Influence of Eicosanoids on Renal Function of DOCA-Salt Hypertensive Rats

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SUMMARY The present study examined the contribution of changes in the synthesis or degradation (or both) of renal eicosanoids to the alterations in renal hemodynamics observed in deoxycorticosterone acetate (DOCA)-salt hypertensive rats. Renal blood flow and glomerular filtration rate were markedly reduced in DOCA-salt hypertensive rats compared with values observed in control rats given water or saline to drink. The abnormalities in renal hemodynamics in the hypertensive rats were associated with an increase in the excretion of thromboxane B₂, an increase in the release of thromboxane B₂ from renal cortical tissue slices, and a diminished release of prostaglandin E₂ (PGE₂) from renal medullary tissue. Additionally, the urinary excretion of PGE₂ and 6-keto-prostaglandin F₁α (6-keto-PGF₁α) and the release of 6-keto-PGF₁α by renal cortical and medullary tissue were elevated in rats with DOCA-salt hypertension. Since the excretion of PGE₂ and 6-keto-PGF₁α and the release of 6-keto-PGF₁α by medullary tissue were also elevated in normotensive rats given 1% NaCl solution to drink, these latter changes probably were related to an elevation of sodium intake rather than to the development of hypertension. The functional significance of the alterations in the renal production of thromboxane in DOCA-salt hypertensive rats was evaluated by comparing the effects of a thromboxane synthesis inhibitor and a thromboxane receptor antagonist on renal function in normotensive and DOCA-salt hypertensive rats. The administration of the thromboxane synthetase inhibitor furegrelate and the thromboxane receptor blocker SQ 29548 had no effect on renal hemodynamics in either group. These results suggest that the elevated renal production of thromboxane A₂ is not responsible for the reduction of renal blood flow and glomerular filtration rate in rats with established DOCA-salt hypertension. (Hypertension 12: 287–294, 1988)

KEY WORDS • prostaglandins • thromboxane • renal function • furegrelate • meclofenamate • hemodynamics

RECENT studies by Sugai et al.1 and Zambraski and Ciccone2 demonstrated that the kidneys of deoxycorticosterone acetate (DOCA)-salt hypertensive animals require a higher perfusion pressure to excrete equivalent amounts of sodium and water to amounts from control animals. Accordingly, in DOCA-salt hypertension, the chronic renal function curve depicting the relationship between renal perfusion pressure and the urinary excretion of sodium and water is shifted to the right.1 These shifts in the pressure-diuresis and pressure-natriuresis relationships could be caused by renal vasoconstriction or by an increase in tubular reabsorption of water and electrolytes.3 In animals with DOCA-salt hypertension, renal vasoconstriction and augmented tubular reabsorption of sodium and water may be related to elevations in renal sympathetic nerve activity4 or vasopressin levels5 or disturbances in the production of eicosanoids by the kidney.6

Although the urinary excretion rate of prostaglandin E₂ (PGE₂) is increased in animals treated with mineralocorticoid hormones,7 the synthesis of PGE₂ is depressed in DOCA-salt hypertensive rats.8 A defect in the renal production of PGE₂ may play a role in the changes in renal function in these animals because PGE₂ is a renal vasodilator that promotes the excretion of salt and water.8 Renal vasoconstriction also may be the manifestation of enhanced production of thromboxane A₂ (TXA₂) by the kidney.9 In this regard, increased renal TXA₂ synthesis is known to contribute to the elevated renal vascular resistance observed during potassium

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depletion, a condition that accompanies the development of DOCA-salt hypertension.

The present study examined whether alterations in the renal production of eicosanoids contribute to the changes in renal hemodynamics and sodium and water excretion that accompany the development of DOCA-salt hypertension. First, we determined whether the development of DOCA-salt hypertension in rats was associated with changes in urinary excretion of PGE$_2$, 6-keto-prostaglandin F$_{1\alpha}$ (6-keto-PGF$_{1\alpha}$) and thromboxane B$_2$ (TXB$_2$) or in the production of these eicosanoids by renal cortical or medullary tissue. Second, we investigated the effects of an inhibitor of thromboxane synthetase, furegrelate (U-63557A), and a TXA$_2$ receptor antagonist, SQ 29548, on renal hemodynamics and excretory function in DOCA-salt hypertensive rats and normotensive controls. Finally, we evaluated the contribution of vasodilator prostaglandins in maintaining renal function in DOCA-salt hypertensive rats by studying the effects of meclofenamate in rats pretreated with furegrelate or SQ 29548.

