Hypotensive Action of DuP 753, an Angiotensin II Antagonist, in Spontaneously Hypertensive Rats

Nonpeptide Angiotensin II Receptor Antagonists: X


In conscious 18–21-week-old spontaneously hypertensive rats, DuP 753, a nonpeptide angiotensin II receptor antagonist, given orally at 3 and 10 mg/kg or intravenously at 3, 10, and 30 mg/kg, reduced blood pressure dose dependently. It did not alter heart rate at these doses. At 10 mg/kg i.v., DuP 753 decreased blood pressure significantly for at least 24 hours, suggesting a long duration of the antihypertensive effect. Unlike saralasin, DuP 753 did not cause a transient increase in blood pressure. The acute antihypertensive efficacy of DuP 753 was greater than that of captopril. Our data indicate that, for captopril to reduce blood pressure to a similar extent as that of DuP 753, it would need to be supplemented by a diuretic. DuP 753 did not have an acute diuretic effect. Bilateral nephrectomy, but not inhibition of prostaglandin synthesis, abolished the antihypertensive effect of DuP 753, suggesting that the antihypertensive effect of DuP 753 is dependent on an active renin-angiotensin system. Furthermore, DuP 753 inhibited the pressor response to angiotensin II but not the responses to norepinephrine, vasopressin, and Bay K 8644 (a calcium agonist). As neither DuP 753 nor captopril decreased blood pressure acutely in Wistar-Kyoto normotensive rats, our results suggest that the renin-angiotensin system plays a significant role in the control of blood pressure in spontaneously hypertensive rats. (Hypertension 1990;15:459-468)

The search for nonpeptide angiotensin II (Ang II) receptor antagonists has been pursued for the past 2 decades. It is only recently that it has become feasible to design and synthesize selective nonpeptide Ang II receptor antagonists.1-7 Although these early leads were effective Ang II receptor antagonists in rats when given intravenously, they were either slightly active or inactive when given orally at 100 mg/kg.3,4,6,7 Subsequently, based on these prototype molecules, orally active nonpeptide Ang II receptor antagonists with increased potency were developed.5 DuP 753, 2-n-butyl-4-chloro-5-hydroxymethyl-1-[2′-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl imidazole, potassium salt (Figure 1), has been selected for further characterization and shown to be an orally active, highly selective, competitive, nonpeptide Ang II receptor antagonist in our previous studies.8,9 Unlike saralasin, a peptide Ang II receptor antagonist, DuP 753 does not have partial agonistic effects.9 In renal artery-ligated rats, a high renin hypertensive model, DuP 753 given intravenously or orally decreased blood pressure acutely, and its acute antihypertensive efficacy was similar to that of captopril.10 On the other hand, in conscious deoxycorticosterone acetate hypertensive rats, a very low renin model, DuP 753 given intravenously or orally did not lower blood pressure acutely.10 Thus, it appears that there is a relation between basal plasma renin activity (PRA) and the acute blood pressure-lowering effect of DuP 753 in rats.

It has been reported that captopril and other angiotensin converting enzyme (ACE) inhibitors decrease blood pressure in spontaneously hypertensive rats (SHRs) in which PRA is normal,11,12 whereas saralasin is ineffective.13 As the partial agonistic effect of saralasin (see Reference 14) and the bradykinin-potentiating effect of captopril15 may complicate the interpretation of their blood pressure effects in SHRs, the role of the renin-angiotensin...
system (RAS) in the control of blood pressure in SHRs is not clear. Because DuP 753 does not have partial agonistic and bradykinin-potentiating effects,8-9 it is useful in evaluating the involvement of the RAS in the regulation of blood pressure in SHRs.

Methods

Male SHRs or male Wistar-Kyoto (WKY) normotensive rats, 18-21 weeks old (Charles River Labs., Inc., Kingston, New York), were anesthetized with hexobarbital (90 mg/kg i.p.), and both the right jugular vein and carotid artery were cannulated. The catheters were passed subcutaneously to the dorsal side of the neck and exteriorized. After the rats had completely recovered from anesthesia (at least 2.5 hours after the surgery), the carotid catheter was connected to a Gould pressure transducer (Gould Inc., Oxnard, California) coupled to a Grass polygraph (Grass Instr. Co., Quincy, Massachusetts) for monitoring arterial pressure. Heart rate was recorded by the Grass tachograph (Grass Instr. Co.). The following experiments were carried out in conscious rats. In some groups, however, rats were cannulated at 18-24 hours before the experiment.

