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Central Pressor Mechanisms of Bradykinin in 2-Kidney, 1 Clip Goldblatt Hypertensive Rats

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= ABSTRACT =

Central cardiovascular effects of bradykinin were examined in anesthetized normotensive (NTR) and 2-kidney, 1 clip Goldblatt hypertensive rats (GHR). Bradykinin (0.5~10nmol) was administered into the right lateral cerebral ventricle, while blood pressure and heart rate (HR) were continuously monitored. In both NTR and GHR, intracerebroventricular bradykinin produced a dose-dependent increase in mean arterial pressure (MAP) without significant changes in HR. GHR were more sensitive in the pressor response than NTR. The pressor response to bradykinin was attenuated by treatment with hexamethonium (2.5mg/kg/min, IV) or phentolamine (2mg/kg, IV) in both NTR and GHR. Reserpine treatment (2mg/kg/day, intramuscularly, 2 days) did not affect the central pressor effect of bradykinin in NTR but it attenuated the pressor effect in GHR. Pretreatment with indomethacin (10mg/kg, intraperitoneally) or saralasin (20μg/kg/min, IV) was without effects on the pressor response to bradykinin. These results indicate that the central pressor effect of bradykinin is, at least in part, due to excitation of the autonomic nervous activity. Mechanisms other than the enhanced sympathetic nervous activity cannot be ruled out, however. It is also suggested that the sensitivity to bradykinin is increased in the GHR.

Key Words: Intracerebroventricular, Bradykinin, 2-kidney, 1 clip hypertension.

INTRODUCTION

The direct action of bradykinin on the vascular smooth muscle is to cause a relaxation, eliciting a widespread vasodilation, hypotension and tachycardia (Maxwell et al, 1962; Nakano, 1965; Harrison et al, 1968). In contrast, when bradykinin is administered into the cerebral ventricle it elicits a pressor effect (Correa & Graeff, 1974; Brooks et al, 1986; Lindsey et al, 1988). Furthermore, when it is administered through the carotid artery, the results are conflicting. An increase in blood pressure (Pearson et al, 1969), a decrease (Ricciopo Neto et al, 1974) and a biphasic response (Takahashi & Bunag, 1981) have been reported.

The mechanism underlying the pressor effect of central bradykinin may be of complexity. Evidence has been accumulated to suggest an interaction of the autonomic nervous system (Lambert & Lang, 1970; Takahashi & Bunag, 1981; Wilkinson & Scroop, 1986), prostaglandins (Kondo et al, 1979; Wilkinson & Scroop, 1985) and renin-angiotensin system (Madeddu et al, 1990).

On the other hand, Lindsey et al (1988) found that intracerebroventricular administration of bradykinin elicited a pressor response in normotensive and spontaneously hypertensive rats and they concluded that hypertensive rats were more sensitive to bradykinin than nor-

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motensive rats. Therefore, one may hypothesize that the central effect of bradykinin is altered in the 2-kidney, 1 clip renal hypertensive rats.

The present study deals with the identification of a central pressor effect of bradykinin in normotensive and renal hypertensive rats. Possible mechanisms of the central pressor effect of bradykinin were also investigated.

METHODS

Two-kidney, 1 clip renal hypertension was made using male Sprague-Dawly rats (150-200g) by constriction of the left renal artery with a silver clip (internal gap of 0.2mm) under pentobarbital anesthesia, and were used 3-4 weeks later. Body weight-matched male rats served as control.

On the day of the experiment, animals were anesthetized with sodium pentobarbital (50mg/kg, intraperitoneally). Intracerebroventricular (ICV) administration of bradykinin (Sigma, 0.5~10nmol) was performed through a cannula which had been located 4.5mm from the surface of the skull, 1.5mm lateral and 0.6mm posterior to the bregma. Correct placement of the cannula was confirmed at the end of the experiment by injecting blue dye, checking for the presence of the dye in all the brain ventricles, including the fourth.

MAP and HR were continuously monitored through a pressure transducer (Gould statham P23Db) connected to the right femoral artery. A catheter introduced into the right femoral vein served as a route for intravenous (IV) administration.

Pretreatments with drugs were performed as follows:Hexamethonium (Sigma, 2.5mg/kg/min, IV), phentolamine (Ciba, 2mg/kg, IV, 20 min prior to bradykinin), reserpine (Sigma, 2mg/kg/day, intramuscularly, 2days), indomethacin (Sigma, 10mg/kg, intraperitoneally, 40 min prior to bradykinin) and saralasin (Sigma, 20ug/kg/min, IV) The blood pressure response to ICV bradykinin was examined before and after treatment of each drug, except for reserpine, in which separate animals were used with or without reserpine treatment.

Statistical analysis of independent data was accomplished with Student's t test. Results are presented as means ± SE.