Materials and Methods

Experiments were performed on 71 male Sprague-Dawley rats purchased from Harlan Laboratories (Madison, WI, USA). The rats weighed approximately 250 g at the beginning of the study and were housed in stainless steel cages. Rat chow containing 1% NaCl by weight was provided ad libitum throughout the study. All surgical procedures were conducted with strict adherence to published guidelines, and the protocols in this study received prior approval by the animal care committees of the Medical College of Wisconsin and the University of Tennessee.

The rats were anesthetized with ketamine (100 mg/kg) and acepromazine (2 mg/kg) or pentobarbital (60 mg/kg), and the right kidney was surgically removed. The animals were given 40,000 units of Penstrep (penicillin G, streptomycin) postoperatively to prevent infection. One week later, the rats were assigned to one of three groups. Group 1 served as the normal salt diet control group. These rats were given tap water to drink and received a high salt diet throughout the study. Group 2 served as the normotensive controls given a 1% NaCl solution to drink throughout the study and were assigned to one of three groups. Group 1, the control rats given a 1% NaCl solution to drink to elevate sodium intake (Group 2), and the rats with DOCA-salt hypertension (Group 3). The rats were anesthetized with an intraperitoneal injection of pentobarbital, the kidneys were removed, and the rates of release of eicosanoids from renal cortical and medullary tissue were determined. The kidneys were first flushed with 50 to 60 ml of Krebs-Ringer solution containing 118 mM NaCl, 4.7 mM KCl, 2.5 mM CaCl$_2$, 1.2 mM KH$_2$PO$_4$, 1.17 mM MgSO$_4$, 8.4 mM dextrose, and 25 mM NaHCO$_3$. The kidneys were hemisected, and the inner medulla was removed from the cortex. The inner medulla and cortex were sliced into 0.5-mm sections using a Stadie-Riggs microtome (Thomas Scientific, Philadelphia, PA, USA). The tissue slices were placed in flasks containing 2 ml of Krebs solution and arachidonic acid (16.5 $\mu$M; Nu-Check, Elysian, MN, USA). The tissue slices were incubated for 15 minutes with agitation (100 cycles/min) at 37°C under an atmosphere of 5% CO$_2$ and 95% O$_2$. The selection of a 15-minute incubation period was based on preliminary experiments indicating that the rate of eicosanoid release was linear for the first 20 minutes of an incubation. At the end of the incubation period, the tissue slices were removed from the flasks and dried in an oven. Eicosanoids released into the incubation media were measured by radioimmunoassay as described previously. The results are presented as nanograms of immunoreactive eicosanoids released during the 15-minute incubation period per milligram dry weight of tissue.

Protocol 1: Biochemical Studies

Biochemical studies were performed to assess the effects of a chronically elevated sodium intake and DOCA-salt hypertension on the urinary excretion of PGE$_2$, 6-keto-PGF$_{1\alpha}$ (a prostacyclin metabolite), and TXB$_2$ (a TXA$_2$ metabolite), as well as on the in vitro release of these eicosanoids by renal cortical and medullary tissue. In the fifth week of the experiment, six rats from each group were placed individually in metabolic cages and a 24-hour urine sample was collected from each rat in a container kept on dry ice for measurement of the urinary excretion of eicosanoids. Urinary concentrations of PGE$_2$, 6-keto-PGF$_{1\alpha}$, and TXB$_2$ were determined by radioimmunoassay after extraction of the samples using methods previously described. The urinary excretion of each eicosanoid was calculated as the product of the 24-hour urine volume times the urinary concentration and was expressed as nanograms excreted per 24 hours. After the excretion of eicosanoids was measured, the rats were anesthetized by an intraperitoneal injection of pentobarbital, the kidneys were removed, and the rates of release of eicosanoids from renal cortical and medullary tissue were determined. The kidneys were first flushed with 50 to 60 ml of Krebs-Ringer solution containing 118 mM NaCl, 4.7 mM KCl, 2.5 mM CaCl$_2$, 1.2 mM KH$_2$PO$_4$, 1.17 mM MgSO$_4$, 8.4 mM dextrose, and 25 mM NaHCO$_3$. The kidneys were hemisected, and the inner medulla was removed from the cortex. The inner medulla and cortex were sliced into 0.5-mm sections using a Stadie-Riggs microtome (Thomas Scientific, Philadelphia, PA, USA). The tissue slices were placed in flasks containing 2 ml of Krebs solution and arachidonic acid (16.5 $\mu$M; Nu-Check, Elysian, MN, USA). The tissue slices were incubated for 15 minutes with agitation (100 cycles/min) at 37°C under an atmosphere of 5% CO$_2$ and 95% O$_2$. The selection of a 15-minute incubation period was based on preliminary experiments indicating that the rate of eicosanoid release was linear for the first 20 minutes of an incubation. At the end of the incubation period, the tissue slices were removed from the flasks and dried in an oven. Eicosanoids released into the incubation media were measured by radioimmunoassay as described previously. The results are presented as nanograms of immunoreactive eicosanoids released during the 15-minute incubation period per milligram dry weight of tissue.

