Kidney-Induced Hypertension Depends on Superoxide Signaling in the Rostral Ventrolateral Medulla

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Abstract—Reactive oxygen species in peripheral cardiovascular tissues are implicated in the pathogenesis of 2 kidney-1 clip hypertension. We recently identified an imbalance between reactive oxygen species generation and oxidant scavenging in the rostral ventrolateral medulla (RVLM) of 2 kidney-1 clip in rats. We tested whether enhanced superoxide signaling in RVLM of 2 kidney-1 clip rats contributes to the chronic hypertension via sympathetic activation in conscious rats. We enhanced superoxide scavenging in RVLM by overexpressing cytoplasmically targeted superoxide dismutase using an adenoviral vector (Ad-CMV-CuZnSOD) in Wistar rats (male, 150 to 180 g) in which the left renal artery was occluded partially 3 weeks earlier. Hypertension was documented using radiotelemetry recording of arterial pressure in conscious rats for 6 weeks. Renovascular hypertension elevated both serine phosphorylation of p47phox subunit of NADPH and superoxide levels in RVLM. The elevated superoxide levels were normalized by expression of CuZnSOD in RVLM. Moreover, the hypertension produced in the 2 kidney-1 clip rats was reversed 1 week after viral-mediated expression of CuZnSOD. This antihypertensive effect was maintained and associated with a decrease in the low-frequency spectra of systolic blood pressure variability, suggesting reduced sympathetic vasomotor tone. The expression of CuZnSOD was localized to RVLM neurons, of which some contained tyrosine hydroxylase. None of the above variables changed in control rats receiving Ad-CMV-eGFP in RVLM. In Goldblatt hypertension, superoxide signaling in the RVLM plays a major role in the generation of sympathetic vasomotor tone and the chronic sustained hypertension in this animal model. **(*Hypertension*. 2010;56:290-296.)**

Key Words: hypertension ■ renal ■ blood pressure ■ heart rate ■ brain ■ free radicals

Involvement of oxidative stress in the pathology of arterial hypertension was reported in various animal models, including the renovascular 2 kidney-1 clip (2K-1C),[1–3] the 1 kidney-1 clip,[4] angiotensin II (Ang II)–induced hypertension,[5–7] Dahl salt-sensitive (desoxycorticosterone acetate-salt) hypertension,[8] spontaneously hypertensive rats (SHRs),[9,10] and stroke-prone SHRs.[11,12] In addition, oxidative stress also plays an important role in humans with renovascular hypertension[13] and essential hypertension.[14] From these studies it is clear that oxidative stress acts at the level of the vascular wall but also within the brain. The renin-angiotensin-aldosterone system plays a major role in the 2K-1C model.[15] Ang II stimulates superoxide ($O_2^{\cdot -}$) radical generation by increasing the activity of NADPH oxidase within peripheral blood vessel walls.[16–18]

However, there is evidence that reactive oxygen species (ROS) in the brain are involved in neuronal signaling, contributing to sympathoexcitation and hypertension.[12,19] Intracerebroventricular infusion of an NADPH oxidase inhibitor antagonizes both the increase in renal sympathetic nerve activity and pressor response induced by centrally administered Ang II.[20,21] In the brain, virally mediated overexpression of superoxide dismutase (SOD), the enzyme responsible for $O_2^{\cdot -}$ breakdown, also abolishes the central pressor effect of Ang II.[7]

The 2K-1C rat model reflects renovascular hypertension.[22] The seminal work of Johansson et al[23] indicated activation of the sympathetic nervous system in human renovascular hypertensives. In this regard, the rostral ventrolateral medulla (RVLM) is an important region for the maintenance of the hypertension.[24,25] Because the RVLM is a key regulatory of sympathetic activity,[26] a change in ROS activity here may be an essential mechanism involved in generating excessive sympathetic activity in the 2K-1C model. We identified an imbalance between ROS generation and oxidant scavenging in the RVLM that promoted $O_2^{\cdot -}$ generation. In an acute