Evaluation of Oral Antihypertensive Effect in Spontaneously Hypertensive Rats

Group 1. After a 30-minute stabilization period, single intravenous doses of DuP 753 at 3, 10, and 30 mg/kg, captopril at 3, 10, 30, and 100 mg/kg, or saralasin at 1 or 10 mg/kg, were given, and the experiment was monitored for 30-120 minutes. In rats treated with DuP 753 at 10 mg/kg i.v., blood samples (1 ml each) were collected for PRA determination in the control period and at 120 minutes after dose administration.

Group 2. After establishing the maximal antihypertensive intravenous doses of DuP 753 and captopril from the group 1 experiment as described above, captopril was given at its maximal antihypertensive dose (10 mg/kg), and 60 minutes later vehicle at 1 ml/kg or DuP 753 at its maximal antihypertensive dose (10 mg/kg) was given intravenously. The experiment was monitored for 2 hours. In another group of rats, DuP 753 was given at 10 mg/kg i.v., and vehicle at 1 ml/kg or captopril at 10 mg/kg was given intravenously 60 minutes later. The experiment was then monitored for 2 hours.

Group 3. To determine the effect of a diuretic on the antihypertensive effects of DuP 753 and captopril, SHRs were pretreated with furosemide (10 mg/kg s.c.) at 22 and 4 hours before the experiment and were not allowed access to water after the first dose of furosemide. DuP 753 at 10 mg/kg i.v. or captopril at 10 mg/kg i.v. was given, and the experiment was monitored for 2 hours. In rats treated with DuP 753, blood samples (1 ml each) were collected for PRA determination in the control period and at 120 minutes after dose administration.

Group 4. SHRs were surgically prepared with arterial and venous catheters as described above at 18-24 hours before the experiment. To correlate the antihypertensive and Ang II inhibitory effects, DuP 753 was given intravenously at 10 mg/kg in one group of rats, and the experiment was monitored for 24 hours. In another group of rats, DuP 753 was given at 10 mg/kg i.v., and Ang II (0.1 μg/kg i.v.) was also injected at 15 minutes before the injection of DuP 753 and at 0.5, 1, 2, 3, 4, 5, 6, 7, and 24 hours after injection.

Group 5. To ascertain the specificity of DuP 753, cumulative intravenous injections of DuP 753 at 1 and 10 mg/kg were given at an interval of 70 minutes. Ang II at 0.1 μg/kg i.v., norepinephrine at 0.3 μg/kg i.v., vasopressin at 0.03 IU/kg i.v., or Bay K 8644 (a calcium channel activator that has been reported to cause cardiac contractility and constriction of vascular smooth muscle, presumably by enhancing calcium influx through calcium channels in the cell membrane16) at 10 μg/kg i.v. were given 15 minutes before the injection of DuP 753 and at 60 minutes after the injection of DuP 753. Only one agonist was tested in each rat.

Group 6. To examine the effect of DuP 753 on urine output, the bladders of the SHRs were cannul-
lated for urine collection. Urine was collected every 30 minutes before and for 2 hours after the administration of DuP 753 at 10 mg/kg i.v.

Group 7. To study the involvement of vasodilating prostaglandins in the acute antihypertensive effect of DuP 753, rats were pretreated with vehicle at 1 ml/kg i.v. or indomethacin at 5 mg/kg i.v. Fifteen minutes later DuP 753 was given at 10 mg/kg i.v., and the experiment was monitored for 2 hours.

Group 8. To evaluate the role of the kidney in the antihypertensive effect of DuP 753 and captopril, vehicle at 1 ml/kg i.v. or DuP 753 at 10 mg/kg i.v. was given to groups of SHRs that had been bilaterally nephrectomized at 18-24 hours before the experiment. In another group of nephrectomized SHRs, hydralazine was given at 0.3 mg/kg i.v. to ascertain the vasodilating capacity of nephrectomized SHRs. In some bilaterally nephrectomized SHRs, blood samples (1 ml each) were collected in the control period for PRA determination.