Protocol 2: Renal Clearance Studies

Clearance experiments were performed on the normotensive control rats given tap water to drink (Group 1), the control rats given a 1% NaCl solution to drink to elevate sodium intake (Group 2), and the rats with DOCA-salt hypertension (Group 3).
tion of Inactin (100 mg/kg) and were placed on a warming table to maintain body temperature at 37 °C. Cannulas were placed in the jugular vein for infusions and in the femoral artery for measurement of mean arterial pressure. The ureter of the left kidney was cannulated for urine collections, and a 2-mm flowprobe was placed on the left renal artery for measurement of renal blood flow (RBF) using an electromagnetic flowmeter (Model 501, Carolina Instruments, King, NC, USA). During the experiment, the rats were infused with a 0.9% NaCl solution at a rate of 100 μl/min. [3H]Inulin (2 μCi/ml) was included in the infusion solution to allow for the measurement of glomerular filtration rate (GFR).

After the surgical procedure and a 1-hour equilibration period, urine and plasma samples were collected during two 20-minute periods. The rats (Group 1, n = 6; Group 2, n = 7; Group 3, n = 6) then received an intravenous injection of furegrelate (2 mg/kg) to inhibit thromboxane synthesis. After a 30-minute equilibration period, urine and plasma samples were collected during two 20-minute experimental periods. The rats were then given an intravenous injection of meclofenamate (2 mg/kg) to inhibit cyclooxygenase. After a 30-minute equilibration period, urine and plasma samples were again collected during two additional 20-minute experimental periods.

In preliminary experiments (n = 13) we found that TXB2 levels in blood samples allowed to clot for 30 minutes fell significantly from 26 ± 6 to 7 ± 3 ng/ml after administration of a 2 mg/kg dose of furegrelate. In previous experiments, we demonstrated that a 2 mg/kg dose of meclofenamate effectively inhibits renal cyclooxygenase activity and reduces urinary PGE2 excretion in surgically prepared rats. Moreover, we performed experiments on six control rats maintained on a high salt diet (Group 2) and on six DOCA-salt hypertensive rats (Group 3) to determine the effects of furegrelate on the urinary excretion of TXB2. These rats were surgically prepared as described except that [3H]inulin was not infused. Urine samples were collected for measurement of TXB2 excretion during a control period and after the administration of furegrelate and meclofenamate.

In other experiments, we examined the effects of a thromboxane receptor antagonist on the renal function of seven control rats (Group 2) and seven rats with DOCA-salt hypertension (Group 3). The experimental protocol was identical to that just described except that, after the control period, the rats received an intravenous infusion of the TXA2 receptor antagonist SQ 29548 (2 μg/kg/min), instead of furegrelate. We have previously reported that an SQ 29548 infusion of 2 μg/kg/min blocked the pressor effect of the thromboxane receptor agonist U-46619 in rats.

Analytical Techniques

[3H]Inulin concentrations of urine and plasma samples were measured using a liquid scintillation spectro-photometer. GFR was calculated as the urine-plasma inulin concentration ratio times urine flow and was factored per gram kidney weight. The sodium and potassium concentrations of all samples were determined using flame photometry. The osmolality of the samples was measured using a freezing point osmometer (Precision Instruments, Sudbury, MA, USA).

