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Effects of Intracerebroventricular Captopril on the Central Pressor Response to Bradykinin in Normotensive and Hypertensive Rats

Cheol Ho Yeum and Pyung Jin Yoon

Department of Physiology, Chosun University Medical School, Kwangju 501-759

=ABSTRACT=

Captopril, an inhibitor of angiotensin converting enzyme, is also known to inhibit the degradation of bradykinin. We examined the effects of intracerebroventricular (ICV) captopril on the central pressor response to bradykinin in normotensive, 2-kidney, 1 clip Goldblatt (GHR) and deoxycorticosterone acetate (DOCA)-salt hypertensive rats. Captopril (1 mg) and bradykinin (5 nmol) were administered into the right lateral cerebral ventricle, and blood pressure and heart rate were continuously monitored throughout the experiment. ICV captopril alone did not affect the blood pressure within 10 minutes but it significantly augmented the central pressor response to bradykinin in GHR. On the contrary, captopril was without effect on the pressor response to bradykinin in normotensive and DOCA-salt rats. These findings indicate that endogenous kinins are not critical in regulating arterial pressure in normotensive and DOCA hypertensive rats. However, in GHR, an enhanced activity of the brain kallikrein-kinin system in maintaining the high blood pressure is suggested.

Key Words: Captopril, Intracerebroventricular bradykinin, Goldblatt hypertension

INTRODUCTION

Bradykinin has been known to be a vasodilator peptide which causes hypotension and tachycardia (Nakano, 1965; Harrison et al, 1968). When administered into the cerebral ventricle, however, we and others (Correa & Graeff, 1974; Brooks et al, 1986; Lindsey et al, 1988; Yeum et al, 1992) have previously observed that bradykinin elicits a pressor effect.

Kinins are released in the blood stream from their precursors, and are inactivated by kininase II, an angiotensin converting enzyme (Yang et al, 1970). Thus, the degradation of bradykinin may be inhibited by captopril, an inhibitor of the converting enzyme. Madeddu et al (1990) found that central administration of captopril caused an increase in blood pressure in spontaneously hypertensive rats but no change in normotensive rats. They speculated that the brain kallikrein-kinin system plays a role in the central regulation of blood pressure in hypertensive rats.

Furthermore, the pressor response to centrally administered bradykinin was more sensitive in genetically (Lindsey et al, 1988) or renovascular (Yeum et al, 1992) hypertensive rats than in normotensive animals. Taken together, we hypothesized that the role of central kinin sys-

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tem in regulating blood pressure is potentiated in experimental hypertension. Captopril, either alone or combined with bradykinin, was administered intracerebroventricularly in normotensive (NTR), 2-kidney, 1 clip Goldblatt (GHR) and deoxycorticosterone acetate (DOCA)-salt hypertensive rats.

METHODS

2-kidney, 1 clip hypertension was made in male Sprague-Dawley rats (150~200 g) by clipping the left renal artery with a silver clip having an internal gap of 0.2 mm; the contralateral kidney was left untouched. DOCA hypertensive rats underwent nephrectomy and were given subcutaneous implantation of DOCA (200 mg) strip plus NaCl (1 %) drinking. All animals were used 3~4 weeks later. Age-matched male rats served as controls.

The experiment was done under pentobarbital (50 mg/kg, intraperitoneally) anesthesia. Intracerebroventricular (ICV) administration was performed in a volume of 10 ul through a cannula inserted into the right lateral cerebral ventricle. Captopril (Sigma, 1 mg) was injected 30 minutes before administration of bradykinin (Sigma, 5 nmol). Blood pressure and heart rate (HR) were continuously recorded through a pressure transducer (Gould, p23 Db) from the right femoral artery.

Statistical significance was determined using a Student's t test. Results are expressed as means±SEM.

RESULTS

Cardiovascular responses to captopril

Mean arterial pressure (MAP) in GHR (172±4 mmHg) and DOCA hypertensive rats (143±5 mmHg) were significantly higher than in NTR (118±6 mmHg). The ICV administraton of captopril (1 mg) caused a decrease in MAP in both NTR and GHR, while it was without effect in DOCA hypertensive rats. The depressor response to captopril began in 20 minutes, and remained for 1 hour following the injection. The blood pressure fall was accompanied by an increase in HR (Fig. 1).