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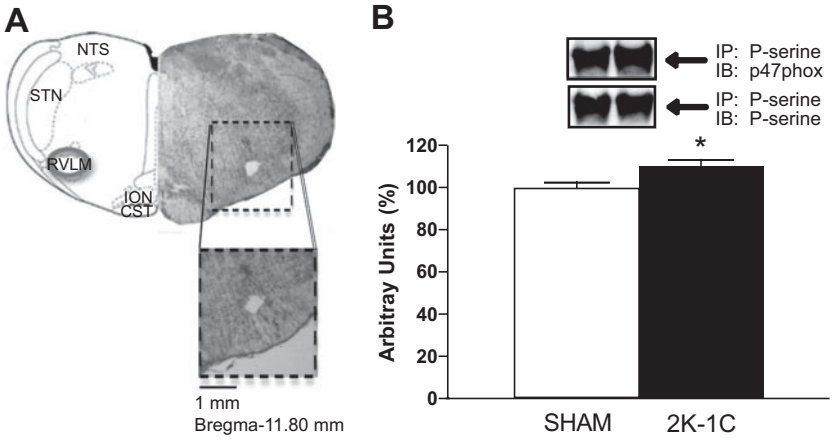

Figure 1. A, Schematic representation of the site of RVLM (left) and bilateral punches on right. CST indicates corticospinal tract; ION, inferior olivary nucleus; AN, ambiguus nucleus; NTS, nucleus of the tractus solitarii; STN, spinal trigeminal nucleus. B, Serine p47phox phosphorylation in sham (n=5) and 2K–1C (n=4) rats after 6 weeks of clipping. Protein was extracted and was used for immunoprecipitation (IP) with antiphosphoserine antibody. The aliquots were subjected to SDS-PAGE and immunoblotted (IB) with p47phox or antiphosphoserine antibody (loading control). Serine phosphorylation of p47phox is a key step for NADPH oxidase activation. Therefore, a significantly increase of serine phosphorylation of p47phox was detected in 2K–1C rats after 6 weeks of clipping. *$P<0.05$ vs sham.

study, Tempol, a metal-independent SOD mimetic, was microinjected into the RVLM of anesthetized rats and produced a transient, dose-dependent decrease in blood pressure and renal sympathetic nerve activity in 2K-1C animals.[3] However, it remains unknown whether long-term antioxidant treatment of the RVLM can affect renal-induced hypertension in awake animals. Thus, we hypothesized that there is a persistent increase in oxidative stress within the RVLM of the 2K-1C model that leads to increased neuronal excitability, excessive sympathetic activity, and chronic hypertension. Therefore, we examined whether increased chronic scavenging of $O_2^{\cdot-}$ in the RVLM of the 2K-1C model would revert the hypertension. To permit chronic $O_2^{\cdot-}$ scavenging we used an adenovirus to overexpress CuZnSOD[7] in the RVLM of conscious 2K-1C rats.

Methods

The experiments of virus transfection, telemetry, and immunohistochemistry were performed in the University of Bristol and approved by United Kingdom Home Office Guidelines on Animals (Scientific Procedures) Act of 1986 (Personal Licence No. 30/8202). The Western blotting and dihydroethidium (DHE) protocol were approved by the ethics in research committee of the Federal University of Sao Paulo School of Medicine (process No. 0662/04). Male Wistar rats (n=54, 150 to 180 g) were housed individually, allowed normal rat chow and drinking water ad libitum, and were kept on a 12-hour light/12-hour dark cycle. The study was divided into 3 independent series of experiments. Please see the online Data Supplement at http://hyper.ahajournals.org for details of the experimental protocol (Table S1).

Renovascular Hypertension Model

Rats were anesthetized with ketamine (60 mg/kg) and medetomidine (250 μg/kg) intramuscularly, and the left renal artery was partially obstructed with a silver clip of 0.2 mm width[15]; this occlusion reduced renal blood flow significantly.[27] Control animals (sham) were submitted to the same surgical procedure without partial renal artery occlusion. Anesthesia was reversed with atipamezole (1 mg/kg).

Western Blotting

Please see the online Data Supplement for details of p47phox serine phosphorylation in the RVLM. And Figure 1A shows the histology of the RVLM punches.

Telemetric Recording of Arterial Pressure

The radiotransmitters (Data Sciences International; TA11PAC40) were implanted the same day of clipping to record arterial pressure from the abdominal aorta as described previously.[28] A computer-based acquisition system, Hey Presto telemetry software (Mizuno software),[29,30] was used for acquiring, displaying, storing, and analyzing the telemetry data. Please see the online Data Supplement for details.

