Renal Injury Caused By Intrarenal Injection of Phenol Increases Afferent and Efferent Renal Sympathetic Nerve Activity

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Intrarenal injection of phenol in rats causes a persistent elevation in blood pressure (BP) and in norepinephrine (NE) secretion from the posterior hypothalamus (PH), and downregulation of neuronal nitric oxide synthase (nNOS) and interleukin-1β (IL-1β) in the PH. These studies suggest that afferent impulses from the kidney to the brain may be responsible for hypertension associated with renal injury. Downregulation of nNOS and IL-1β, two modulators of sympathetic nervous system (SNS) activity may mediate this activation. In this study we measured the effects of intrarenal phenol injection on peripheral SNS activity by direct renal nerve recording, plasma NE, nNOS, and IL-1β abundance in the brain. We also determined whether renal denervation or administration of clonidine prevented these effects of phenol.

Acutely, the phenol injection increased both afferent and efferent renal sympathetic nerve activity, decreased urinary sodium excretion, and increased plasma NE. Three weeks after the phenol injection, BP and plasma NE remained elevated. Renal denervation and pretreatment with clonidine prevented the increase in BP and plasma NE caused by phenol. Chronic renal injury caused by phenol was associated with decreased abundance of IL-1β and nNOS in the PH.

These studies have shown that a renal injury caused by phenol injection increases BP and central as well as peripheral SNS activity, which persist long after the injury. Renal denervation and antiadrenergic drugs abolish the effects of phenol on BP and plasma NE. Because NO and IL-1β modulate SNS activity, the stimulatory action of phenol on the SNS could be mediated by downregulation of nNOS and IL-1β in the brain. Am J Hypertens 2002; 15:717–724 © 2002 American Journal of Hypertension, Ltd.

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A wealth of experimental and clinical evidence has accumulated, supporting the notion that increased activity of the sympathetic nervous system (SNS) may play an important role in the pathogenesis of hypertension associated with renal disease. The turnover rate and the secretion of norepinephrine (NE) from the posterior hypothalamic (PH) nuclei were greater in rats with chronic renal failure (CRF) caused by 5/6 nephrectomy. Bilateral dorsal rhizotomy prevented the development of hypertension and the increase in NE turnover. We have also shown that injection of 50 μL of phenol in the cortex of the lower pole of one kidney causes an immediate and persistent elevation of BP and NE secretion from the PH in the rat in the absence of any appreciable perturbation of renal function. These effects can be prevented by renal denervation. Microneurographic studies of sympathetic activity measured in the peroneal nerves have shown that patients with end-stage renal disease (ESRD) manifest greater SNS activity than control subjects. In all, these studies suggest that afferent impulses from an injured kidney may activate the area of the brain involved in the noradrenergic regulation of blood pressure (BP) and contribute to hypertension.

Although NE secretion from the PH provides important insights into brain pathways that regulate SNS activity, it does not provide a measure of peripheral SNS activity. To this end, in the current studies we evaluated the effects of an intrarenal injection of phenol on peripheral SNS activity measured by direct renal nerve recordings and plasma NE concentration. In addition, we studied the effects of renal denervation and administration of clonidine on BP and plasma NE measured 3 weeks after the phenol renal injury.

We have previously shown that nitric oxide (NO) and interleukin-1β (IL-1β) modulate the activity of the SNS in the brain. We have also shown that immediately after...
renal injury with phenol, the abundance of IL-1β and the neuronal isoform of NO synthase (nNOS) decreases in the PH nuclei, the locus coeruleus (LC), and paraventricular nuclei (PVN). We have proposed that this mechanism may mediate the activation of SNS in the phenol renal injury model. To determine whether reduced abundance of nNOS and IL-1β is responsible for the chronic activation of SNS activity in the phenol renal injury model, we measured the abundance of IL-1β and nNOS 3 weeks after the renal injury.