Effects of captopril on the pressor response to bradykinin

ICV bradyinin (5 nmol) transiently increased MAP in NTR, the magnitude of which was slightly enhanced by treatment with ICV captopril (1 mg). No significant changes in HR were observed (Fig. 2).

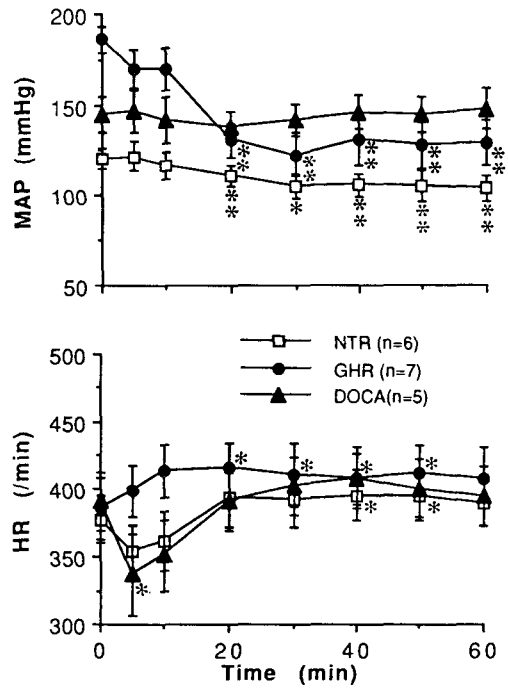

*Fig. 1. Effects of intracerebroventricular captopril on the mean arterial pressure (MAP) and heart rate (HR) in normotensive (NTR), 2-kidney, 1 clip hypertensive (GHR) and DOCA-salt hypertensive rats. At time 0, captopril (1 mg) was administered intracerebroventricularly. *P<0.05, **P<0.01, campared with 0 min value. n=number of animals.*

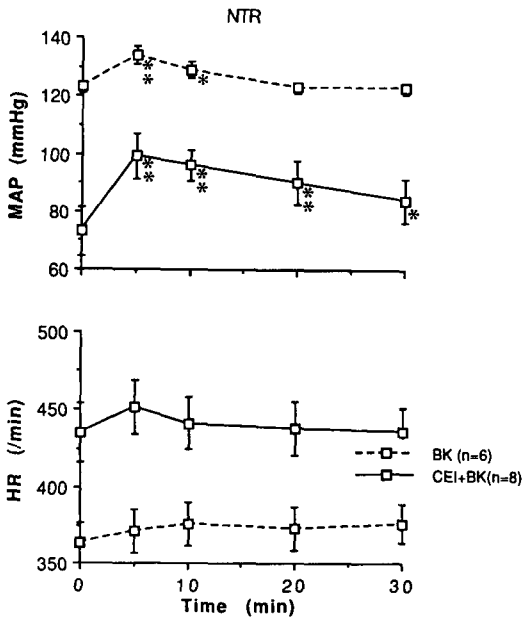

*Fig. 2. Changes in mean arterial pressure (MAP) and heart rate (HR) in normotensive rats injected with intracerebroventricular (ICV) bradykinin (BK, 5 nmol). CEI (converting enzyme inhibitor)+BK represents captopril treated group (1 mg, ICV). BK was injected intracerebroventricularly at time 0 and captopril was administered 30 min before the BK. *P<0.05, **P<0.01, compared with 0 min value. n=number of animals.*