In Vivo Gene Transfer into RVLM

Ad-CuZnSOD (1.2×10^8 plaque-forming units/μL), a recombinant E1-deleted adenoviral vector encoding human cytoplasmic SOD, was used as described previously.[31,32] As a control, Ad-eGFP (1.57×10^9 plaque-forming units/μL) expressing enhanced green fluorescent protein (eGFP) was used.[28] Three weeks after renal artery clipping or sham surgery, animals were reanesthetized, and five 100-nL injections per side of viral suspension[33] (either Ad-CuZnSOD or Ad-eGFP) were made into the RVLM at separate sites spanning 12.0 to 12.4 mm caudal to the bregma to the lambda, 1.7 to 1.8 m lateral to the midline, and 8.0 mm below the dorsal medullary surface (bite bar: −3.5 mm).[34] Each injection was made over 1 minute. The RVLM was initially mapped out with glutamate (indicate n=6) in the experimental rats before injection of the virus and identical coordinates used thereafter. Indeed, when the injection missed RVLM, rats were excluded from the analysis, but these animals did not show an attenuated pressor effect with viral transfection (data not shown) indicating site specificity. Viral injections were made at 3 weeks after clipping so that the expression of SOD was coincident with the rise in arterial pressure/changes in autonomic variables. Recordings of arterial pressure were made for a further 3 weeks. Note that viral expression is known to last for ≤4 weeks.[7] There was no difference in the weight of rats between all of the groups at any time point in our study. Please see Figure S1 in the online Data Supplement, which shows the degree of spread.

Measurement of $O_2^{\cdot-}$ in the RVLM of 2K-1C Rats

The $O_2^{\cdot-}$ in the RVLM was analyzed 3 weeks after microinjection of either Ad-CuZnSOD or Ad-eGFP. Please see the online Data Supplement for details.

Validating CuZnSOD Transduction in the RVLM In Vivo

Double fluorescence immunohistochemistry was performed for CuZnSOD with either tyrosine hydroxylase (TH) or neuronal nuclei (NeuN) to confirm the presence of expression in RVLM neurons (please see the online Data Supplement for details).

Data Analysis

Results were presented as the mean±SEM. The telemetry data were evaluated using 2-way ANOVA followed by a Bonferroni or Tukey posttest with statistical software (Graphpad Prism 4.0). DHE fluorescence intensity was quantified using Leica software and differences analyzed using a 1-way ANOVA followed by the Tukey posttest. The level of statistical significance was defined as $P<0.05$.

