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ATTENUATION BY BRADYKININ OF ADRENERGICALLY-INDUCED VASOCONSTRICTION IN THE ISOLATED PERFUSED KIDNEY OF THE RABBIT: RELATIONSHIP TO PROSTAGLANDIN SYNTHESIS

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1 In the isolated kidney of the rabbit perfused with oxygenated Tyrode solution, we studied the effect of bradykinin on the vasoconstriction evoked by sympathetic nerve stimulation (3 Hz, 1 ms) and by injections of noradrenaline (50 to 75 ng) in the presence and in the absence of indomethacin (1 μg/ml), an inhibitor of prostaglandin biosynthesis. Prostaglandin E(PGE)-like material in the renal effluent was measured by bioassay after extraction with organic solvents and separation by thin layer chromatography.

2 Bradykinin in concentrations of 10 to 100 ng/ml reduced the vasoconstrictor response to sympathetic nerve stimulation and to injected noradrenaline. Also, the peptide (1 to 10 ng/ml) increased the basal release of PGE-like material and the release induced by sympathetic nerve stimulation.

3 Indomethacin, 1 μg/ml, diminished the inhibitory effect of bradykinin on the vasoconstrictor response to nerve stimulation, minimized the reduction of the noradrenaline-induced vasoconstriction caused by bradykinin (100 ng/ml), and abolished the release of PGE-like material.

4 This study indicates that bradykinin reduces the renal vascular reactivity to adrenergic stimuli and suggests that part of the action of the kinin at the vascular adrenergic neuroeffector junction in the rabbit kidney depends upon the biosynthesis of renal prostaglandins.

Introduction

Bradykinin, a nonapeptide released by plasma kallikrein from a protein substrate, increases biosynthesis of prostaglandins by stimulating the deacylation process that makes available free arachidonic acid for conversion to cyclic endoperoxides, the precursors of prostaglandins and thromboxane A_2 (McGiff, Terragno, Malik & Lonigro, 1972; Colina-Chourio, McGiff, Miller & Nasjletti, 1976; Needleman, Bronson, Wyche & Sivakoff, 1978). Synthesis of prostaglandins in the kidney is continuous and may influence the reactivity of the renal vasculature to vasoconstrictor stimuli. For example, in the kidney of rabbit, exogenous arachidonic acid is converted into products that reduce adrenergically-induced vasoconstriction (Frame, Hedqvist & Aström, 1974; Malik & McGiff, 1975). Conversely, inhibition of prostaglandin synthesis increases the vasoconstriction produced by sympathetic nerve stimulation (Malik & McGiff, 1975). Recently it has been shown that endogenous arachidonic acid released by bradykinin from tissue phospholipids is selectively converted to prostaglandin E_2 (PGE_2) in the rabbit kidney perfused with Krebs solution (Needleman *et al.*, 1978). This prostaglandin mimics the inhibitory effect of exogenous arachidonic acid on renal vasoconstrictor responses to sympathetic nerve stimulation (Frame *et al.*, 1974; Malik & McGiff, 1975). A corollary of these observations is that bradykinin may reduce adrenergically-induced renal vasoconstriction by stimulating synthesis of PGE_2. These experiments were designed to study the effects of bradykinin on the vasoconstrictor responses of the isolated Tyrode-perfused kidney of the rabbit to sympathetic nerve stimulation and to injected noradrenaline. The studies were conducted before and during inhibition of prostaglandin biosynthesis by indomethacin (Vane, 1971) which enables those actions of bradykinin related to stimulation of prostaglandin synthesis to be distinguished. Thus, any modification of the effect of bradykinin during prostaglandin synthesis blockade would suggest an action component involving prostaglandins. A preliminary account of these results has been presented elsewhere (Malik & Nasjletti, 1977a).

