Kinins, Nitric Oxide, and the Hypotensive Effect of Captopril and Ramiprilat in Hypertension

Victoria Cachofeiro, Tohru Sakakibara, and Alberto Nasjletti

We investigated the role of kinins in the acute depressor effect of captopril and ramiprilat in spontaneously hypertensive rats. Since the vasodepressor action of kinins may be linked to the generation of prostaglandins and endothelium-derived relaxing factors, we also investigated the role of prostaglandins and nitric oxide in the blood pressure reduction caused by angiotensin converting enzyme inhibitors. To this end, we contrasted the hypotensive effects of captopril (10 mg/kg i.v.), ramiprilat (2 mg/kg i.v.), and the angiotensin II antagonist DuP 753 (30 mg/kg i.v.) in spontaneously hypertensive rats with and without pretreatment with a kinin antagonist (D-Arg-Pro-Hyp-Gly-Thi-Ser-D-Phe-Thi-Arg-trifluoroacetic acid) (200 μg/kg/min i.v.), an inhibitor of nitric oxide synthesis (L-arginine monomethyl ester) (15 mg/kg+10 mg/kg/hr i.v.), or an inhibitor of prostaglandin synthesis (indomethacin) (10 mg/kg i.v.). The kinin antagonist did not affect blood pressure in spontaneously hypertensive rats but did attenuate the hypotensive effect of captopril and ramiprilat; the kinin antagonist did not minimize the depressor action of DuP 753. The nitric oxide synthesis inhibitor increased blood pressure in spontaneously hypertensive rats and attenuated the hypotensive effect of captopril, ramiprilat, and DuP 753, but it did not impede the hypotensive effect of sodium nitroprusside. Pretreatment of hypertensive rats with indomethacin did not modify the acute hypotensive effect of ramiprilat or captopril. These data suggest a contribution of endogenous kinins and nitric oxide to the acute antihypertensive effect of captopril and ramiprilat in spontaneously hypertensive rats and of nitric oxide to the hypertensive effect of DuP 753. (Hypertension 1992;19:138–145)

Inhibitors of angiotensin I converting enzyme (ACE) (kininase II, E.C. 3.4.15.1), an enzyme that catalyzes conversion of angiotensin I to angiotensin II and degradation of bradykinin and related kinins,1 decrease blood pressure in clinical and experimental hypertension.2 The antihypertensive effect of ACE inhibitors is attributed primarily to diminished formation of angiotensin II, a pressor peptide that contributes to the pathogenesis of certain forms of hypertension.3,4 The antihypertensive effect of ACE inhibitors also is partially attributable to diminished degradation of kinins,5,6 vasodepressor peptides that promote antihypertensive functions including the synthesis of endothelium-derived relaxing factors and vasodepressor prostaglandins.5,7 Contribution of kinins to the acute antihypertensive effect of ACE inhibitors is evidenced by reports that such an effect is poorly expressed in hypertensive rats deficient in kininogen and kinins (Brown Norway rats with two kidney, one-clip hypertension)8 and is attenuated by the administration of kinin antibodies9 or kinin antagonists in models of renin-dependent hypertension in standard strains of rats.10,11

Spontaneously hypertensive rats (SHR) respond with marked lowering of blood pressure to acute treatment with ACE inhibitors.12 An argument against the participation of kinins in the mediation of the acute hypotensive effect of ACE inhibitors in SHR is that one of such agents, captopril, does not lower blood pressure further in SHR pretreated with DuP 753, a nonpeptide antagonist of angiotensin II.13 On the other hand, according to recent studies, SHR exhibit increased systemic and renal vasodilatory responsiveness to bradykinin,14,15 a feature that would be expected to amplify the expression of the kinin-mediated component in the antihypertensive effect of ACE inhibitors.
This study was designed to investigate the role of endogenous kinins in the acute antihypertensive effect of the ACE inhibitors captopril and ramiprilat in SHR. Since the vasodepressor action of kinins may be linked to the generation of prostaglandins and endothelium-derived relaxing factors, we also investigated the role of prostaglandins and nitric oxide (NO), recently identified as an endothelium-derived vasodilatory factor, in the blood pressure response to ACE inhibitors in SHR. Toward this end, the effect on blood pressure of treatment with captopril or ramiprilat was contrasted in SHR with and without pretreatment with a kinin antagonist, an inhibitor of NO synthesis, or an inhibitor of prostaglandin synthesis.