Statistics

Mean values ± 1 SE are presented. The significance of differences in mean values, measured during several periods within a group, was evaluated using an analysis of variance for repeated measures followed by a Bonferroni test. Between-group comparisons were evaluated using a one-way analysis of variance and the Bonferroni test. A p value below 0.05 using a two-tailed test was considered significant.

Results

Systolic arterial pressure averaged 138 ± 3 and 141 ± 4 mm Hg, respectively, in the control rats given water and 1% NaCl solution to drink for 5 weeks. Systolic pressure was significantly elevated to 212 ± 5 mm Hg in the DOCA-salt hypertensive rats. The effects of these treatments on the urinary excretion of eicosanoids are summarized in Figure 1. Urinary excretion rates of TXB2, 6-keto-PGF1α, and PGE2 were all significantly elevated in the DOCA-salt hypertensive rats relative to the values in control rats given tap water to drink (Group 1). Urinary TXB2 excretion in the DOCA-salt hypertensive rats was also higher than that observed in control rats given saline to drink (Group 2). In contrast, the urinary excretion rates of PGE2 and 6-keto-PGF1α were not different in the DOCA-salt hypertensive rats and the control rats given 1% NaCl solution to drink.

Figure 2 illustrates the in vitro release of eicosanoids from renal cortical and medullary tissue slices. Relative to the eicosanoid release by renal tissue of the control rats given water or 1% NaCl solution to drink, DOCA-salt hypertensive rats exhibited increased release of TXB2 and 6-keto-PGF1α from slices of renal cortex and a diminished release of PGE2 from renal medullary slices. The release of 6-keto-PGF1α by the renal medulla of DOCA-salt hypertensive rats exceeded the values observed in control rats given water to drink, but it was not different from the values observed in the control rats given 1% NaCl solution to drink.

The effects of furegrelate and meclofenamate on renal hemodynamics and sodium and water excretion are depicted in Figures 3 and 4. In the control rats given water to drink, furegrelate had no effect on urine flow, sodium excretion, RBF, or GFR. Subsequent administration of meclofenamate to block renal cyclooxygenase activity also did not alter renal hemodynamics or the excretion of sodium and water in these animals. In contrast, furegrelate altered renal function in the control rats given 1.0% NaCl solution to drink (Group 2). Urine flow declined
FIGURE 1. Twenty-four-hour urinary excretion of thromboxane B₂, 6-keto-PGF₁α, and PGE₂ in DOCA-salt hypertensive rats and in uninephrectomized control rats given tap water or 1% NaCl solution to drink before the experiment. Mean values ± 1 SE from six rats per group are presented.

by 38% (see Figure 3), and urine osmolality increased significantly from 484 ± 39 to 674 ± 78 mosm/kg · H₂O after administration of furegrelate. Subsequent administration of meclofenamate had no additional effect on urine flow or urinary osmolality in these animals.

Sodium excretion was not significantly altered after administration of furegrelate in the control rats drinking saline solution, but it did fall by 38% after these rats received meclofenamate. Furegrelate produced a small but nonsignificant rise in RBF in the control rats drinking 1% NaCl solution. GFR was unaltered by furegrelate. Administration of meclofenamate to this group of control rats had no effect on renal hemodynamics.

In DOCA-salt hypertensive rats, mean blood pressure was elevated 50 mm Hg in comparison to pressures measured in either control group (see Figure 4). Basal urine flow and sodium excretion, however, were not different in the three groups of rats. RBF and GFR were reduced by 50% in the DOCA-salt hypertensive rats in comparison to the values measured in control rats drinking water or saline (see Figure 4). Meclofenamate did not affect renal hemodynamics in DOCA-salt hypertensive

FIGURE 2. Release of prostanoids from renal cortical and medullary tissue from DOCA-salt hypertensive rats and control animals given tap water or 1% NaCl solution to drink. Mean values ± 1 SE from six rats per group are presented. TXB₂ = thromboxane B₂.

FIGURE 3. Effect of furegrelate and meclofenamate (meclo) on urine flow and sodium excretion in DOCA-salt hypertensive rats and control rats given tap water or 1% NaCl solution to drink. Asterisk indicates significant difference (p < 0.05) from respective control value. Dagger indicates significant difference (p < 0.05) between value after furegrelate and value after furegrelate and meclofenamate. kwt = kidney weight.
RENAL EICOSANOIDS IN HYPERTENSIVE RATS/Roman et al.