RESULTS

Cardiovascular reponses to bradykinin

The ICV administration of bradykinin (5nmol) transiently increased MAP in both

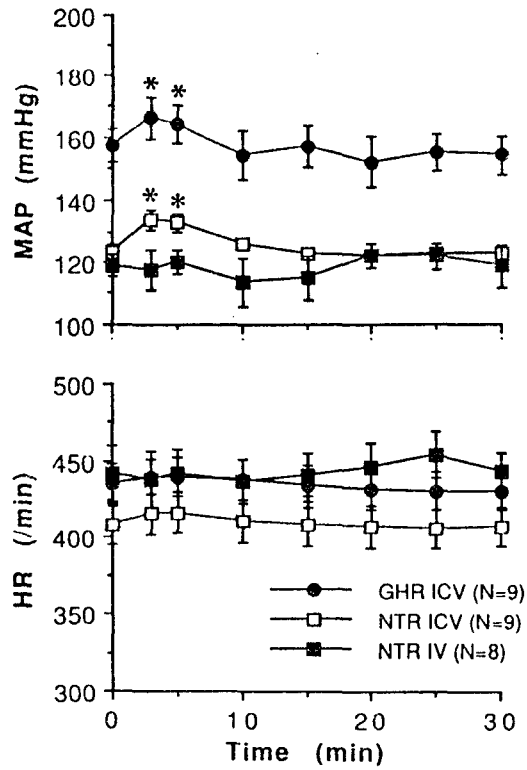

*Fig. 1. Mean arterial pressure (MAP) and heart rate (HR) in normotensive (NTR) and 2-kidney, 1 clip Goldblatt hypertensive rats (GHR) injected with intracerebroventricular (ICV) bradykinin (5 nmol). The results obtained by the intravenous (IV) injection of the same dose of bradykinin in NTR are also shown. Each point represents mean ± SE. * P<0.05, compared to the basal value. N = number of animals.*

NTR and GHR. Significant changes in HR were noted neither in NTR nor in GHR. The IV injection of the same dose of bradykinin was without effects on MAP and HR (Fig.1). Vehicle (10ul saline) alone injected ICV did not affect MAP or HR. The pressor effect of ICV bradykinin (0.5~10nmol) was dose-dependent (Fig.2). Nineteen out of 112 experiments showed biphasic responses consisting of initial vasodepression followed by a pressor effect.

Effects of drug treatments on the pressor response

The pressor response to ICV bradykinin was attenuated by treatment with hexamethonium (2.5mg/kg/min) or phentolamine (2mg/kg). Reserpine treatment (2mg/kg/day) did not affect the pressor response to bradykinin in NTR but was associated with a significant attenuation of the pressor response in GHR. The treatment with indomethacin (10mg/kg) or saralasin

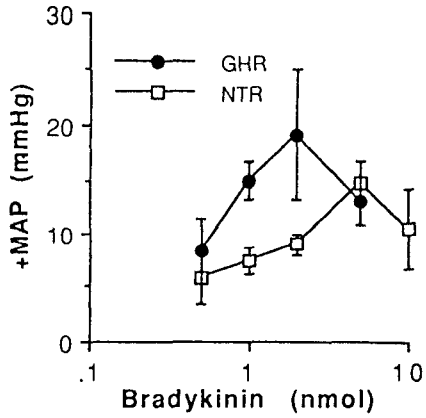

Fig. 2. Dose-pressor response curves for the bradykinin injected into the ventricles of NTR and GHR. Each point represents the mean ± SE obtained from 5 to 10 rats. + MAP denotes increase in mean arterial pressure following the drug injection. The dose of bradykinin was serially increased after complete return of the blood pressure to the basal level.

Table I. Increases of mean arterial pressure (mmHg) following the intracerebroventricular injection of bradykinin before and after treatments with various drugs

Drugs	Before	After	N
NTR			
hexamethonium	11.5±1.2	6.6±1.0**	8
phentolamine	11.2±1.6	6.2±0.9*	6
reserpine	(14.8±2.0)#	15.4±1.6	10
indomethacin	10.5±1.2	11.3±1.2	6
saralasin	13.9±1.4	12.3±2.5	7
GHR			
hexamethonium	14.8±1.9	10.5±2.3*	6
phentolamine	11.0±2.9	2.8±1.1*	4
reserpine	(15.0±1.8)#	1.8±0.6**	4
indomethacin	12.6±1.0	8.3±1.9	7
saralasin	8.6±0.8	9.6±1.2	5

The amounts of bradykinin administered were 5 and 1 nmol in NTR and GHR, respectively. Values are means±SE. Hexamethonium (2.5mg/kg/min, started before 30 min prior to bradykinin and continued throughout the experiment), phentolamine (2mg/kg, 20 min prior to bradykinin), reserpine (2mg/kg/day, 2days), indomethacin (10mg/kg, 40 min prior to badykinin), saralasin (20ug/kg/min, started before 30 min prior to bradykinin and continued throughout the experiment). #Pressor response to ICV bradykinin in control rats without drug treatment was denoted and was compared with that in the reserpine-treated rats (non-paired comparison). * $P<0.05$, ** $p<0.01$; compared to the value before treatment (paired comparison). N=number of animals.