Methods

Studies were performed on male SHR (12–15 weeks old) and age-matched Wistar-Kyoto (WKY) normotensive rats from Charles River, Wilmington, Mass. The animals were fed ad libitum a standard chow (Ralston Purina Co., St. Louis, Mo.) and were given tap water to drink.

On the day of the experiment, rats under light methoxyflurane (Pitman-Moore, Inc., Muldelein, Ill.) anesthesia were instrumented with catheters (PE-50) placed in the right carotid artery and the right jugular vein for monitoring arterial pressure and intravenous administration of drugs, respectively. Blood pressure was continuously measured with a Statham transducer (model P23ID, Statham Division, Gould Inc., Oxnard, Calif.) and recorded on a Grass polygraph (model 7D, Grass Instruments Co., Quincy, Mass.). Catheters were brought to the exterior at the nape of the neck. Rats were allowed to recover from the anesthesia (120–150 minutes) before the beginning of the experiments, and they were awake and unrestrained in their cages during the experiments.

Protocol 1

These experiments were conducted to investigate the effect of ACE inhibitors captopril and ramiprilat, a more lipophilic agent, on the blood pressure of either WKY rats or SHR with and without pretreatment with the kinin antagonist D-Arg-Arg-Pro-Hyp-Gly-Thi-Ser-D-Phe-Thi-Arg-trifluoroacetic acid (TFA), which is known to reduce the vasodepressor effect of bradykinin. For this purpose, the blood pressure of WKY rats and SHR was monitored before and during continuous intravenous infusion of kinin antagonist (200 µg/kg/min) or saline vehicle for up to 75 minutes, and captopril (10 mg/kg) or ramiprilat (2 mg/kg) were given as an intravenous bolus injection 15 minutes after the onset of either infusion. In a related study, in SHR undergoing intravenous infusion of kinin antagonist (200 µg/kg/min) or saline vehicle, blood pressure was monitored before and after the angiotensin II receptor antagonist DuP 753 was administered as an intravenous bolus (30 mg/kg) 15 minutes after the onset of either infusion.

The effect of treatment with ramiprilat on the concentration of kinins in arterial plasma was examined in a complementary study in SHR. Rats received an intravenous injection of ramiprilat (2 mg/kg) or vehicle only. Sixty minutes later, the animals were anesthetized with methoxyflurane, the aorta was exposed through a midline abdominal incision, and aortic blood (4.0 ml) for assay of plasma kinins was rapidly drawn into a plastic syringe containing a mixture of inhibitors of kallikrein and of kininas. The concentration of kinins in duplicate plasma samples was measured by radioimmunoassay after sample purification by the method of Ando and Shimamoto. The concentration of kinins in plasma is expressed as picograms per milliliter. The bradykinin antibody was a gift from Dr. Kazuaki Shimamoto, Sapporo Medical College, Sapporo, Japan, and [125I]Tyr3-bradykinin was obtained from New England Nuclear, Boston, Mass.

Protocol 2

These experiments were designed to investigate the effect of the kinin antagonist on the blood pressure of SHR pretreated with either captopril, ramiprilat, or DuP 753. To this end, SHR received an intravenous injection of captopril (10 mg/kg), ramiprilat (2 mg/kg), or DuP 753 (30 mg/kg). Sixty minutes later, when the maximal hypotensive effect of these drugs had been achieved and blood pressure was stable, the rats were infused intravenously for 15
minutes with either kinin antagonist (200 μg/kg/min) or vehicle only.