Evaluation of Intravenous Antihypertensive Effect in Wistar-Kyoto Rats

After a 30-minute stabilization period, a single intravenous injection of DuP 753 at 10 mg/kg, captopril at 10 mg/kg, or vehicle was given to groups of WKY rats, and the experiment was monitored for 2 hours.

Analyses and Statistics

PRA was determined by radioimmunoassay17 with a DuPont New England Nuclear radioimmunoassay kit (Boston, Massachusetts). Statistical analyses used were correlation, analysis of variance, and Duncan's new multiple range test for multiple comparison.18 These analyses were carried out by a computer package, STATISTICAL ANALYSIS SYSTEM (SAS Institute Inc., Cary, North Carolina), in a Vax 8650 computer. The level of significance was taken at p<0.05. All data were expressed as mean±SEM.

Drugs

DuP 753 was given intravenously at 1 ml/kg in saline and orally at 5 ml/kg in distilled water. Captopril, saralasin, and hydralazine were injected in saline at 1 ml/kg. Bay K 8644 was dissolved in a mixture of 0.1N HCl, water, polyethylene glycol 400, and 5% dextrose (18:7:25:50). Indomethacin was dissolved in a mixture of 5% NaHCO3 and 5% dextrose (18:82). Ang II, hydralazine, indomethacin, norepinephrine, saralasin, and vasopressin were obtained from Sigma Chemical Co. (St. Louis, Missouri). DuP 753,2 captopril, and Bay K 8644 were synthesized at E. I. du Pont de Nemours and Company (Wilmington, Delaware). Both the potassium and the sodium salts of DuP 753 were used in these studies. They were water soluble and were shown to be pharmacologically equivalent in preliminary studies.

Results

Evaluation of Oral Antihypertensive Effect in Spontaneously Hypertensive Rats

In SHRs, DuP 753 given orally decreased mean arterial pressure in a dose-dependent manner at 3 (n=6) and 10 (n=5) mg/kg p.o. on mean arterial pressure and heart rate in conscious spontaneously hypertensive rats. Values represent mean±SEM. Overall effect of DuP 753 at 10 mg/kg p.o., but not 3 mg/kg p.o., on mean arterial pressure was significantly different from vehicle (p<0.05). Effects of DuP 753 on heart rate were not significantly different from vehicle.
Mean arterial pressure (mm Hg)

Spontaneously Hypertensive Rat

Mean arterial pressure (mm Hg)

Heart rate (beats/min)

Spontaneously Hypertensive Rat

FIGURE 3. Line graphs showing effects of vehicle (n=5) and DuP 753 at 3 (n=6), 10 (n=6), and 30 (n=6) mg/kg i.v. on mean arterial pressure and heart rate in conscious spontaneously hypertensive rats. Values represent mean±SEM. Overall effects of DuP 753 at 3, 10, and 30 mg/kg i.v. on mean arterial pressure were significantly different from vehicle (p<0.05). Effects of DuP 753 on heart rate were not significantly different from vehicle.

significant decrease in mean arterial pressure from 130±7 to 120±5 mm Hg at 3 hours after dose administration, respectively (p<0.05).

Evaluation of Intravenous Antihypertensive Effect in Spontaneously Hypertensive Rats

DuP 753 given intravenously at 3, 10, and 30 mg/kg (n=6 per dose) caused a dose-dependent decrease in mean arterial pressure, whereas the vehicle (n=5) did not change mean arterial pressure (Figure 3). The blood pressure–lowering effects of DuP 753 at these doses were sustained for at least 2 hours (Figure 3), whereas the overall effects of DuP 753 on heart rate were not significantly different from the vehicle control (Figure 3). Basal PRA was significantly elevated by DuP 753 at 10 mg/kg i.v. from 10.4±1.2 to 63.1±5.3 ng angiotensin I (Ang I)/ml/hr (p<0.05, n=6).

Unlike saralasin at 10 mg/kg i.v. (n=6), DuP 753 (n=6) did not cause a transient increase in mean arterial pressure at the same dose and had a greater decrease in mean arterial pressure and longer dura-

significant decrease in mean arterial pressure from 130±7 to 120±5 mm Hg at 3 hours after dose administration, respectively (p<0.05).

FIGURE 4. Line graph showing effects of saralasin (n=6) and DuP 753 (n=6) at 10 mg/kg i.v. on mean arterial pressure in conscious spontaneously hypertensive rats. Values represent mean±SEM. Overall effect of DuP 753 on mean arterial pressure was significantly different from that of saralasin (p<0.05).