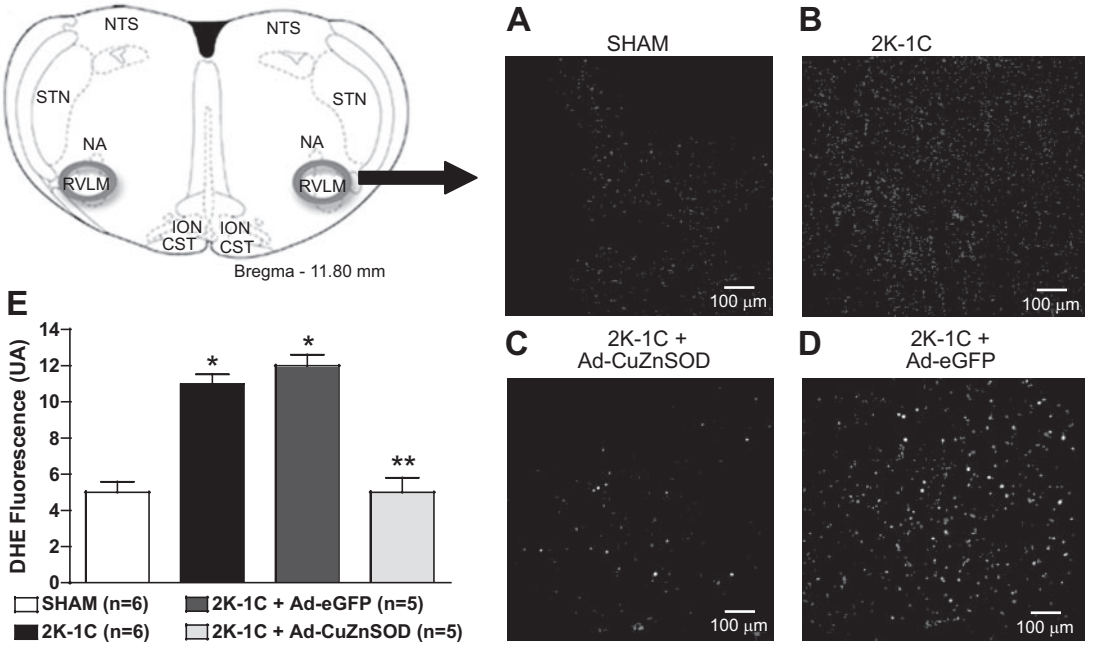

Figure 2. The brain stems of sham (A), 2K–1C (B), and 2K–1C animals receiving Ad-CuZnSOD (C) and Ad-eGFP (D) in the RVLM were incubated for 30 minutes in DHE dye, 1 mol/L as per Zimmerman et al.[7] Four representative sections through the RVLM imaged with a laser confocal microscope show that, in RVLM tissue exposed to Ad-CuZnSOD, there is less $O_2^{\cdot-}$. Maximal DHE fluorescence was quantified and found to be significantly reduced in the presence of CuZnSOD (E). Tissues were studied 6 weeks after clipping and 3 weeks after gene transfer. *$P<0.05$ vs sham and **$P<0.05$ vs 2K–1C.

Results

Activation of NADPH Oxidase in 2K-1C Rats

Serine phosphorylation of p47phox is a key step for NADPH oxidase activation. To evaluate NADPH oxidase activation in 2K-1C hypertension, an immunoprecipitation protocol was used. Punched-out RVLM tissues were immunoprecipitated with antiphosphoserine antibody and submitted to SDS-PAGE. The membranes were then immunoblotted with antip47phox antibody. A significant increase of serine phosphorylation of p47phox was detected in 2K-1C rats after 6 weeks of clipping (sham: 100±2.3% versus 2K-1C: 110±3.1%; $P<0.05$; Figure 1B).

$O_2^{\cdot-}$ Levels in the RVLM of Rats Transduced With Ad-CuZnSOD and Ad-eGFP

Figure 2 depicts the contrasting levels of $O_2^{\cdot-}$ in the RVLM of sham, 2K-1C, and 2K-1C rats transduced with Ad-CuZnSOD and Ad-eGFP. It is notable that, in the RVLM in which CuZnSOD had been overexpressed, there was considerably less DHE immunofluorescence compared with 2K-1C expressing Ad-eGFP; this was confined to the RVLM as sections rostral or caudal exhibited marked DHE immunofluorescence that was at the same level compared with control animals.

Ad-CuZnSOD and Ad-eGFP in the RVLM on Arterial Pressure and Systolic Blood Pressure Variability in Sham and 2K-1C Rats

The systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MBP) were initially recorded via radiotelemetry for 3 weeks before microinjection of either Ad-CuZnSOD or Ad-eGFP into the RVLM and for a further 3 weeks after viral transfection. In all of the rat groups, baseline levels of SBP, DBP, and MBP were similar, as shown in Table S2. In the third week after renal artery clipping, SBP, DBP, and MBP were all elevated in 2K-1C rats compared with the sham group. Arterial pressure in the 2K-1C animals rats increased gradually and significantly for 2 weeks after clip placement but plateaued by the fifth week. Ad-CuZnSOD administration into the RVLM of 2K-1C or sham rats was performed at the end of the third week. SBP, DBP, and MBP in sham groups injected with either Ad-CuZnSOD or Ad-eGFP in the RVLM were unaffected (SBP: see Figure 3A; MBP and DBP: see Figure S2). In contrast, 1 week after transduction of the RVLM of 2K-1C rats with Ad-CuZnSOD, arterial pressure was reduced significantly (SBP: from 181±8 to 140±12 mm Hg, $P<0.05$; DBP: from 142±8 to 103±3 mm Hg, $P<0.05$; MBP: from 174±13 to 115±7 mm Hg, $P<0.05$). These values remained unchanged for the remainder of the experimental period. These data suggest that virally mediated expression of CuZnSOD in the RVLM reversed the 2K-1C–induced hypertension. In contrast, arterial pressure remained elevated and was unchanged in the Ad-eGFP 2K-1C group (Figure 3).

