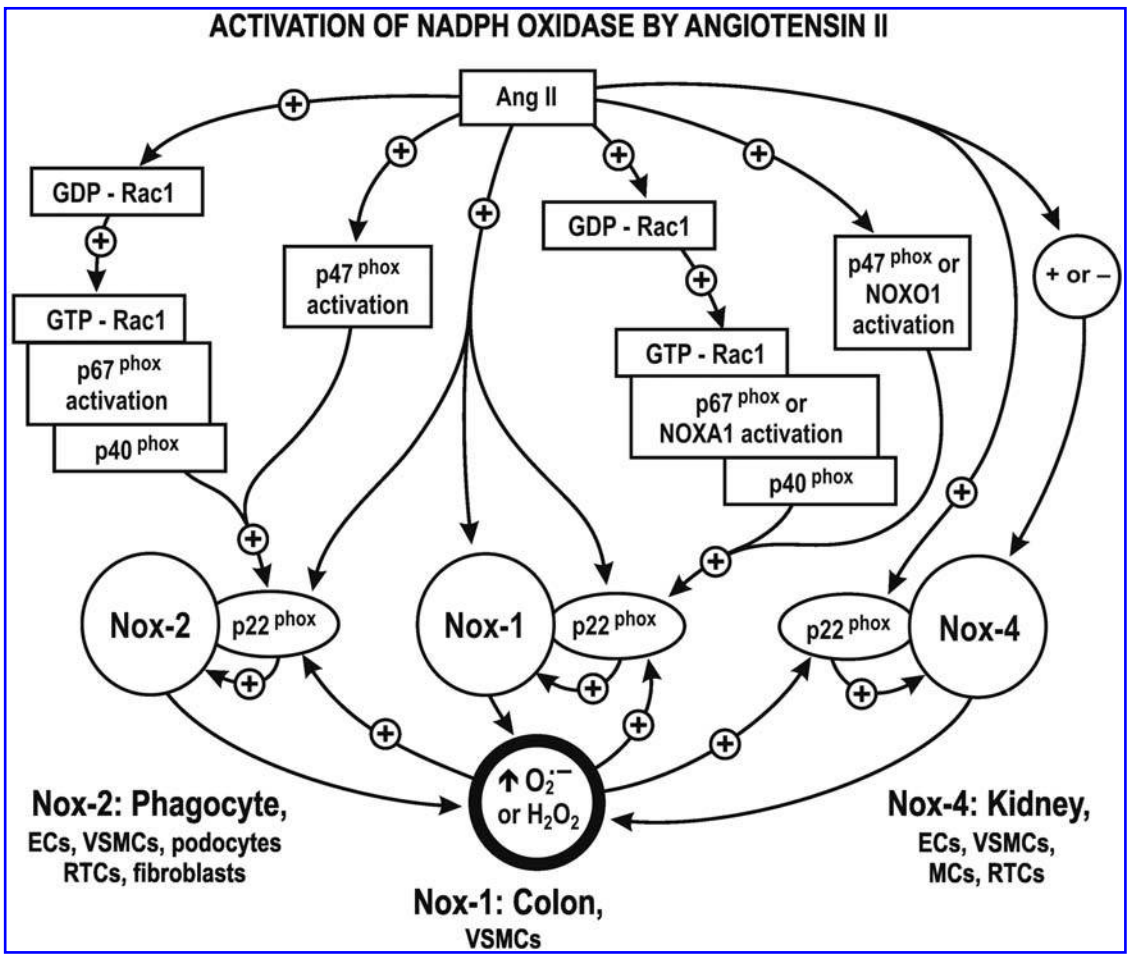

FIG. 5. Flow diagram of some effects of Ang II infusion on NADPH oxidase components. For explanation, see text.

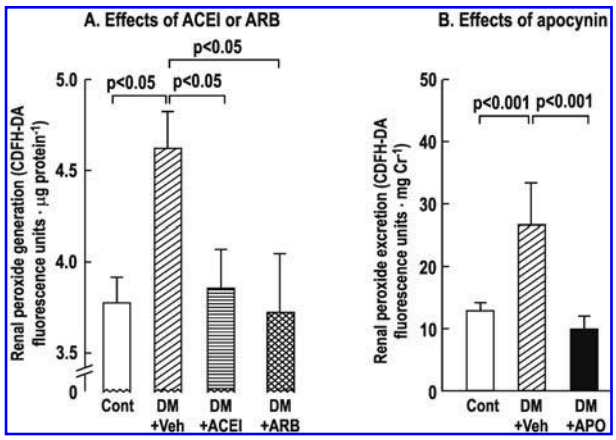

FIG. 6. Mean ± SEM values for renal peroxide production in control rats (Cont) and rats with streptozotocin-induced diabetes mellitus (DM) given a vehicle (Veh), or angiotensin-converting enzyme inhibitor (ACEI), or an AT1 receptor blocker (ARB) (A) or apocynin (APO) to inhibit p47*phox* membrane assembly. Redrawn from Refs. 3 and 46, with permission.