To compare the antihypertensive efficacies of captopril and DuP 753 in SHRs (Figure 5), single intravenous doses of captopril and DuP 753 that produced the maximal change in mean arterial pressure were determined (n=6 per dose of each compound). As shown in Figure 5, both captopril and DuP 753 caused maximal decreases in mean arterial pressure at 10 mg/kg i.v. At their maximal antihypertensive doses, the acute maximal antihypertensive effect and the duration of DuP 753 were significantly greater than those of captopril (Figure 5).

As shown in Figure 6, captopril at 10 mg/kg i.v. significantly decreased mean arterial pressure for at least 3 hours. DuP 753 at 10 mg/kg i.v. caused an additional blood pressure–lowering effect in SHRs that were pretreated with captopril (Figure 6). In contrast, captopril at 10 mg/kg i.v. did not significantly change mean arterial pressure in SHRs that were pretreated with DuP 753 at 10 mg/kg i.v. (Figure 6).

Effects of furosemide on the antihypertensive responses to captopril at 10 mg/kg i.v. and DuP 753 at 10 mg/kg i.v. are shown in Figure 7. Basal PRA was significantly elevated by furosemide from 10.4±1.2 to 24.9±1.1 ng Ang I/ml/hr (p<0.05, n=6). Furosemide slightly lowered mean arterial pressure in SHRs (Figure 7). Pretreatment of SHRs with furosemide enhanced both the onset and the maximal antihypertensive effect of captopril (Figures 7 and 8). Although furosemide enhanced the onset of antihypertensive effect of DuP 753 at 10 mg/kg i.v. (Figure 7), it did not alter the absolute maximal change in mean arterial pressure (Figure 8). Basal PRA was significantly elevated by DuP 753 at 10
maximal Δ in mean arterial pressure (mm Hg) -

Figure 5. Top panel: Line graph showing comparison of maximal antihypertensive effects of single intravenous doses of captopril and DuP 753 in conscious spontaneously hypertensive rats. Values represent mean±SEM and n=6 per dose for each compound. Bottom panel: Line graph showing effects of captopril at 10 mg/kg i.v. (n=6) and DuP 753 at 10 mg/kg i.v. (n=6) on mean arterial pressure in conscious spontaneously hypertensive rats. Values represent mean±SEM. Overall effect of DuP 753 on mean arterial pressure was significantly different from that of captopril (p<0.05).

Mean arterial pressure (mm Hg) -

Figure 6. Top panel: Line graph showing effect of captopril pretreatment (10 mg/kg i.v.) on the blood pressure effects of DuP 753 (10 mg/kg i.v., n=6) and its saline vehicle (1 ml/kg i.v., n=6) in spontaneously hypertensive rats. Captopril decreased blood pressure significantly for at least 3 hours (p<0.05). DuP 753 but not the saline vehicle caused a further reduction in blood pressure at 90 to 180 minutes (p<0.05). Bottom panel: Line graph showing effect of DuP 753 pretreatment (10 mg/kg i.v.) on the blood pressure effects of captopril (10 mg/kg i.v., n=7) and its saline vehicle (1 ml/kg i.v., n=9) in spontaneously hypertensive rats. In the first group, DuP 753 decreased blood pressure significantly for at least 3 hours (p<0.05). Neither saline vehicle nor captopril altered blood pressure significantly. Values represent mean±SEM.

Mean arterial pressure (mm Hg) -

At 1 mg/kg i.v., DuP 753 did not significantly alter the pressor response to Ang II at 0.1 μg/kg i.v. (39±3 vs. control 42±1 mm Hg, n=8). At 10 mg/kg i.v., DuP 753 inhibited the pressor response to Ang II (n=8) but not the pressor responses to norepinephrine (n=8) and Bay K 8644 (n=4) (Figure 10). The pressor response to vasopressin was enhanced by DuP 753 (n=7).

DuP 753 (n=6) at 10 mg/kg i.v. caused a significant decrease in blood pressure for at least 2 hours but did not increase urine output during this antihypertensive period (Figure 11), suggesting that diuresis is not involved in the effect of DuP 753.