Methods

Male New Zealand white rabbits, weighing 2.5 to 3.0 kg, were anaesthetized with sodium pentobarbitone

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(25 mg/kg i.v.). The abdomen was opened by a midline incision, and the kidney, the renal artery with its sympathetic nerve plexus, and the abdominal aorta were exposed. The aorta was ligated below and above the renal artery and a polyethylene cannula was immediately inserted into the renal artery and flushed with heparinized saline (100 units/ml). The kidney was isolated with the renal vein and the ureter intact and placed in a thermostatically controlled chamber and perfused with Tyrode solution at a constant rate of 10 ml/min by means of a Harvard peristaltic pump (model 1210) as described by Malik & McGiff (1975). Tyrode solution of the following composition (mM) was used: NaCl 137, KCl 2.7, $CaCl_2$ 1.8, $MgCl_2$ 1.1, $NaHCO_3$ 12, NaH_2PO_4 0.42, and D (+)-glucose 5.6. Changes of perfusion pressure were measured with a mercury manometer and recorded on a kymograph with an isotonic lever. The changes in perfusion pressure were magnified about 10 times to record the alterations in pressure produced by low frequency of nerve stimulation and by injections of small amounts of noradrenaline. The pressure in the cannula before perfusion of the kidney was 40 mmHg at a flow rate of 10 ml/min and during perfusion of the kidney, the average pressure in the cannula increased to 75 mmHg (range 70 to 80 mmHg).

Experimental protocol

Studies on the vasoconstrictor responses to stimulation of sympathetic nerves and to injected noradrenaline were carried out as follows. Alterations in perfusion pressure reflected changes in vascular resistance, for the rate of perfusion was kept constant. The sympathetic nerve plexus was stimulated by means of a bipolar platinum electrode at 3 Hz with supramaximal biphasic rectangular pulses of 1 ms in duration for 22 s at 4 min intervals. Noradrenaline, 50 to 75 ng, was infused in a volume of 0.05 ml at 4 min intervals directly into the arterial cannula over a period of 15 to 20 s with a Braun-Melsungen infusion pump. Stimulation of sympathetic nerves or injections of noradrenaline, repeatedly at 4 min intervals, evoked reproducible vasoconstrictor responses over a period of 3 to 4 h. The evidence indicating that the sympathetic nerves to the rabbit kidney are postganglionic adrenergic nerves was presented earlier (Malik & McGiff, 1975). The vasoconstrictor responses to nerve stimulation and to injected noradrenaline were studied before and during infusions of bradykinin (1 to 100 ng/ml), in the absence and in the presence of indomethacin (1 μg/ml) in the perfusion medium.

Stimulation of prostaglandin production during infusion of bradykinin was assessed in six isolated kidneys perfused with Tyrode solution. The venous effluent from each kidney was collected for four periods of 5 min each, separated by 15 min intervals, and was assayed for its content of PGE-like substance after extraction and thin-layer chromatography. The first and third period served as control while during the second and fourth periods, bradykinin was infused in concentrations of 1 and 10 ng/ml, respectively. In another series of experiments, indomethacin 1 μg/ml, was added to the perfusion fluid and the content of PGE-like substance(s) in the perfusion fluid determined before and during infusion of bradykinin 10 ng/ml. In four additional experiments we measured the concentration of PGE-like substance(s) in the venous effluent collected for periods of 5 min before and during stimulation of the renal nerves (3 Hz, 1 ms duration for 5 min). In another series of four experiments bradykinin, 10 ng/ml, was infused and the content of PGE-like substance in the renal venous effluent was determined before and during sympathetic nerve stimulation in the presence and absence of indomethacin, 1 μg/ml, in the perfused medium.

Determination of prostaglandins

The content of PGE-like substance(s) in the venous effluent of perfused kidneys was determined as follows: samples were acidified to pH 3 with 1 N HCl and extracted with ethyl acetate. Lipids in the organic phase were extracted subsequently with 0.1 M potassium phosphate buffer, pH 8.0; the aqueous phase was separated, acidified to pH 3.0 with 1 N HCl and extracted with chloroform. The chloroform phase was evaporated to dryness and the lipid residue was dissolved in chloroform-methanol (4:1, v/v), applied as band on a silica gel thin-layer chromatographic (t.l.c.) plate (Silica Gel S-254, 0.5 mm, Brinkman Instruments), and chromatographed using the solvent system chloroform:methanol:acetic acid (18:2:1, by volume). Marker plates, prepared by spotting 10 μg of authentic PGE_2, $PGF_{2\alpha}$, PGD_2 and thromboxane B_2 (TxB_2) were developed concurrently with preparative plates until the solvent had reached 16 cm from the origin. Only the zone of the preparative plate corresponding to the position of authentic PGE_2 was scraped off and eluted with chloroform:methanol (4:1, v/v). The eluate was dried in nitrogen, reconstituted in 0.15 M NaCl, and bioassayed for content of PGE-like substance(s) using PGE_2 as reference standard. Efflux of PGE-like material (flow rate × concentration) was expressed as nanograms of PGE_2 equivalent per min (ng/min). The values were uncorrected for losses incurred on extraction and chromatographic purification. In six experiments, after addition of 50 ng of authentic PGE_2 to 50 ml of venous effluent obtained from a kidney perfused with Tyrode solution containing indomethacin, we recovered 65 ± 6% (±s.e.) of PGE-like material. The concentration of PGE-like substance(s) in samples were