Effect of furegrelate and meclofenamate (meclo) on renal blood flow (RBF), glomerular filtration rate (GFR), and mean arterial pressure in DOCA-salt hypertensive rats and control rats drinking water or 1% NaCl solution. Asterisk indicates significant difference (p < 0.05) from respective control value. There was no significant difference between values after furegrelate and values after furegrelate and meclofenamate. Double dagger indicates significant difference (p < 0.05) from the corresponding values measured in either normotensive control group. Mean values ± 1 SE from six to seven rats per group are presented. kwt = kidney weight.

Mean arterial pressure was unaltered after furegrelate administration, but it fell significantly after the hypertensive rats were given meclofenamate (see Figure 4).

Furegrelate produced a 42% fall in urine flow and an increase in urine osmolality from 468 ± 38 to 561 ± 9 mosm/kg · H2O in the DOCA-salt rats (see Figure 3). Meclofenamate had no additional effect on the excretion of water. Sodium excretion tended to decline after furegrelate administration, but this decrease was not significant. Subsequent administration of meclofenamate to the DOCA-salt hypertensive rats reduced sodium excretion to 41% of its initial value.

The effect of furegrelate on the urinary excretion of TXB2 is presented in Figure 5. Urinary excretion of TXB2 was similar in the DOCA-salt hypertensive rats and the control rats drinking 1% NaCl solution, averaging approximately 40 pg/min. This value corresponds to a 24-hour excretion of 58 ng/day and is 10-fold to 20-fold higher than the excretion rates measured in the conscious rats (see Figure 1). Furegrelate produced a 60% fall in the urinary excretion of TXB2. The excretion of TXB2 was further reduced to less than 15% of its initial value after administration of meclofenamate in both groups.

The effects of the thromboxane receptor antagonist SQ 29548 on renal function of control rats maintained on a high-salt diet and DOCA-salt hypertensive rats are summarized in Table 1. Infusion of SQ 29548 had no effect on urine flow or urine osmolality in either group of rats. Sodium excretion was not significantly altered by SQ 29548. Renal hemodynamics were relatively constant throughout the experiment in the control rats. In the DOCA-salt hypertensive animals, SQ 29548 did not alter RBF or GFR, but both fell significantly after these rats were given meclofenamate. Mean arterial pressure was stable throughout the experiment in the control rats. Blood pressure decreased significantly after administration of SQ 29548 in the DOCA-salt hypertensive rats, and it was further reduced after these rats received meclofenamate.

Discussion

This study demonstrates that RBF and GFR are reduced in rats with established DOCA-salt hypertension. These changes in renal hemodynamics are associated with an elevated urinary excretion of TXB2, an increased release of TXB2 from renal cortical tissue slices, and a diminished release of PGE2 from renal medullary tissue. Additionally,
DOCA-salt hypertensive rats feature an augmented urinary excretion of PGE2 and 6-keto-PGF1α and increased release of 6-keto-PGF1α from slices of the renal cortex and the medulla. The urinary excretion of PGE2 and 6-keto-PGF1α and the release of 6-keto-PGF1α from renal medullary slices also were elevated in normotensive control rats given saline to drink, suggesting that these latter changes in renal eicosanoid excretion and release probably are related to an elevation in sodium intake rather than to the development of hypertension. The association of hypertension and changes in the urinary excretion and production of TXB2 by renal tissue was first reported in spontaneously hypertensive rats.

Subsequently, it was confirmed in rats with reduced renal mass hypertension, Dahl salt-sensitive hypertensive rats, two-kidney, one-clip hypertensive rats, and rats with angiotensin II–salt–induced hypertension. In DOCA-salt hypertensive rats, the augmentation of the urinary excretion of TXB2 and the release of this substance from renal medullary tissue may be related to disturbances in electrolyte balance or to hypertensive glomerular injury with attendant infiltration by white blood cells or to the stimulation of other cells in the kidney that express thromboxane synthetase (or to all three). In this regard, DOCA-salt hypertensive rats are known to become hypernatriemic and hypokalemic. Potassium depletion has been shown to augment TXB2 release from renal tissue slices in rats. Similarly, the release of TXB2 from renal tissue was also found to increase in dogs made chronically hypernatriemic by arterial infusion of hypertonic NaCl solution.