Before the RVLM viral injection, the values of low-frequency power of the SBP (LF SBP) and very low frequency power of the SBP (VLF SBP) in the 2K-1C were not different from the control group (please see Table S3). In sham groups receiving microinjections of either Ad-CuZnSOD or Ad-eGFP into the RVLM, both LF SBP and VLF SBP were unaffected (Figure 3B and 3C).

We compared the LF SBP between 2K-1C+Ad-CuZnSOD and 2K-1C+Ad-eGFP groups. During the first week after viral injections, we found a significant drop in LF SBP in the

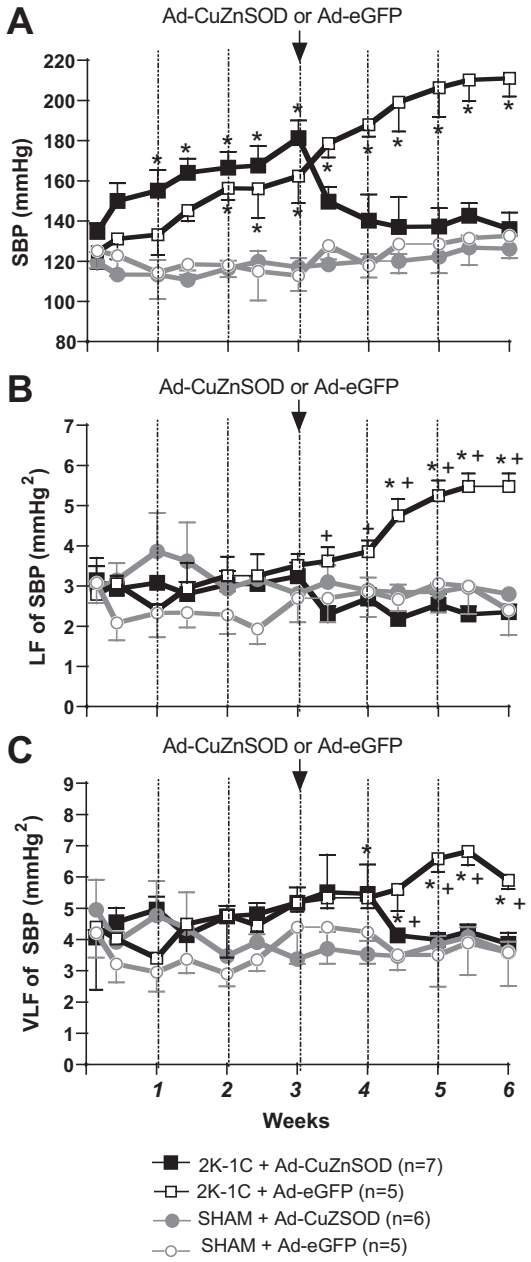

Figure 3. A, Summary of SBP recorded by radiotelemetry before and after microinjection of Ad-CuZnSOD and Ad-eGFP into the RVLM for 6 weeks. Values are expressed as the mean±SEM. These results showed that the blood pressure of hypertensive animals increased gradually and significantly over 2 weeks, reaching a plateau by the fifth week after clipping. A microinjection of Ad-CuZnSOD in the RVLM prevented 2K–1C hypertension. However, hypertension was observed in the Ad-eGFP group. B, Spectral parameters of low frequency power of the SBP (LF SBP) and (C) very low frequency power of the SBP (VLF SBP) calculated by Hey-Presto software in the Goldblatt model. Spectral analysis suggests that 2K–1C hypertension is associated with an increase in vasomotor sympathetic tone during the fourth week after renal artery clipping and is attenuated by Ad-CuZnSOD but not Ad-eGFP in the RVLM. *$P<0.05$ vs sham. +$P<0.05$ vs 2K–1C+CuZnSOD (2-way ANOVA followed by the Tukey posttest).