**Methods**

**Animals and Surgical Methods**

Male Sprague-Dawley rats weighing 200 to 250 g were used for these studies. Rats received normal rat chow (ICN Nutritional Biochemical, Cleveland, OH) and tap water. After anesthesia with sodium pentobarbital (35 mg/kg, intraperitoneally) we implanted catheters (PE-10) in a femoral artery and vein for subsequent measurements of arterial pressure and administration of drugs. Then, we placed the rats in a stereotactic apparatus, implanted a 2-mm long Teflon 22-gauge guide cannula (IV Catheter Placement Unit; Critikon, Inc., Tampa, FL) using coordinates anterior–posterior –4.0 mm and lateral ±0.4 mm; vertical (V) = 8 mm, and secured the guide in place with dental cement. A 28-gauge stainless steel stylus was lowered through the guide cannula to a depth of 1.5 mm dorsal to the dorso-ventral (DV) coordinate for PH, namely –8.5 mm from the skull surface. The stylus was removed from the guide cannula and replaced with a microdialysis probe (CMA Microdialysis AB, Stockholm, Sweden), which was secured to the guide with sticky wax. The inlet tubing of the dialysis probe was connected by PE 20 tubing to a 1-mL disposable syringe driven by a microinfusion pump (Razel, model A-99, Razel Scientific Instruments, Inc., Stamford, CT), and an infusion of artificial cerebrospinal fluid (aCSF) (in millimoles per liter: Na+ 150, K+ 3.0, Ca2+ 1.4, Mg2+ 0.8, phosphorus 1.0, Cl− 155 at pH 7.2) was initiated at a rate of 1.7 µL/min. The PE-10 tubing was attached to the outlet side of the probe and the free end led to a 0.5-mL vial set in a small box of ice. The vial contained 2 µL of 0.1 N HCl for preservation of NE. All samples were immediately frozen and stored at −80°C until the time of assay.

After 90 min of dialysis equilibration, dialysate samples were collected every 5 min for the entire duration of the experiment.

**Study 1: Acute Effects of Intrarenal Phenol on BP, NE Secretion From the PH, and Plasma NE Concentration**

After a dorsal incision, we exposed the left kidney and injected 50 µL of 10% phenol in the lower pole. Control rats received 50 µL of normal saline. For these acute studies, we continuously recorded arterial BP (Physiograph, Grass Instrument Co., Quincy, MA) and collected dialysate from the PH immediately before the infusion and every 5 min for 60 min thereafter. Heparinized arterial blood samples (300 to 400 µL) were drawn before and 60 min after the injection of phenol or normal saline for measurements of plasma NE concentration. The blood was replaced with equal amounts of normal saline. Blood was collected in prechilled tubes, centrifuged in a refrigerator centrifuge, and plasma stored at −80°C until assayed.

**Study 2: Acute Effects of Intrarenal Injection of Phenol on RSNA and Urinary Sodium Excretion**

Rats were prepared for renal nerve recording according to the method of Lundin and Thoren, as modified by DiBona et al. The left kidney, left renal artery, and abdominal aorta were exposed retroperitoneally through a flank incision. A renal nerve branch, which is usually found in the angle between the aorta and the renal artery, was dissected free from fat and connective tissue for approximately 10 mm. The nerves were then placed on thin bipolar platinum electrodes (Cooner Wire Co., Cathsworth, CA) connected to a high impedance probe Grass HIP 511 (Grass Instrument Co.). Renal sympathetic nerve activity (RSNA) was amplified (×10,000 to 50,000) and filtered with a Grass 511 bandpass amplifier. The amplified and filtered signal was channeled to a Tektronix 5113 oscilloscope (Tektronix, Inc., Beaverston, OR) for visual evaluation, to an audio-amplifier/loud speaker (Grass model Am 8 audio monitor) for auditory evaluation and to a rectifying voltage integrator (Grass model 7P 10). The voltage-integrated frequency discharge was then displayed on a Grass polygraph. The quality of the renal nerve activity was assessed during operation by examining the magnitude of changes in recorded RSNA during sinoaortic baroreceptor unloading with an injection of acetylcholine (1 µg, intravenously) and during sinoaortic baroreceptor loading with the injection of NE (5 µg, intravenously). When an optimal recording was achieved, the nerve on the electrode was isolated with silicone rubber (Wacker Sil-Gel 604 Wacker, Inc., Munich, Germany). The electrode cable was exteriorized through the incision. The flank incision was closed and the animals were placed in Lucite-restraining cylinders that permit forward and backward motion, where the rats were left for 3 to 4 hours to recover. During this time the animals were kept warm under heated lamps, and received an intravenous infusion of 30 µL/min of 5% dextrose in water. After recovery from anesthesia, arterial pressure, heart rate, and RSNA were continuously monitored.