Protocol 3

These experiments were performed to investigate the contribution of NO to the acute antihypertensive effect of ACE inhibitors. SHR and WKY rats received intravenously either the NO synthesis inhibitor \( \text{N}^2\)-monomethyl-L-arginine (LNMMA) (15 mg/kg bolus injection plus infusion at 10 mg/kg/hr) or vehicle only. Captopril (10 mg/kg), ramiprilat (2 mg/kg), or DUP 753 (30 mg/kg) were injected intravenously 15 minutes later, and their effects on the blood pressure of rats with and without LNMMA pretreatment were compared. In a related study, the effect of treatment with LNMMA on the blood pressure-lowering effect of bradykinin and sodium nitroprusside was examined in WKY rats and SHR anesthetized by sodium pentobarbital (60 mg/kg i.p.). The animals were given an intravenous injection of LNMMA (15 mg/kg or vehicle only, followed 15–20 minutes later by an intravenous infusion of bradykinin (10 μg/kg/min for 10 minutes) or sodium nitroprusside (10 μg/kg/min for 10 minutes).

Protocol 4

These experiments were performed to investigate the role of prostaglandins in the acute antihypertensive effect of ACE inhibitors. SHR and WKY rats received an intravenous injection of the cyclooxygenase inhibitor indomethacin (10 mg/kg) or vehicle only. Captopril (10 mg/kg) or ramiprilat (2 mg/kg) were injected intravenously 15 minutes later, and their effects on the blood pressure of rats with and without indomethacin pretreatment were compared. Ramiprilat and DUP 753, 2-n-butyl-4-chloro-5-hydroxymethyl-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole, potassium salt,13 were obtained from Hoescht AG, Frankfurt, FRG, and from E.I. du Pont de Nemours & Co., Wilmington, Del., respectively. The kinin antagonist D-Arg-Arg-Pro-Hyp-Gly-Thi-Ser-D-Phe-Thi-Arg-TFA (Hyp, L-4-hydroxyproline; Thi, B-2-thienyl-l-alanine) was synthesized by Drs. J. Stewart and R. Vavrek (Denver, Colo.). Captopril and indomethacin were purchased from Sigma Chemical Co., St. Louis, Mo., and \( \text{N}^2\)-monomethyl-L-arginine, acetate salt, was purchased from Calbiochem Co., La Jolla, Calif.

The results are expressed as mean±SEM. Comparison of the effects of the different drugs in SHR and WKY rats were made by computer-assisted two-way analysis of variance for multiple comparisons, using the Complete Statistical System (CSS) program (Statsoft Inc., Tulsa, Okla.). An a posteriori contrast test, incorporated into the CSS program, was applied according to the Bonferroni method whenever a level of significance was found (p<0.05). All other data were analyzed using an unpaired Student’s t test.

Results

Figure 1 contrasts the effect of captopril on blood pressure of WKY rats and SHR with and without kinin antagonist pretreatment. The basal blood pressure of SHR exceeded that of WKY rats (178±8 versus 104±8 mm Hg, p<0.01). Infusion of kinin antagonist at 200 μg/kg/min did not modify the blood pressure of either SHR (181±6 mm Hg) or WKY rats (106±3 mm Hg). Captopril given intravenously at 10 mg/kg caused a time-dependent decrease of mean blood pressure in both normotensive and hypertensive animals without kinin antagonist pretreatment. This effect was greater in SHR than in WKY rats (p<0.05). Kinin antagonist pretreatment did not modify the blood pressure–lowering effect of captopril in WKY rats but curtailed the effect in SHR. As a result of this, 45 and 60 minutes after captopril administration, the blood pressure reduction elicited by captopril was clearly attenuated (p<0.05) in SHR undergoing infusion of kinin antagonist.