2K-1C+AdCuZnSOD group compared with the control animals that developed hypertension (2K-1C+Ad-eGFP; from 3.8±0.2 to 2.6±0.2 mm Hg^2; $P<0.0002$; Figure 3B). This drop in LF SBP coincided precisely with the start of the fall in arterial pressure in the 2K-1C+CuZnSOD group and provides evidence that sympathetic activity is reduced as arterial pressure is lowered in these animals. The VLF SBP increased from 5.0±0.4 to 6.4±0.3 mm Hg^2 ($P<0.05$) in the 2K-1C 2 weeks after Ad-eGFP viral transfection and persisted (Figure 3C). Comparing VLF SBP between the Ad-eGFP and Ad-CuZnSOD 2K-1C groups indicated that the latter showed a reduction 1 week after viral injection from 6.8±0.3 to 3.9±0.1 mm Hg^2 ($P<0.05$) and, therefore, some what delayed relative to the start of the fall in arterial pressure in the Ad-CuZnSOD group.

Data from our spectral analysis did not show changes in respiratory frequency, suggesting no influence on respiratory rhythm-generating neurons. Please see this result in the online Data Supplement (Figure S3).

Location of RVLM Sites Transduced With Ad-CuZnSOD

Based on the localization of CuZnSOD immunoreactivity and eGFP expression, highly comparable regions were transduced with both viruses (Ad-CuZnSOD and Ad-eGFP) in 2K-1C and sham groups. Double staining with TH (Figure 4A) confirmed that ≈70±0.4% of catecholaminergic C1 cells expressed SOD. Indeed, the double staining with NeuN (Figure 4B) confirmed the health of neurons. These were located bilaterally and found ventral to the compact division of the nucleus ambiguus and lateral to inferior olive and, therefore, in the RVLM.

Discussion

The present study reveals major advances in our understanding of chronic renovascular hypertension. In the Goldblatt model, we have found the following: (1) increased serine phosphorylation of the p47phox subunit of NADPH in the RVLM; (2) increased $O_2^{\cdot-}$ production in the RVLM; and (3) chronic reversal of the hypertension by raising the levels of SOD within the RVLM bilaterally, which is accompanied with a fall in low-frequency spectra of SBP. The latter persists for >3 weeks in conscious rats, which is coincident with the reported expression duration of CuZnSOD using our virus[7] and is associated with reduced $O_2^{\cdot-}$ levels within the RVLM. We also show that the effective antioxidant in RVLM for renovascular hypertension targets cytoplasmic SOD[35] RVLM neurons, many of which contain TH. Our data support the notion that intracellular $O_2^{\cdot-}$ in RVLM neurons (including C1 cells) is a critical signaling mechanism underlying the development of raised sympathetic vasomotor tone and hypertension in the 2K-1C rat model.

Commonality of ROS Signaling in Brain for Numerous Hypertensive Animal Models

A previous study showed that microinjections of Tempol into the RVLM decreased blood pressure in a dose-dependent manner in stroke-prone SHRs but not in Wistar Kyoto rats.[12] Furthermore, injection of adenovirus encoding the MnSOD gene into the RVLM of stroke-prone SHRs decreased MBP and heart rate but had no effect on cardiovascular parameters in Wistar Kyoto rats.[12] However, until now it was not known whether a similar mechanism in RVLM mediated the arterial