To determine whether the measured RSNA on the left side (the same side as the phenol injection) was due to afferent or efferent impulses, in a group of 5 rats, renal nerve recordings were obtained on the contralateral (right) side.

In a group of 5 rats, multifiber recordings of afferent
renal nerve activity were made from the cut distal end of the left renal nerve affixed to bipolar platinum electrodes.\(^{10}\) This allows exclusive measurements of afferent renal nerve activity.

To measure urinary sodium excretion, the urinary bladder was exposed through a suprapubic midline incision and catheterized by the method of Gellai and Valtin.\(^{11}\) The urine sodium concentration was measured by flame photometry (Instrumentation Laboratory Inc., Lexington, MA).

**Study 3: Chronic Effects of Intrarenal Phenol on BP and Plasma NE Concentration**

After the intrarenal injection of phenol or normal saline, rats were allowed to recover and followed for 3 weeks. Systolic BP was measured weekly by the tail–cuff method using an electrosphygmomanometer and physiograph recorder (MK-III, Narco Byo-Systems, Houston, TX). Before the intrarenal injection of phenol or normal saline, and at the end of the study, 300 to 400 \(\mu\)L of blood was obtained by cutting the tip of the tail for measurement of plasma NE. At the end of the third week, animals were anesthetized with sodium pentobarbital and a carotid artery cannulated for intra-arterial recording of BP and heart rate.

**Study 4: Effects of Renal Denervation on BP and Plasma NE in Rats Injected With Phenol or Normal Saline**

After the intrarenal injection of phenol or normal saline, rats were allowed to recover and followed for 3 weeks. Systolic BP was measured weekly by the tail–cuff method. After the initial 2 weeks of follow-up, rats were anesthetized and subjected to left renal denervation (on the same site of phenol or normal saline injection). Renal denervation was accomplished by cutting all visible renal nerve branches. We have previously shown that this method effectively reduces BP and renal sympathetic nerve activity.\(^{9}\) Before the intrarenal injection of phenol or normal saline, and at the end of the study, 300 to 400 \(\mu\)L of blood was obtained by cutting the tip of the tail for measurement of plasma NE. At the end of the third week, animals were anesthetized with sodium pentobarbital and a carotid artery cannulated for intra-arterial recording of BP and heart rate.

**Study 5: Effects of Clonidine on BP and Plasma NE in Rats Injected With Phenol or Normal Saline**

After the intrarenal injection of phenol or normal saline, rats were allowed to recover and followed for 3 weeks. During this time, both groups of rats received clonidine (0.027 mg/kg/day) in the drinking water. The BP was measured weekly by the tail–cuff method. Before the intrarenal injection of phenol or normal saline, and at the end of the study, 300 to 400 \(\mu\)L of blood was obtained by cutting the tip of the tail for measurement of plasma NE. At the end of the third week, animals were anesthetized with sodium pentobarbital and a carotid artery cannulated for intra-arterial recording of BP and heart rate.