Figure 2 (upper panel) illustrates the effect of ramiprilat on blood pressure of WKY rats and SHR with and without kinin antagonist pretreatment. The contribution of NO to the acute antihypertensive effect of ACE inhibitors. SHR and WKY rats received intravenously either the NO synthesis inhibitor LNMMA (15 mg/kg) or vehicle only. Captopril (10 mg/kg), ramiprilat (2 mg/kg), or DUP 753 (30 mg/kg) were injected intravenously 15 minutes later, and their effects on the blood pressure of rats with and without LNMMA pretreatment were compared. In a related study, the effect of treatment with LNMMA on the blood pressure-lowering effect of bradykinin and sodium nitroprusside was examined in WKY rats and SHR anesthetized by sodium pentobarbital (60 mg/kg i.p.). The animals were given an intravenous injection of LNMMA (15 mg/kg or vehicle only, followed 15–20 minutes later by an intravenous infusion of bradykinin (10 μg/kg/min for 10 minutes) or sodium nitroprusside (10 μg/kg/min for 10 minutes).

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attenuated in SHR undergoing infusion of kinin antagonist. However, as revealed by complementary experiments, the arterial plasma concentration of kinins was similar in SHR with (123±24 pg/ml, n=9) and without (128±46 pg/ml, n=4) ramiprilat treatment. The effect of the angiotensin II antagonist DuP 753 on the blood pressure of SHR with (170±7 mm Hg) and without (169±6 mm Hg) kinin antagonist pretreatment is depicted in Figure 2 (lower panel). DuP 753 at 30 mg/kg induced a sharp and prolonged reduction of blood pressure that was similar in rats with and without pretreatment with the kinin antagonist.

Figure 3 shows the effect of kinin antagonist on the blood pressure of SHR pretreated with captopril, ramiprilat, or DuP 753. Sixty minutes after the onset of drug treatment, blood pressure had decreased (p<0.05) from 176±6 to 143±5 mm Hg with captopril, from 166±8 to 119±7 mm Hg with ramiprilat, and from 166±4 to 133±8 mm Hg with DuP 753. In these settings, the kinin antagonist infused intravenously over a 15-minute period increased (p<0.05) blood pressure by 17±2 and 11±2 mmHg in SHR pretreated with captopril and ramiprilat, respectively, but was without effect on the blood pressure of rats pretreated with DuP 753. Vehicle infusion did not affect blood pressure in any of the aforementioned settings.

Figures 4–6 illustrate the effects of captopril, ramiprilat, and DuP 753, respectively, on blood pressure of SHR and WKY rats with and without pretreatment with LNMMA, an inhibitor of NO synthesis. Intravenous injection of LNMMA at 15 mg/kg plus infusion at 10 mg/kg/hr increased (p<0.01) blood pressure in WKY rats from 100±4 to 122±4 mm Hg and in SHR from 169±5 to 190±5 mm Hg. The administration of vehicle alone did not change blood pressure in either group of rats. In WKY rats, pretreatment with LNMMA did not modify the modest reduction of blood pressure induced by captopril (Figure 4), ramiprilat (Figure 5), or DuP 753 (Figure 6). In contrast, in SHR pretreated with LNMMA, the blood pressure–lowering effect of captopril (Figure 4) and ramiprilat (Figure 5) were greatly attenuated. Unexpectedly, the blood pressure–lowering effect of DuP 753 (Figure 6) in SHR pretreated with LNMMA also was attenuated. In related experiments, comparison of the blood pressure reduction elicited by bradykinin (10 µg/kg/min i.v.) before and after LNMMA treatment (15 mg/kg i.v.) revealed that the hypotensive effect of the kinin was attenuated (p<0.05) by the inhibitor of NO synthesis in both WKY rats (−41±2 versus −18±5 mm Hg) and SHR (−68±2 versus −26±6 mm Hg). In contrast,
after LNMMA treatment, the hypotensive effect of sodium nitroprusside (10 μg/kg/min i.v.) was increased (p<0.05) in WKY rats (-70±5 versus -45±4 mm Hg) while remaining unchanged in SHR (-67±9 versus -60±4 mm Hg).