As shown in Figure 12, when compared with the vehicle control group, indomethacin did not alter the antihypertensive effect of DuP 753 at 10 mg/kg i.v.,
suggesting that vasodilating prostaglandins were not involved in this response (n=6 per group).
Spontaneously Hypertensive Rats

**Discussion**

DuP 753 given either orally or intravenously exhibited an acute antihypertensive effect in conscious 18–21-week-old SHRs. PRA in these conscious SHRs with recently implanted catheter was found to be slightly higher than normal. The fact that plasma samples for PRA were obtained at 2.5 hours after the surgical procedure is probably responsible for the elevated PRA. However, DuP 753 also lowered blood pressure in another group of SHRs that might have a normal PRA as these rats were cannulated at 18–24 hours before the experiment (Figure 9). DuP 753 was effective in maintaining an antihypertensive effect for at least 4 days after repeated daily oral dosing at 10 mg/kg. No tolerance to its antihypertensive effect was noted as the fifth dose of DuP 753 decreased blood pressure to a similar level as that of the single oral dose of 10 mg/kg of DuP 753. The antihypertensive effect of DuP 753 in SHRs is consistent with the findings reported by others, and it is shown in the present study that ACE inhibitors such as captopril or enalapril also lowered blood pressure in this model. As DuP 753 or captopril did not reduce blood pressure in WKY rats, these data suggest that RAS plays an important role in the control of blood pressure in SHRs. However, as shown previously by Pals et al and confirmed in the present study, saralasin had a minimum hypotensive effect and caused a transient increase in blood pressure at 1 and 10 mg/kg i.v. in SHRs. The lack of blood pressure-lowering effect of saralasin is probably due to its pronounced agonistic activity in this normal renin hypertensive model. In contrast, DuP 753 at 10 mg/kg i.v. did not exhibit an agonistic effect. It should be noted that the antihypertensive effect of DuP 753 in SHRs was not associated with a significant increase in heart rate. Apparently, the lack of reflex tachycardia is a common effect observed with blockers of the RAS, and its mechanism is still not clear.

The acute maximal antihypertensive efficacy of DuP 753 has been found to be greater than that of captopril in SHRs. In rats pretreated with captopril at its maximal dose, DuP 753 at its maximal dose decreased blood pressure further. The possibility that other actions unrelated to the blockade of Ang II account for the greater antihypertensive efficacy of DuP 753 cannot be excluded from the present study. However, such a property of DuP 753 has not yet been demonstrated as both the in vitro and in vivo studies indicate that DuP 753 is a selective Ang II receptor antagonist. As shown in this study, DuP 753 inhibited the pressor response to Ang II but not to norepinephrine and Bay K 8644. Interestingly, the pressor effect of vasopressin was enhanced after the injection of DuP 753 in SHRs. A similar enhance-
In rats pretreated with DuP 753, captopril did not significantly lower blood pressure. As DuP 753 has been proven to be a selective Ang II receptor antagonist, this result suggests that the acute antihypertensive effect of captopril in SHRs is mainly due to the blockade of the formation of Ang II. However, there may be differences between the acute and chronic antihypertensive effects of captopril in SHRs. For instance, it has been reported that long-term treatment of SHRs with captopril caused a progressive cumulative decrease in blood pressure resulting in a normalization of blood pressure after 6 months of dosing. Whether the greater chronic antihypertensive effect of captopril in SHRs is due to a more complete blockade of the RAS or to other actions remains to be investigated. Further studies to compare the chronic antihypertensive effects of captopril and DuP 753 in SHRs are underway.

Because higher PRA is required for the antihypertensive response to captopril and diuretics are known to elevate the PRA, diuretics are frequently used to potentiate the antihypertensive effect of captopril in essential hypertensive patients. In conscious SHRs, furosemide was shown to increase PRA and to enhance the antihypertensive effect of captopril in SHRs. Interestingly, furosemide enhanced the onset but not the antihypertensive effect of the maximal dose of DuP 753 (10 mg/kg i.v.). This is in contrast to the findings observed in Sprague-Dawley normotensive rats that furosemide unmasked the hypotensive effect of DuP 753. The mechanism accounting for the lack of potentiation of the hypotensive effect of DuP 753 at 10 mg/kg i.v. by furosemide in SHRs is not clear. The present data, however, indicate that for captopril to reduce blood pressure to a similar extent as that produced by DuP 753 at 10 mg/kg i.v., a diuretic supplement is required. Therefore, our study agrees well with the clinical reports that captopril requires a diuretic to achieve a greater decrease in blood pressure. More importantly, our results suggest that DuP 753 may be used as a monotherapy in hypertensive patients without the supplement of diuretics. An increase in PRA after DuP 753 was observed in both the control and furosemide-treated SHRs. This is probably due to the blockade of Ang II-mediated negative feedback on renin release or to the hypotensive action-induced reflex sympathetic stimulation of renin release by DuP 753. An increase in PRA in SHRs after captopril was also observed (personal observations) and has been reported by others.