The urinary excretion of 6-keto-PGF1α is increased in rats with angiotensin II–induced hypertension and in hypertensive rats of the Lyon strain, but it is unchanged in rats with two-kidney, one-clip hypertension. In DOCA-salt hypertensive rats, the increased urinary excretion and renal tissue release of 6-keto-PGF1α may be the consequence of an elevated sodium intake alone, since in our study similar abnormalities in the urinary excretion and renal tissue release of 6-keto-PGF1α were noted in normotensive control rats given 1% NaCl solution to drink.

The urinary excretion of PGE2 is unchanged or decreased in spontaneously hypertensive rats, decreased in hypertensive Dahl salt-sensitive rats, and unchanged in rats with two-kidney, one-clip hypertension. In the present study, augmentation of urinary PGE2 excretion in DOCA-salt hypertensive rats was associated with a diminished release of PGE2 from renal medullary tissue slices. The dissociation between the excretion of PGE2 and its release from renal medullary tissue cannot be explained in unequivocal terms. One possibility is that, while the release of eicosanoids from renal tissue slices is an index of their synthesis and metabolism, this in vitro information may not always reflect the production of eicosanoids in vivo.

The functional significance of the augmented production of renal eicosanoids is amenable to clarification by investigation of the effects of eicosanoid synthesis inhibitors and receptor antagonists on renal hemodynamics and the excretion of water and electrolytes. For example, inhibitors of thromboxane synthesis have been reported to increase RBF or GFR (or both) in potassium-depleted rats, during the development of hypertension in the spontaneously hypertensive rat, and in rats with reduced renal mass. From these observations it may be deduced that, in each of these experimental conditions in which renal production of TXA2 is increased, changes in thromboxane levels in the kidney partially contribute to the reduction in RBF.

In the present study, rats with established DOCA-salt hypertension also exhibited depressed RBF and GFR that was associated with an increased urinary excretion and tissue release of TXB2. However, inhibition of thromboxane synthesis by furegrelate and blockade of TXA2 receptors by SQ 29548 did
not increase RBF or GFR. Accordingly, TXA₃ does not appear to be responsible for the abnormalities in renal hemodynamics in rats with established DOCA-salt hypertension. Such perturbations in renal hemodynamics may be attributable to increased sympathetic activity and vasopressin levels or to structural abnormalities in renal vasculature such as glomerulosclerosis and thickening of the glomerular basement membrane. Since the excretions of PGE₂ and 6-keto-PGF₁α were elevated in DOCA-salt hypertensive rats, it is unlikely that the reduction in RBF and GFR was caused by a deficit in the renal levels of vasodilator eicosanoids. Indeed, our finding that meclofenamate lowered GFR in DOCA-salt hypertensive rats pretreated with SQ 29548 suggests that GFR is supported in part by elevated levels of vasodilator eicosanoids.

Blood pressure in DOCA-salt hypertensive rats fell during treatment with SQ 29548, but it was not affected by the administration of furegrelate. Blood pressure also fell after meclofenamate was given to DOCA-salt hypertensive rats pretreated with furegrelate or SQ 29548. These findings raise the possibility that eicosanoids contribute to the hypertension in DOCA-salt hypertensive rats. Relative to this point, a recent study suggested that eicosanoids are contributory elements in the pathogenesis of severe angiotensin II-salt-induced hypertension in rats. In summary, this study demonstrates that rats with severe DOCA-salt hypertension exhibit depressed RBF and GFR, increased urinary excretion of TXB₂, increased release of TXB₂ from renal cortical tissue slices, and diminished release of PGE₂ from renal medullary tissue slices. Additionally, DOCA-salt hypertensive rats feature increased urinary excretion of PGE₂ and 6-keto-PGF₁α and augmented release of 6-keto-PGF₁α from renal cortical and medullary tissue. Neither inhibition of thromboxane synthesis by furegrelate nor blockade of TXA₂ receptors by SQ 29548 increased RBF and GFR in DOCA-salt hypertensive rats. These data suggest that changes in the renal production of TXA₂ are not responsible for the abnormal renal hemodynamics in rats with established DOCA-salt hypertension.

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