(20μg/kg/min) had no significant effects on the pressor response to bradykinin in both NTR and GHR (Table 1).

DISCUSSION

Bradykinin injected into the lateral ventricle of NTR caused a pressor response. In a few cases, bradykinin showed biphasic responses (Takahashi & Bunag, 1981) consisting of initial depression followed by a pressor effect. The same dose of the drug injected IV was without significant effects on the blood pressure, suggesting that the cardiovascular effect of ICV bradykinin may be confined to the central nervous system and cannot be attributable to a leakage of the drug into the systemic circulation.

In spite of the pressor response, no significant changes in HR were noted following the ICV bradykinin. These findings are in agreement with those reported by Correa & Graeff (1975) who also found no changes of HR in rats. Other investigators (Graeff et al, 1969; Wilkinson & Scroop, 1985) reported a tachycardia accompanied by the pressor response when injected into the cerebral ventricles in unanesthetized rabbits or continuously infused into the carotid and vertebral artery in dogs. The discrepancy in the HR response may be ascribed to differences in species or methods employed.

The pressor responses were dose-dependent. This finding brings about the possibility that bradykinin acts at specific receptor sites in the central nervous system. Correa & Graeff (1975) reported that the pars ventralis of the lateral septal area is involved in the pressor action of bradykinin, while others (Wilkinson & Scroop, 1985) suggested the area postrema as site of action.

The pattern of the pressor response in GHR was similar to that in NTR. However, the GHR were more sensitive than NTR. The maximal pressor effect was noted at 2 nmol in GHR, and at 5 nmol in NTR. In addition, the dose-response curve was steeper in GHR than in NTR. An exaggerated sympathetic response to bradykinin has been found in spontaneously hypertensive rats (Bunag & Takahashi, 1981). Lindsey et al (1988) have also shown that spontaneously hypertensive rats were more sensitive to bradykinin injected into the lateral ventricle, and they suggested these rats have a markedly reduced kininase activity and increased receptor sensitivity. The greater sensitivity of GHR in the present study may also be attributed to alterations in receptor sensitivity or central kininase activity.

The pressor effect of ICV bradykinin may be related to an enhanced activity of the peripheral sympathetic nervous system. This is substantiated by the findings that either the ganglionic blocker hexamethonium or the α-adrenergic antagonist phentolamine prevented or diminished the effect in both NTR and GHR. This is in agreement with the previous report in which sympathetic nervous activity was referred as mechanisms responsible for the pressor effect of bradykinin (Lambert & Lang, 1970). In addition, withdrawal of cardiac vagal tone was also suggested as the central pressor mechanism of bradykinin in dogs (Wilkinson & Scroop, 1986). Taken together, it may be postulated that the central pressor action of bradykinin was mediated by modulation of the peripheral autonomic nervous activity.

Although the pressor effect of ICV bradykinin was attenuated by pretreatment with hexamethonium or phentolamine, the reserpine treatment, which effectively depletes catecholamines from the brain as well as the peripheral tissues, did not affect the hypertensive effect of bradykinin in NTR. Although catecholamine synthesis was to some extent impaired by the chemical sympathectomy, that achieved by reserpine, the relative increase in MAP was similar to that of intact animals following intravenous administration of bradykinin antagonist (Mulinari et al, 1988). They suggested an up-regulation of adrenergic receptors in reserpinized animals. Our findings may also have been due to such an increased receptor sensitivity in the central nervous

system.

On the contrary, the pressor effect was attenuated by the reserpine in GHR. We could not exclude the possibility that sympathetic nervous activity may be altered in GHR such as has been shown in spontaneously hypertensive rats (Bunag & Takahashi, 1981).

It has been suggested that bradykinin stimulates prostaglandin synthesis and release in the central nervous system (Kondo et al, 1979 ; Takahashi & Bunag, 1981) as well as in the peripheral tissue (McGiff et al, 1972). Neverthless, our results indicate that peripheral prostaglandins may not be essential for the expression of the hypertensive action of ICV bradykinin in GHR as well as in NTR. However, we do not exclude the pssibility that prostaglandins may mediate the pressor effect of bradykinin in the central nervous system (Wilkinson & Scroop, 1985), since indomethacin was administered peripherally.

Furthermore, the pressor response was unaffected by saralasin. The effector system for the bradykinin-induced pressor response may not be accounted for by an activation of the peripheral renin-angiotensin system.

In summary, our study provides evidence that the ICV bradykinin elicits a pressor response which is more sensitive in GHR than in NTR. It is suggested that the central pressor effect of bradykinin is, at least in part, due to excitation of the autonomic nervous activity in GHR as well as in NTR. It should also be noted that the central pressor response to bradykinin was not completely abolished by pretreatment with hexamethonium, phentolamine or reserpine. Therefore, mechanisms other than the enhanced sympathetic nervous activity may not be ruled out in the central action of bradykinin.

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