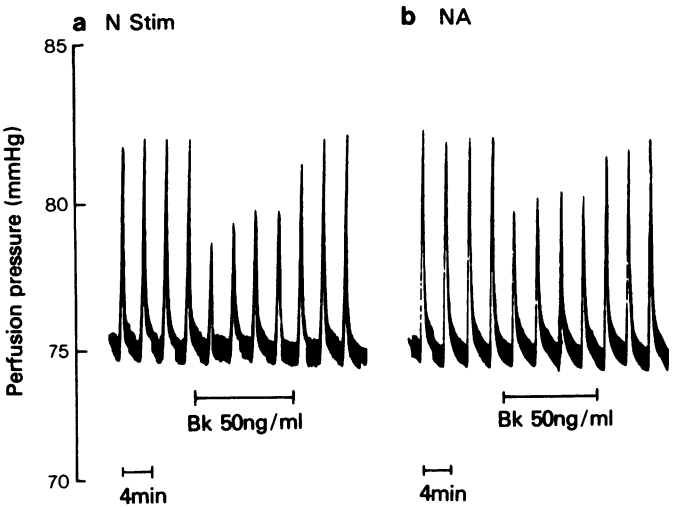

Figure 1 Effects of bradykinin (Bk) on the vasoconstrictor responses to sympathetic nerve stimulation (N Stim) (a) (3 Hz, 1 ms) and to injections of noradrenaline (b) (NA) (65 ng) in the isolated Tyrode-perfused rabbit kidney. Each tracing illustrates the vasoconstrictor responses of a different kidney.

determined by bracket assay on strips of rat stomach superfused with Krebs solution (3 ml/min). The reconstituted eluate of the chromatographic plate corresponding to the migration of PGE_2 contained a material which contracted the assay tissue like authentic PGE_2.

The following drugs were used: noradrenaline bitartrate (Levophed, Winthrop), concentration expressed as the free base, synthetic bradykinin diacetate (Protein Research Foundation, Minoh-Shi), indomethacin (Sigma) and prostaglandin E_2 (PGE_2), $PGF_{2\alpha}$ tromethamine, PGD_2 and TxB_2 (Upjohn Company). Indomethacin was dissolved in Tyrode solution. Bradykinin diacetate was dissolved in saline and then added to the perfusion fluid.

Statistical analysis

Paired and unpaired t tests were performed according to the methods described by Steel & Torrie (1960). The data are expressed as means ± s.e. mean. $P < 0.05$ was considered statistically significant.

Results

Effects of bradykinin on the vasoconstrictor response to sympathetic nerve stimulation and to injected noradrenaline

Stimulation of sympathetic nerves at a frequency of 3 Hz or injection of noradrenaline (50 to 75 ng) produced equivalent constriction of the renal vasculature and raised perfusion pressure. Infusion of bradykinin for 16 min did not alter the basal perfusion pressure but reduced the vasoconstriction produced by both adrenergic stimuli (Figure 1). Bradykinin, 1 to 100 ng/ml, caused a dose-related reduction in the vasoconstriction evoked by sympathetic nerve stimulation (Table 1). The inhibitory action of bradykinin on the vasoconstriction evoked by nerve stimulation was maximal at 4 min but waned during the infusion of the peptide at 50 and 100 ng/ml for 16 min (Table 1). Nonetheless, the vascular responses to nerve stimulation during infusion of bradykinin at 4 and 16 min were significantly lower than control responses (Table 1). After addition of indomethacin (1 μg/ml) to the perfusion medium, bradykinin (10 to 100 ng/ml) reduced the vasoconstriction evoked by nerve stimulation but the reduction was smaller than in the absence of indomethacin (Table 1). Infusion of bradykinin at 10 to 100 ng/ml, but not at 1 ng/ml, caused reduction in the vasoconstriction evoked by injection of noradrenaline (Table 2). The maximal effect of bradykinin in reducing the vascular response to injected noradrenaline was apparent at 4 min and persisted throughout the infusion (Table 2). After addition of indomethacin (1 μg/ml) to the perfusion medium, infusion of bradykinin at 50 and 100 ng/ml, but not at 10 ng/ml, resulted in significant reduction of the vasoconstriction evoked by injection of noradrenaline However, the reduction effected by bradykinin at 100 ng/ml of the vascular response to noradrenaline was greater in the absence than in the presence of indomethacin (Table 2).