Figure 7 contrasts the effect of captopril (upper panel) and ramiprilat (lower panel) on blood pressure in SHR with and without pretreatment with the cyclooxygenase inhibitor indomethacin. The intravenous administration of indomethacin at 10 mg/kg did not modify the blood pressure of SHR (169±13 mm Hg). Pretreatment with indomethacin did not significantly affect the fall in blood pressure elicited by captopril or ramiprilat in SHR. Similarly, the modest reduction of blood pressure elicited by captopril in WKY rats was nearly identical in animals with and without indomethacin pretreatment (−14±2 versus −12±3 mm Hg, −15±3 versus −16±2 mm Hg, −13±3 versus −17±3 mm Hg, and −10±3 versus −8±3 mm Hg at 15, 30, 45, and 60 minutes, respectively, after onset of treatment with captopril).

Discussion

The present study demonstrates that pretreatment with an antagonist of kinins significantly attenuates the acute blood pressure–lowering response to intravenous administration of captopril or ramiprilat in SHR. The study also documents that blood pressure rises during intravenous infusion of kinin antagonist in SHR pretreated with captopril or ramiprilat, resulting in partial reversal of the acute antihypertensive effect of either ACE inhibitor. Because the kinin antagonist is without effect on the acute hypotensive effect of the angiotensin II receptor blocker DuP 753 in SHR, the modest reduction of blood pressure elicited by captopril in WKY rats, or the blood pressure of otherwise untreated SHR and WKY rats, specificity can be ascribed to the effect of this agent in impeding the acute antihypertensive action of captopril and ramiprilat in SHR. This is not to say that the kinin antagonist interferes with the antihypertensive effect of ACE inhibitors in SHR only. Indeed, it was previously reported that kinin antagonist pretreatment also attenuates the blood pressure–lowering effect of enaprilat in rats with hypertension induced by aortic ligation between the renal arteries11 and of ramipril in rats with two kidney, one-clip hypertension.8 Additionally, a kinin antagonist also was found to increase blood pressure in rats with two kidney, one-clip hypertension that had been pretreated with enalapril, resulting in partial reversal of the antihypertensive effect of the ACE inhibitor.10 Our finding that a kinin antagonist can attenuate or reverse partially the blood pressure–lowering ef-
ACE inhibitors may be expected to increase blood and tissue levels of vasodepressor kinins as a consequence of diminished ACE catalyzed degradation of kinins in vivo. However, in the present study the concentration of kinins in arterial plasma was nearly identical in SHR with and without ramiprilat treatment. Similarly, enaprilat was reported not to increase the arterial plasma kinin concentration of rats with aortic ligation-induced hypertension. These observations are particularly interesting since the vasodepressor effect of ramiprilat in SHR and of enaprilat in rats with aortic ligation-induced hypertension were attenuated by pretreatment with a kinin antagonist. Thus, the possibility arises that the kinin-mediated component of the acute antihypertensive effect of ACE inhibitors is related to tissue rather than to circulating kinins. Pertainning to this point, recent studies have demonstrated expression of glandular kallikrein in arterial vessels and of kallikrein and kininogen in aortic smooth muscle cells.

Our finding that pretreatment with LNMMA attenuates the hypotensive effect of bradykinin in WKY rats and SHR is generally consistent with the results of previous studies that implicate NO in the mechanism of kinin-induced vasodilation and hypertension, thus raising the possibility that NO participates in the mediation of that component of the antihypertensive effect of ACE inhibitors that is related to kinins. In the present study, comparison of the blood pressure-lowering effect of captopril and ramiprilat in SHR with and without pretreatment with LNMMA reveals that the acute antihypertensive effect of both ACE inhibitors is diminished in SHR pretreated with the NO synthesis inhibitor. These findings are consistent with a contributory role of NO in the acute blood pressure-lowering effect of ACE inhibitors in SHR. Whether the NO-mediated component of the hypotensive effect of ACE inhibitors in SHR is the manifestation of activation of NO synthesis by endogenous kinins is yet to be established. A recent study showed that the ACE inhibitor perindopril enhances endothelium-dependent vasorelaxing responses to bradykinin that are mediated by NO. However, perindopril also was reported to amplify endothelium-dependent vasorelaxing responses to acetylcholine and thrombin.