**Study 6: Effect of Renal Phenol Injection on nNOS and IL-1\(\beta\) Expression in the Brain**

At the end of the experiments, rats were sacrificed by decapitation, and brains immediately removed, frozen in dry ice, and stored at −80°C until assay, but for no longer than 3 weeks. Brains were cut into consecutive 200-\(\mu\)m sections in a cryostat at −20°C and bilateral micropunches 0.5 mm in diameter from several brain nuclei obtained according to rat atlas.\(^{12–14}\) The coordinates for the PH were anterior–posterior from −3.5 to −4.1 mm; lateral ±0.4 mm; \(V = 8\) mm; for the PVN were anterior–posterior from −1.4 to −2.0 mm; lateral ± 0.3 mm; \(V = 7.9\) mm; for the LC were anterior–posterior from −9.8 mm to −10.2 mm; lateral ±1.4 mm; \(V = 7.2\) mm. The nuclei so isolated were used to measure IL-1\(\beta\) and nNOS mRNA gene expression.

Total RNA extraction and reverse transcription (RT) were performed by methods previously described by us.\(^{15,16}\) Polymerase chain reaction (PCR) was performed on the RT product using specific oligonucleotide primers for either nNOS or IL-1\(\beta\) derived from cDNAs cloned from rat brain\(^{15}\) (GenBank accession X59949) or rat liver.\(^{16}\) A master mix of PCR reagents was made for duplex reactions containing primers for the housekeeping gene β-actin (GenBank accession Joo691) and primers for either nNOS (GenBank, accession X59949), or IL-1\(\beta\) (accession number M98820).

The RT-PCR products were quantified by the method of Higuchi and Dollinger.\(^{17}\) Fluorescence was measured in a fluorescence spectrofluorometer (F-2000, Hitachi Ltd., Tokyo, Japan). Excitation was at 280 nm and emitted light was selected at 590 nm. Results were expressed as a ratio of the resultant optical densities for the specific gene to β-actin.

Random hexamers, dithiothreitol (DTT), Super ScripTM Super RT with reaction buffer (5 ×) (20 mmol/L Tris-HCl, 10 mmol/L NaCl, 0.1 mmol/L EDTA, 1 mmol/L DTT, 0.01% NP 40, and 50% glycerol), Taq DNA polymerase with reaction buffer (10 ×) (50 mmol/L Tris-HCl, 10 mmol/L NaCl, 0.1 mmol/L EDTA, 5 mmol/L DTT, and 50% glycerol, and 1.0% Triton X-100), deoxynucleotide mixture (dNTP) and MgCl\(_2\) were purchased from Gibco-BRL (Gaithersburg, MD).

**Location of Probe**

At the end of the experiments, we deeply anesthetized the rats prepared for NE secretion from the PH by intravenous sodium pentobarbital (60 mg/kg) and we perfused trans-
cardially a 10% formaldehyde solution. We removed the brains and stored them in formalin at least for 3 days at which time we cut serial 50-μm slices and stained with cresyl violet. Only rats with probes properly implanted in the PH nuclei were considered for further analysis.

**NE Microassay**

We used a highly sensitive microradioenzymatic assay. We add 10 μL of dialysate to 5 μL of reaction mixture containing 1 μL of 3.7 mol/L Tris base (with 0.37 mol/L EGTA and 1.8 mol/L MgCl₂ at pH 8.2), 0.06 μL of 36 mmol/L benzoxyamine, 1.5 μL of S-[methyl-H] adenosyl-L-methionine and 2.4 μL of partially purified catechol-O-methyltransferase and incubate for 60 min at 37°C. The sensitivity of this method is 0.5 pg.

Data were analyzed by analysis of variance, and by the Fisher’s test for comparisons among groups using the computer program Statview and Graphics 4.5 (Aabacus Concepts, Inc., Berkeley, CA). Results are expressed as mean ± SEM.