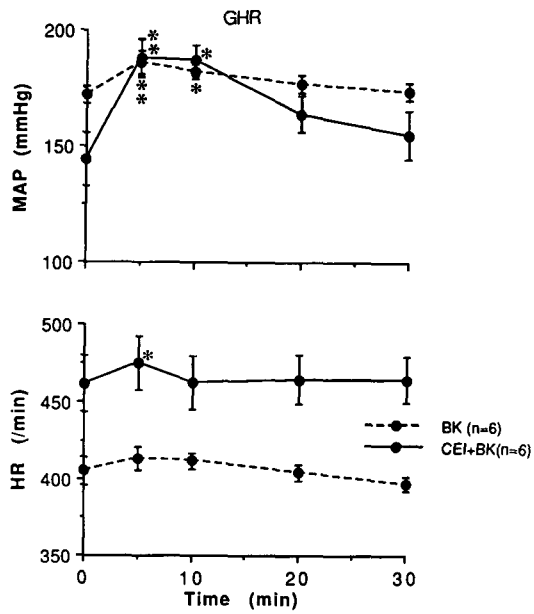

*Fig. 3. Changes in mean arerial pressure (MAP) and heart rate (HR) in 2-kidney, 1 clip hypertensive rats injected with intracerebroventricular (ICV) bradykinin (BK, 5 nmol). CEI+BK respresents captopril treated guoup (1 mg, ICV). BK was injected intracerebroventricularly at time 0 and captopril was administered 30 min before the BK. *P<0.05, **P<0.01, compared with 0 min value. n=number of animals.*

The central pressor response to bradykinin was markedly enhanced by treatment with captopril in GHR, as shown in Fig. 3. ICV bradykinin transiently increased HR in captopril-treated group.

In DOCA hypertensive rats, ICV captopril did not affect the magnitude of the pressor response to bradykinin (Fig. 4).

The maximal pressor effects of bradykinin are summarized in Fig. 5. ICV captopril significantly enhanced the maximal pressor effects of bradykinin in GHR, while significant alterations were not noted either in NTR or in DOCA hypertensive rats.

DISCUSSION

Kinin levels can be increased not only by stimulation of their release but also by inhibition of the enzymes responsible for their degradation (Kariya et al, 1982; Diz, 1985). The pressor response induced by inhibition of kininase II was observed only under high doses of captopril (Unger et al, 1981), that is why 1 mg of captopril was used in this experiment. The action of brain kininase is rapid, as suggested by the relatively high pressor threshold dose and the short half-life of ICV administered bradykinin (Madeddu et al, 1990). The

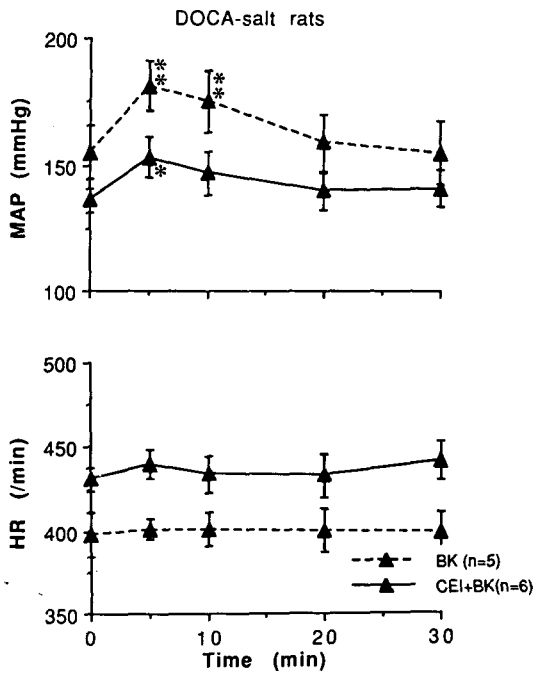

*Fig. 4. Changes in mean arerial pressure (MAP) and heart rate (HR) in DOCA-salt hypertensive rats injected with intracerebroventricular (ICV) bradykinin (BK, 5 nmol). CEI + BK respresents captopril treated guoup (1 mg, ICV). BK was injected intracerebroventricularly at time 0 and captopril was administered 30 min before the BK. *$P<0.05$, **$P<0.01$, compared with 0 min value. n=number of animals.*

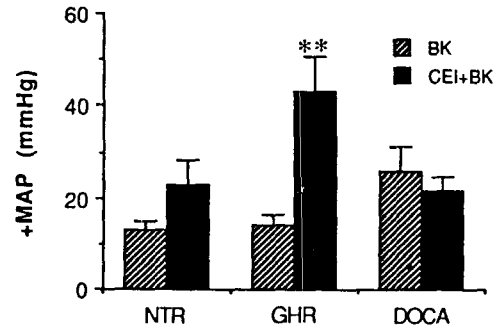

*Fig. 5. Comparison of the maximal pressor effects of bradykinin (BK, 5 nmol) with and without pretreatment of captopril (1 mg) in normotensive (NTR), 2-kidney, 1 clip hypertensive (GHR) and DOCA-salt hypertensive rats. CEI + BK represents captopril treated group. Captopril was administered 30 min before the injection of BK. Each point represents the mean of 5~10 experiments. **$P<0.01$, compared with the value in BK administration.*

pressor response to bradykinin was observed transiently within 5~10 minutes following the central administration (Takahashi & Bunag, 1981; Lindsey et al, 1988; Yeum et al, 1992).