In an attempt to explain a greater antihypertensive efficacy of DuP 753 in SHRs, a series of experiments was conducted to examine possible mechanisms accounting for this greater effect. The present study shows that DuP 753 did not alter urine output in conscious SHRs, although it still lowered blood pressure, suggesting that diuresis is not involved in the antihypertensive effect of DuP 753. We also demonstrate that indomethacin, a cyclooxygenase inhibitor, did not block this response to DuP 753. The dose of
indomethacin used has been shown to be effective in reducing urinary prostaglandin E2 excretion by 80% for at least 2 hours. Therefore, our results suggest that prostaglandins do not contribute to the acute antihypertensive effect of DuP 753.

In our next experiment, we studied whether the antihypertensive effect of DuP 753 in SHRs is related to the blockade of the RAS. We hypothesized that even though the SHR has normal PRA, it is possible that this index may not indicate the actual activity of the system (see References 27 and 28). Although a number of extrarenal tissues have been shown to be capable of synthesizing renin or isorenins, the kidney is still the major source of renin (see Reference 24). Thus, removal of both kidneys should significantly reduce the influence of the RAS.

Several studies have shown that bilateral nephrectomy performed at 18–24 hours before the experiment abolishes the hypertensive effect of ACE inhibitors in SHRs (References 12, 29, and personal observations). However, these studies on ACE inhibitors do not rule out that nephrectomy may affect the potentiation of bradykinin by ACE inhibitors in SHRs. Because renal vasodilator prostaglandins do not appear to be involved in the antihypertensive action of DuP 753 and because DuP 753 is a selective Ang II receptor antagonist, it is likely that bilateral nephrectomy abolishes the release of renin from the kidney and consequently lowers the formation of Ang II, which accounts for the blockade of the antihypertensive effect of DuP 753.

Several studies have shown that bilateral nephrectomy performed at 18–24 hours before the experiment abolishes the hypertensive effect of ACE inhibitors in SHRs and dogs. The reasons for the discrepant results may be that these studies were carried out in anesthetized animals that were nephrectomized at 1–6 hours before the injection of the ACE inhibitors, whereas the studies described above were conducted in conscious animals that were nephrectomized at 18–24 hours before the experiment. If the ACE inhibitors were administered shortly after bilateral nephrectomy, there may still be a significant influence of the RAS on blood pressure that may account for their depressor responses.

Because the PRA is normal in the SHR, it is unlikely that circulating Ang II is responsible for the high blood pressure. This is supported by our finding that a specific Ang II monoclonal antibody KAA8, which neutralizes circulating Ang II, did not lower blood pressure in SHRs (unpublished data from our laboratory). It is, therefore, tempting to speculate that vascular renin derived from the kidney contributes to the local generation of Ang II for the maintenance of the vascular tone in SHRs. A similar hypothesis was also suggested by Thurston et al. Further, Ang II may be produced in the vasculature from other pathways that are insensitive to the inhibition of ACE inhibitors. Consequently, DuP 753 is more efficacious than captopril or other ACE inhibitors in blocking the influence of vascular RAS in SHRs. When the SHRs are sodium-depleted after furosemide treatment, the circulating Ang II, which is elevated, may play a more important role than the locally generated Ang II in the control of blood pressure. As the circulating Ang II is mostly formed via the pulmonary circulation, which is sensitive to the blockade of ACE inhibitors, captopril and DuP 753 reduce blood pressure to a similar extent in furosemide-treated SHRs. These speculations certainly require further investigation for confirmation. Nevertheless, our study indicates that this new class of nonpeptide Ang II receptor antagonists could become useful tools to define the role of the RAS in various physiological and pathophysiological states.

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