**Results**

**Study 1: Acute Effects of Intrarenal Phenol on BP, NE Secretion From the PH, and Plasma NE Concentration**

Intrarenal injection of phenol caused a significant increase in arterial BP, NE secretion from the PH (Fig. 2) and heart rate (321 ± 4.5 v 351 ± 6.2 beats/min, P < .05). The pressor response and the increased release of NE were already evident 5 min after the intrarenal injection of phenol. The findings confirm those of a previous study.

Injection of phenol in the kidney increased plasma NE levels from 377 ± 4.16 to 473 ± 4.72 pg/mL (P < .001) 60 min after the phenol injection, whereas intrarenal injection of saline caused no change in plasma NE levels (376 ± 5.21 and 368 ± 3.18 pg/mL, respectively). The NE levels for these experiments were measured from blood samples collected from the femoral artery.

In three anesthetized rats, we injected phentholamine intravenously (0.5 mg/kg body weight) 30 min after the intrarenal administration of phenol. This completely normalized the BP.

**Study 2: Acute Effects of Intrarenal Injection of Phenol on RSNA and Urinary Sodium Excretion**

Injection of phenol in the left kidney of Sprague-Dawley rats increased RSNA by approximately 28% on the side of the phenol injection. Like with the increase in NE secretion from the PH, the increase in RSNA was apparent after only 5 min of the injection of phenol (Fig. 1). On the other hand, injection of phenol in the left kidney increased the RSNA on the contralateral side by only 14% to 15%.

To selectively measure afferent renal nerve activity, we selectively sectioned one renal nerve as distally as possible from the kidney and measured activity on the proximal segment of the nerve. Intrarenal injection of phenol caused an increase in renal afferent nerve activity of only 8% to 10% (Fig. 2).

In all, these findings indicate that the intrarenal phenol injection stimulates both afferent and efferent renal nerves. Intrarenal administration of phenol reduced urinary sodium from 46.8 ± 4.1 to 26.8 ± 2.4 μEq/h (P < .002). In contrast, intrarenal injection of normal saline did not alter the urinary sodium excretion (45.1 ± 2.7 and 42.8 ± 2.5 μEq/h, respectively) (Fig. 3).

**Study 3: Chronic Effects of Intrarenal Injection of Phenol on BP and Plasma NE**

We measured intra-arterial systolic and diastolic BP 3 weeks after intrarenal phenol injection and found it still to be greater (P < .01) in rats injected with phenol (138/98 ± 2.66/1.02 mm Hg) than rats injected with normal saline (108/68 ± 1.23/2.55 mm Hg). At this time, plasma NE
levels were also still greater in rats injected with phenol compared to baseline levels (858 ± 49.3 v 548 ± 33.2 pg/mL; \( P < .01 \)), than in rats that had received an intrarenal injection of saline (531 ± 46.3 v 550 ± 43.6 pg/mL, respectively).

**Study 4: Effects of Renal Denervation on BP and Plasma NE in Rats Injected With Phenol or Normal Saline**

Renal denervation performed 2 weeks after intrarenal phenol injection completely normalized arterial systolic and diastolic BP (101/63 ± 3.15/1.44 v 138/98 ± 2.66/1.02 mm Hg; \( P < .001 \)), plasma NE (463 ± 76.0 v 858 ± 49.3 pg/mL; \( P < .05 \)), and heart rate (330 ± 9.14 v 351 ± 6.15 beats/min). Renal denervation had no appreciable effects on BP, plasma NE, or heart rate in control rats.

**Study 5: Effects of Clonidine on BP and Plasma NE in Rats Injected With Phenol or Normal Saline**

In rats injected with phenol, administration of clonidine in the drinking water (0.027 mg/kg/day) for 3 weeks, completely normalized BP and reduced plasma NE and heart rate to levels even lower than those seen in untreated control rats. In control rats, clonidine had no significant effects on arterial systolic and diastolic BP (103/62 ± 2.55/3.39 v 108/68 ± 1.23/2.55 mm Hg at baseline; \( P = .08 \)), but significantly reduced both plasma NE levels (392 ± 29.2 v 531 ± 46.3 pg/mL; \( P < .05 \)) and heart rate (274 ± 7.01 v 321 ± 4.53 beats/min; \( P < .05 \)).