In the present study, comparison of the blood pressure reduction elicited by DuP 753 in SHR with and without LNMMA pretreatment reveals that the hypotensive effect of the angiotensin II antagonist is minimized in rats receiving the inhibitor of NO synthesis. However, pretreatment with LNMMA did not impede the hypotensive effect of sodium nitroprusside in SHR and WKY rats, arguing against the possibility that LNMMA attenuates vasodilator responsiveness in a nonspecific manner. Collectively, these findings suggest involvement of NO in the acute hypotensive effect of DuP 753 in SHR. The mechanism underlying such an involvement is unknown, since information on whether DuP 753 stimulates NO

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**FIGURE 7.** Line graphs show change of mean arterial pressure (MAP) induced by captopril (10 mg/kg i.v.) (upper panel) or ramiprilat (2 mg/kg i.v.) (lower panel) in spontaneously hypertensive rats (SHR) pretreated with vehicle or indomethacin (10 mg/kg i.v.). Results are mean ± SEM. n, Number of experiments.

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The effect of captopril and ramiprilat in SHR and a brief report that passive immunization with kinin antibodies reduces the acute hypotensive effect of captopril in SHR, suggest participation of kinins in the acute antihypertensive effect of ACE inhibitors in this model of hypertension. Conceivably, the kinin-mediated component of the blood pressure-lowering effect of ACE inhibitors may have a favored expression in SHR because vasodilatory responsiveness to kinins appears to be increased in this model. This does not detract from the role of diminished generation of angiotensin II as a determining factor of the antihypertensive effect of ACE inhibitors in SHR, animals in which renin antibodies and the angiotensin II receptor antagonist DuP 753 also were shown to lower blood pressure. Previous studies have suggested contribution of kinins to the antihypertensive effect of ACE inhibitors in rats with aortic ligation-induced hypertension and two kidney, one-clip hypertension, which are classical models of angiotensin II–dependent hypertension. Reports that kinins decrease vasoconstrictor responsiveness to angiotensin II23,24 raise the possibility that the kinin-mediated component of the acute antihypertensive effect of ACE inhibitors in SHR and rats with renovascular hypertension relates, at least in part, to interference with pressor mechanisms initiated by angiotensin II.
synthesis is lacking. An intriguing possibility is that vascular NO synthesis in SHR is stimulated by increments of blood flow that may follow blockade of vascular angiotensin II receptors with DuP 753. In this respect, there are reports that the endothelium of perfused arterial vessels, in response to increases in flow, a relaxing factor resembling NO.29,30

In agreement with the notion that kinins and vasodepressor prostaglandins contribute in an interrelated manner to the antihypertensive effect of ACE inhibitors, one or more ACE inhibitor was shown to promote vascular prostaglandin E2 synthesis via a kinin-mediated mechanism31,32 and to increase the circulating levels of a prostaglandin E2 metabolite and the renal excretion of 6-keto-prostaglandin F1α in SHR.33 Moreover, the acute antihypertensive effect of captopril in patients with essential hypertension was attenuated by concurrent treatment with either indomethacin or aspirin.34

In the present study, however, pretreatment of SHR with indomethacin did not attenuate the acute blood pressure-lowering response to the administration of captopril or ramiprilat, thus arguing against an involvement of vasodepressor prostaglandins in the antihypertensive effect of either ACE inhibitor in SHR. Previous studies also have documented that the antihypertensive effect of captopril in SHR either remains unchanged or is enhanced by concurrent treatment with inhibitors of prostaglandin synthesis.35,36

In summary, we found that the acute antihypertensive effect of captopril and ramiprilat in SHR is specifically attenuated by both a kinin antagonist and an inhibitor of NO synthesis. Based on these observations, we suggest that both kinins and NO participate in the implementation of the acute antihypertensive effect of ACE inhibitors in SHR.

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**KEY WORDS** • bradykinin • nitric oxide • prostaglandins • essential hypertension • kinins • angiotensin II
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