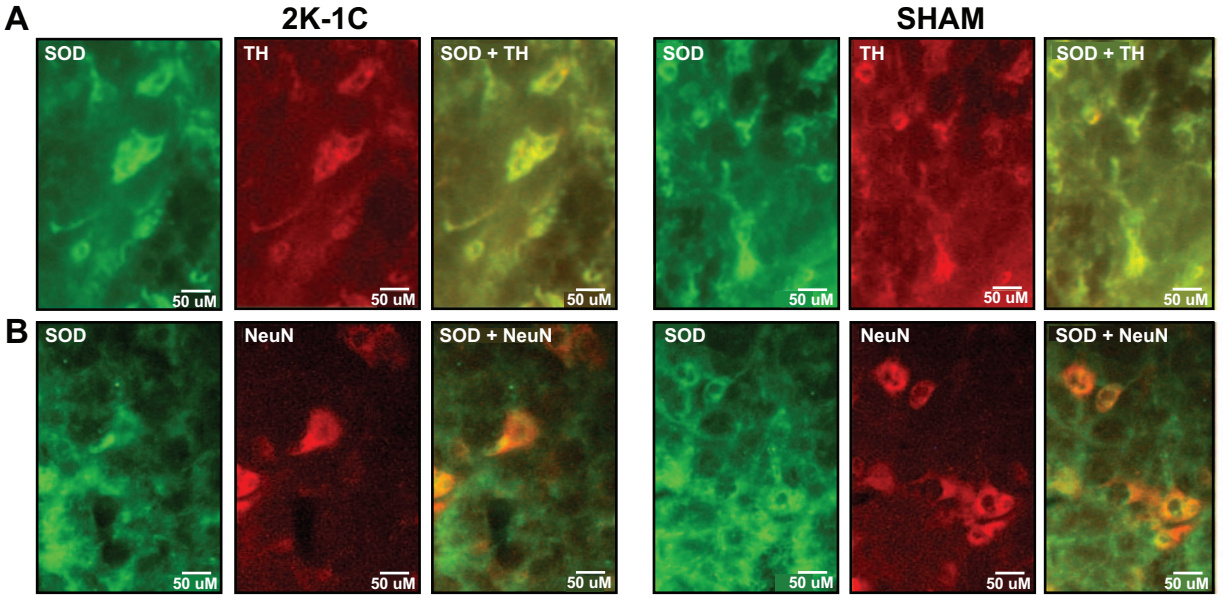

Figure 4. Cellular localization of Ad-CuZnSOD in the RVLM. A, Representative photomicrographs show immunofluorescence of SOD (left), TH (center), and merged images (SOD+TH; right) 3 weeks after microinjection of Ad-CuZnSOD into the RVLM in 2K–1C and sham rats. B, Photomicrographs show SOD and NeuN immunoreactivity in 2K–1C and sham rats. Costaining with NeuN and TH confirmed transfection of neurons, many of which were catecholaminergic (C1).

hypertension in the 2K-1C rat model. Elucidation of such data may be of great value in terms of identifying the commonality of mechanisms between different types of hypertension and, therefore, may greatly assist in generic approaches for treating this multifactorial-based disease.

Using intracerebroventricular administration of either Ad-MnSOD or Ad-CuZnSOD, Zimmerman et al[6] reported prevention of centrally mediated Ang II–induced pressor responses. However, they also showed that Ad-ECSOD (targeted to the extracellular matrix) did not prevent development of Ang II–induced hypertension.[7,21] These results suggest that Ang II infusion caused an increase in intracellular $O_2^{\cdot-}$ in the subfornical organ. The data from the present study indicate that $O_2^{\cdot-}$ signaling within the RVLM is an essential mechanism that contributes to 2K-1C hypertension, but whether this is also based on intracellular signaling is not known. Interestingly, there is evidence that Ang II levels are essential for increasing glutamatergic mechanisms driving RVLM neuronal excitability in the 2K-1C model 6 weeks after clipping[36]; this coincides with raised levels of sympathetic drive in the 2K-1C model (see Figure 2). This is consistent with the finding that downregulation of gene expression and enzyme activity of the antioxidant CuZnSOD in the RVLM may underlie the augmented levels of radical $O_2^{\cdot-}$ in the RVLM, leading to oxidative stress, sympathoexcitation, and hypertension in the SHR.[37]

Autonomic Mechanisms Underpinning 2K-1C Hypertension and Effect of Blocking $O_2^{\cdot-}$ Signaling in RVLM

It remains unclear how a renovascular insult (such as in the Goldblatt model) leads to excessive cellular production of $O_2^{\cdot-}$ in the RVLM. One possibility is that this is caused by raised circulating Ang II, but this remains to be tested. However, the present data indicate that the mechanism involves serine phosphorylation of the p47phox subunit of NADPH in the RVLM, which is consistent with our previous finding of elevated mRNA expression of 2 NADPH oxidase subunits, p47phox and gp91phox, in the RVLM of the Goldblatt rat.[2] Intriguingly, Ang II type 1 receptor stimulation can both phosphorylate the p47phox subunit and activate the cytoplasmic subunits of NADPH that bind to their membrane subunits, resulting in the intracellular production of $O_2^{\cdot-}$.[38]

Research over the last decade has revealed that $O_2^{\cdot-}$ is implicated in the regulation of neuronal excitability, as well as in neurotransmitter release.[39] Glutamatergic activity, for instance, is increased in the RVLM in 2K-1C. Bergamaschi et al[24] showed that microinjection of kynurenic acid into the RVLM produced a long-lasting decrease in arterial pressure in 2K-1C rats.