**Study 6: Chronic Effects of Intrarenal Phenol on IL-1β and nNOS Abundance in the PH, PVN, and LC**

Three weeks after the intrarenal injection of phenol, the abundance of nNOS and IL-1β in the PH, PVN, and LC was lower than that of rats that had received an intrarenal injection of saline (Fig. 4).

**Discussion**

The major novelty of this study is the demonstration that a renal injury caused by the injection of phenol in the cortex of one kidney stimulates renal afferent pathways. These pathways seem to integrate with brain nuclei involved in the noradrenergic control of BP, resulting in activation of efferent SNS pathways, sodium retention and hypertension. In the current studies, the activation of efferent sympathetic pathways was demonstrated by direct recording of RSNA, and by measurements of plasma NE concentrations.

To determine whether the increase in RSNA on the side of phenol injection was due to activation of the afferent nerve activity, the efferent nerve activity, or both, we performed additional experiments. In a group of rats, we measured RSNA after sectioning the renal nerves as distally as possible from the kidney and measured activity on the proximal segment of the nerve. In these rats, intrarenal injection of phenol caused a significant increase in afferent nerve activity (14% to 15%). In a separate group of rats, we measured contemporarily RSNA on the left side (the side of phenol injection) and on the opposite side. We observed an increase in RSNA of 28% on the left side (the side of phenol injection), and a significantly lower (\( P < .05 \)) increase (14% to 15%) on the right side. The greater RSNA activity on the left than on the right side may be...
due to activation of both afferent and efferent nerve activity on the side of the phenol injection, whereas only efferent nerve activity may be activated on the contralateral side. Alternatively, the increase in RSNA on the right side seen in the present study could be the result of central excitatory stimuli minus inhibitory renorenal reflexes activated by renal injury on the left side.19,20

These studies are consistent with the notion that the kidney is a sensory organ,21–23 and renal afferent nerves projecting to a number of areas in the central nervous system may contribute to BP regulation.24

We have used NE secretion from the PH as a surrogate marker of brain pathways regulating SNS activity and confirmed that intrarenal injection of phenol activates central noradrenergic pathways.3 This method, however, does not provide a measure of peripheral SNS activity. For this reason, in the current studies, we have measured peripheral SNS activity by direct recording of renal SNS activity and plasma NE levels.

These studies have also confirmed that the increase in BP and in plasma NE levels that follows the intrarenal injection of phenol persists, and renal denervation performed 2 weeks after the injection of phenol, normalizes both BP and plasma NE.8 This excludes the possibility that the effects of phenol on BP might be secondary to the release of hormones from the kidney into the circulation, or diffusion of phenol into the systemic circulation.

In the current studies we also observed that administration of antiadrenergic drugs prevent the increase in BP and in SNS activity caused by intrarenal phenol injection during both the acute and chronic phases of hypertension. In acute experiments, we have shown that intravenous administration of phentolamine (an α1-adrenergic receptor antagonist) given 15 min after the intrarenal injection of phenol normalizes BP.

For the chronic studies, we used clonidine hydrochloride, an imidazoline derivative that lowers BP primarily through stimulation of postsynaptic inhibitory α2-adrenergic receptors located in the nucleus tractus solitarii of the medulla oblongata. This inhibits efferent SNS impulses on the peripheral vasculature resulting in reduced BP and natriuresis.25 Clonidine normalized BP and plasma NE in the chronic phases of hypertension in this model.