Our results demonstrate that the elevation in endogenous kinin levels by ICV captopril cause no change in MAP in NTR and hypertensive rats. These results are not consistent with the observations that ICV administration of captopril increased blood pressureinspontaneously hypertensive rats (Madeddu et al, 1990), although they also observed no change of MAP in NTR. This discrepancy might be explained by different mechanisms maintaining hypertension in the different models of hypertension.

ICV administration of inhibitors of angiotensin converting enzyme exerts a long-lasting hypotension, an effect that was attributed to the blockade of angiotensin II formation (Unger et al, 1981; Phillips & Kimura, 1986), which was also shown in our experiment. The finding that the magnitude of the depressor effect by captopril was more enhanced in GHR than in NTR, suggests an inhibition of the brain renin-angiotensin system by captopril. This speculation is supported by the finding that captopril was without effect in DOCA-hypertensive rats, which are associated with already diminished activity of the renin-angiotensin system. The increase in HR that accompanied the depressor response might be explained by the baroreflex.

In the previous study, we have found that the pressor response to ICV bradykinin was similar in NTR and GHR at the dose of 5 nmol (Yeum et al, 1992), so we used the dose in this experiment. Although captopril alone did not affect the blood pressure within 10 minutes, it

augmented the pressor response to bradykinin both in NTR and GHR. Similar results have shown by Kondo et al (1979) in conscious rats. These observations imply that captopril inhibits the bradykinin-degradation in the brain (Yang et al, 1990). On the other hand, because of the broad substrate specificity of angiotensin converting enzyme (Erdos & Skidgel, 1986), ICV captopril may alter the activity of other pressor peptides such as enkephalins, neurotensin, and substance P, which are potential substrates for angiotensin converting enzyme. However, captopril alone did not cause a pressor response. Therefore the enhanced pressor response to exogenous bradykinin by ICV captopril in the present study might be attributed to an increase in kinin levels.

In DOCA hypertensive rats, ICV captopril did not augment the pressor effect of bradykinin. This finding suggests that the kinin levels may not be altered in the central nervous system in these rats. The role of kallikrein-kinin system in DOCA induced hypertension remains unclear, although the endogenous bradykinin may counteract the elevation of vascular resistance peripherally (Seino et al, 1990).

In spite of the augmented pressor response to bradykinin due to ICV captopril, no significant changes in HR were noted except a tranisent increase in GHR. This finding implies that the augmented pressor effect of bradykinin by ICV captopril is not mediated via a cardiac acceleration. We and others (Correa & Graeff, 1975; Yeum et al, 1992) previously observed that ICV bradykinin elicits a pressor response without change in HR.

ICV captopril significantly augmented the maximal pressor effect of bradykinin only in GHR, suggesting that the brain kallikrein-kinin system plays some role in renal hypertensive rats. The different response to kininase II inhibition in hypertensive and normotensive rats might be caused by a greater sensitivity to kinins (Bunag & Takahashi, 1981), attributed to a dysfunction of the central cardiovascular regulatory mechanisms (Yamori et al, 1970), or to a markedly reduced kininase activity (Lindsey et al, 1988). A major difference in the kallikrein-kinin binding protein between hypertensive and normotensive rats has been found in the brain, which may result in different modulation of kallikrein activity, delivery, and degradation (Chao & Chao, 1988). All these findings support the hypothesis that the altered brain kallikrein-kinin system might be involved in maintaining high blood pressure in hypertension.

In summary, our results suggest that the brain kallikrein-kinin system has a role in maintaining the high blood pressure in renal hypertensive rats.

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