Previous studies showed that the sympathetic nervous system is involved in 2K-1C hypertension. Acute hexamethonium bromide administration in 2K-1C rats caused a greater decrease in arterial pressure and peripheral vascular resistance compared with controls from between 3 and 6 weeks after clipping.[40] This time frame is coincident with when we first detected raised low-frequency power in the SBP, indicative of elevated sympathetic outflow. These findings are in line with the reported increase in renal sympathetic nerve activity in the 2K-1C model.[2] McElroy and Zimmerman, in 1989,[41] showed that the α1-adrenergic receptor affinity for [3H]prazosin binding in hypertensive rabbits was significantly increased in the stenotic but not in the contralateral kidney at 2 weeks after clipping; however, the receptor affinity for both kidneys was significantly increased compared with those of the normotensive control group at 6 weeks of clipping. Taken together with the results from the present study, these findings support the notion that oxidative stress may be a cellular signaling mechanism driving RVLM

neuronal excitability, resulting in elevated sympathetic vasomotor tone.

The mechanisms by which the increase in ROS in the RVLM increased sympathetic nerve activity and blood pressure are not known. These responses might be mediated by an interaction between $O_2^{\cdot-}$ and NO. $O_2^{\cdot-}$ react rapidly with NO, forming peroxynitrite and thereby decreasing the bioavailability of NO.[42] Note that NO in the RVLM causes hypotension and sympathoinhibition.[43] The increase in $O_2^{\cdot-}$ levels in the RVLM might decrease NO bioavailability in RVLM, contributing to the hypertension. However, we cannot rule out a possible role for hydrogen peroxide, which accumulates during $O_2^{\cdot-}$ scavenging.

The pressor response in the 2K-1C animals was associated with an increase in the low frequency of SBP, suggesting an increase in sympathetic vasoconstrictor action. There was also an increase in very low frequency, supporting enhanced neurohumoral-mediated vasoconstriction. These findings are consistent with those of Ponchon and Elghozi,[44] who showed that an increase in the LF SBP occurred after 6 weeks from renal artery clipping. They showed that a reduction of the slow fluctuations in LF SBP after combined blockade of the kallikrein-kinin and the renin-angiotensin systems suggested the contribution of these humoral systems to this LF SBP.[44] Other studies showed that increased LF oscillations of SBP occurred 2 weeks[45] or 6 weeks[46] after clipping. In the present study, transduction of the RVLM with adenovirus expressing CuZnSOD prevented the increased sympathetic vasomotor tone (ie, LF SBP) in 2K-1C, which persisted long term (3 week). Our interpretation is that reduction in sympathetic activity will have additional effects beyond reducing vasomotor tone, such as reducing force of contraction and decrease the level of circulating hormones from the adrenals and the kidney (eg, renin). Thus, chronic oxidative stress in RVLM can contribute to sympathetic hyperactivity in renovascular hypertension. Our data are consistent with a growing body of literature supporting the prosympathoexcitatory effects of $O_2^{\cdot-}$ in RVLM.[47,48]

The present study also shows that chronic $O_2^{\cdot-}$ signaling in the RVLM reduced the tachycardia and prevented a reduction in the gain of the parasympathetic component of the cardiac baroreflex. Please see the online Dat Supplement for the details (Table S4 and Figure S4). We conclude that increased oxidative stress within the RVLM is a major mechanism driving sympathetic vasomotor tone and hypertension in a renovascular and Ang II–dependent experimental model of hypertension.

Perspectives

The RVLM contains many sympathetic premotor neurons involved in the maintenance of sympathetic vasomotor tone and, hence, blood pressure. Changes in neuronal excitability of RVLM neurons are probably a major mechanism involved in increased sympathetic drive in arterial hypertension. Others have shown that changes in neurotransmission in the RVLM contribute to elevated arterial pressure and activation of sympathetic activity. The present study indicates that oxidative stress within the RVLM is exacerbated and is responsible for altered sympathetic outflow in renovascular arterial hypertension. Taken together with other evidence, changes in neuronal excitability in the RVLM are important mechanisms driving tonic sympathetic vasomotor tone in sympathoexcitatory diseases, such as arterial hypertension. Therefore, targeting oxidative stress in the RVLM becomes an obvious aspiration in the quest for combating neurogenic hypertension, whether of central or renal origin.

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Disclosures

None.

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