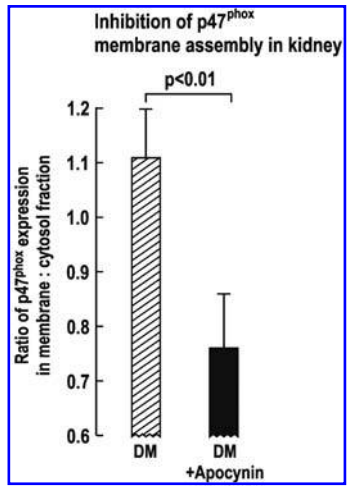

FIG. 8. Mean ± SEM value for the ratio of p47*phox* protein expressed in the cell membranes compared to cytoplasm in the kidney cortex of diabetic rats given a vehicle or apocynin for 4 weeks. Redrawn from Ref. 3, with permission.

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ABBREVIATIONS

AT_1-Rs, acting on type I receptors; AP-1, activator protein-1; ACEI, angiotensin-converting enzyme inhibitor; Ang II, angiotensin II; ARB, angiotensin receptor blocker; AT_2-R, angiotensin type 2 receptors; AA, arachidonic acid; cGMP, cyclic guanosine monophosphate; DOCA, deoxycorticosterone acetate; DM, diabetes mellitus; DPI, diphenyleneiodonium; EC, endothelial cells; ET-1, endothelin-1; EDRF/NO, endothelium dependent relaxation factor/nitric oxide; EGFR, epidermal growth factor receptor; ERK 1/2, extracellular-signal-related kinases 1 and 2; EC-SOD, extracellular superoxide dismutase; IC-SOD, intracellular superoxide dismutase; LPO, lipid peroxidation products; LDL, low density lipoprotein; Mn-SOD, manganese superoxide dismutase; MCs, mesangial cells; MCP-1, monocyte chemoattractant protein-1; Nox, NADPH oxidase; NO, nitric oxide; NoxA1, Nox activator 1; NoxO1, Nox organizer 1; NF-κB, nuclear factor-κB; M, outer medulla; p38MAPK, p38 mitogen-activated protein kinase; PPAR, peroxisome proliferator activated receptor; PMA, phorbol 12-myristate 13-acetate; PDGF, platelet-derived growth factor; $PGF_{2\alpha}$, prostaglandin $F_{2\alpha}$; PKC, protein kinase C; ROS, reactive oxygen species; RVR, renal cortical vascular resistance; siRNAs, small interference RNAs; SHR, spontaneously hypertensive rats; PI3-K, stimulates phosphatidylinositol-3-kinase; $O_2^{\bullet-}$, superoxide; TAL, thick ascending limb; VSMC, vascular smooth muscle.

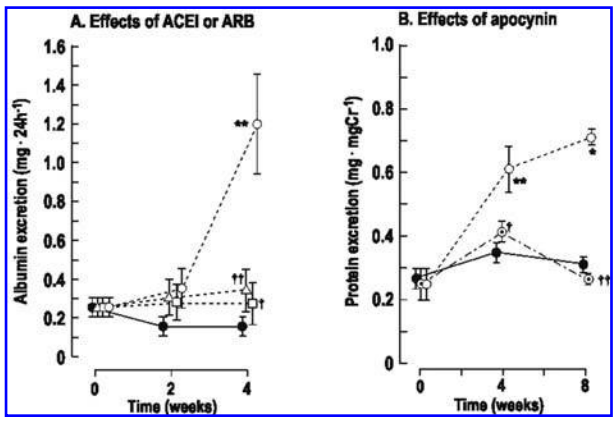

FIG. 7. Mean ± SEM values for the excretion of protein or albumin in control rats (*solid circles* and *continuous lines*) and rats with streptozotocin-induced diabetes mellitus given a vehicle (*open circles* and *broken lines*), an ACEI (*open triangles* and *broken lines*), an ARB (*open squares* and *broken lines*) in panel A, or apocynin (*open circles with dots* and *dot-dashed lines*). Compared to vehicle: †$p < 0.05$; ††$p < 0.01$. Redrawn from Refs. 3 and 46, with permission.

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