One could speculate that the observed changes in SNS activity, IL-1β, and nNOS could be secondary to the increase in BP rather than its cause. This possibility, however, does not seem plausible because the reflex effects of changes in BP on IL-1β, nNOS mRNA abundance, and NE secretion from the PH, are the opposite of those observed in our model. The increase in BP caused by intravenous (not intracerebrovascular) administration of angiotensin II, resulted in a significant decrease in NE secretion from the PH and an increase in IL-1β and nNOS mRNA abundance. On the other hand, infusion of angiotensin II in the lateral ventricle increased BP, RSNA, and NE secretion from the PH, while reducing the abundance of IL-1β and nNOS. All these effects were blocked by losartan, an angiotensin II receptor antagonist.26 In contrast, the decrease in BP caused by phentolamine infusion was associated with an increase, rather than a decrease, in NE secretion from the PH (Dr. VM Campese, personal observations). Other investigators have also shown that NE turnover in the PH increases when arterial pressure decreases and decreases when arterial pressure increases.27

Nitric oxide synthase is present in a specific area of the brain and it is involved in the noradrenergic control of BP.28 The neuronal isoform of NO synthase is an important component of transduction pathways that tonically inhibits the sympathetic outflow from the brainstem.29 Administration of N(G)-methyl-L-arginine to male Wistar rats increases RSNA and BP.30 In normal rats, basal central SNS activity is inhibited by local NO production.5 In 5/6 nephrectomized rats, nNOS-mRNA gene expression and NO(2)/NO(3) content were greater than in control rats. N(G)-nitro-L-arginine methyl ester, an inhibitor of NOS, increased BP and NE turnover rate in the brain of these rats.6

Because of complex relationships existing between cytokines, SNS activity, and NO,31 one possible mediator for
the increase in NO expression is IL-1β. Interleukin-1β activates NOS expression in several organs.32,33 There is also evidence that NO is involved in the IL-1β-induced central activation of SNS outflow in rats.34 Administration of IL-1β in the lateral ventricle of control and 5/6 nephrectomized rats caused a dose-dependent decrease in BP and NE secretion from the PH, and an increase in nNOS-mRNA abundance in several brain nuclei.7 Intracerebrovascular infusion of a specific antitrat IL-1β antibody decreased NOS-mRNA expression in the PH, PVN, and LC of CRF and control rats, and at the same time raising BP and NE secretion from the PH.7 In all, these studies suggest that IL-1β modulates NE secretion from the PH, and this modulation is mediated by local production of NO.

We have also shown that the acute increase in BP and SNS activity that follows intrarenal injection of phenol is associated with reduced abundance of IL-1β and nNOS-mRNA in several brain nuclei, including the PH, PVN, and LC.7 In the current studies we have observed that the abundance of IL-1β and nNOS mRNA is reduced up to 3 weeks after intrarenal infusion of phenol, suggesting that this mechanism may be responsible for the increase in SNS activity and BP. Losartan, an angiotensin II AT₁ receptor antagonist normalized all the effects of phenol injection.35 This suggests that locally released angiotensin II in the brain could mediate these effects. As previously stated, intracerebrovascular infusion of angiotensin II mimics all the effects on BP, SNS activity, nNOS, and IL-1β observed after intrarenal phenol administration.26

In all, these studies suggest that reduction of IL-1β and nNOS expression may mediate the activation of the SNS in the phenol renal injury model and locally produced angiotensin II may be responsible for the downregulation of IL-1β and nNOS expression.

In conclusion, these studies have shown that after an intrarenal injection of phenol, afferent signals from the kidneys cause a reflex increase in peripheral efferent SNS activity resulting in sodium retention and hypertension. The activation of the SNS and the increase in BP persists for 3 weeks after the intrarenal infusion of phenol. Renal denervation or antiadrenergic drugs prevent the increase in BP and sympathetic nerve activity caused by intrarenal phenol injection. Central activation of angiotensin II may reduce the abundance of IL-1β and nNOS in brain nuclei involved in the noradrenergic regulation of BP, which may then result in activation of the SNS and BP elevation.

References