Table 1 Effects of bradykinin (Bk) on the increase in perfusion pressure evoked by sympathetic nerve stimulation (3 Hz, 1 ms) in the isolated kidney of the rabbit

Bradykinin (ng/ml)	*Indomethacin (μg/ml)*	n	*Increase in perfusion pressure (IPP) (mmHg) Control (C)*	*During Bk at 4 min*	*During Bk at 16 min*	*Difference (C − Bk) at 4 min*	*Difference (C − Bk) at 16 min*	*Comparison of Bk-induced difference in IPP with and without indomethacin, P value 4 min*	*P value 16 min*
0	0	10	6.5 ± 0.5	6.5 ± 0.5	6.6 ± 0.5	0.0 ± 0.1	0.1 ± 0.1		
								>0.9	>0.9
0	1	10	7.9 ± 0.3	7.9 ± 0.3	7.9 ± 0.3	0.0 ± 0.1	0.0 ± 0.1		
1	0	6	6.1 ± 0.3	5.4 ± 0.3*	5.4 ± 0.3*	0.7 ± 0.1	0.7 ± 0.1		
10	0	16	5.8 ± 0.2	3.9 ± 0.2*	4.2 ± 0.3*	1.9 ± 0.2	1.6 ± 0.3		
								<0.001	<0.001
10	1	11	7.2 ± 0.4	6.7 ± 0.4**	6.6 ± 0.5**	0.5 ± 0.2	0.6 ± 0.2		
50	0	17	6.5 ± 0.2	3.5 ± 0.2*	4.3 ± 0.2*	3.0 ± 0.2	2.2 ± 0.2[a]		
								<0.005	<0.025
50	1	12	7.9 ± 0.5	6.3 ± 0.4*	6.5 ± 0.4*	1.6 ± 0.3	1.4 ± 0.3		
100	0	11	6.9 ± 0.4	3.2 ± 0.5*	4.3 ± 0.5*	3.7 ± 0.4	2.6 ± 0.3[a]		
								<0.02	>0.2
100	1	6	8.0 ± 0.6	5.8 ± 0.5*	6.0 ± 0.3*	2.2 ± 0.2	2.0 ± 0.5		

Data are expressed as mean ± s.e.; n = number of kidneys.
Comparison of IPP before and during infusion of Bk (paired Student's t test): *$P < 0.05$, **$P < 0.01$.
Comparison of Bk-induced effect on IPP at 4 min and 16 min (paired Student's t test): a = $P < 0.01$.

Table 2 Effects of bradykinin (Bk) on the increase in perfusion pressure evoked by injections of noradrenaline (50 to 75 ng) in the isolated kidney of the rabbit

Bradykinin (ng/ml)	*Indomethacin (μg/ml)*	n	*Increase in perfusion pressure (IPP) (mmHg) Control (C)*	*During Bk at 4 min*	*During Bk at 16 min*	*Difference (C − Bk) at 4 min*	*Difference (C − Bk) at 16 min*	*Comparison of Bk-induced difference in IPP with and without indomethacin, P value 4 min*	*P value 16 min*
0	0	10	6.8 ± 0.3	6.8 ± 0.3	6.8 ± 0.3	0.0 ± 0.1	0.0 ± 0.1		
								>0.9	>0.9
0	1	10	7.5 ± 0.4	7.5 ± 0.3	7.5 ± 0.3	0.0 ± 0.1	0.0 ± 0.1		
1	0	6	6.8 ± 0.4	6.4 ± 0.3	6.6 ± 0.3	0.4 ± 0.2	0.2 ± 0.2		
10	0	16	6.5 ± 0.2	5.9 ± 0.3*	5.9 ± 0.3*	0.6 ± 0.2	0.6 ± 0.2		
								>0.9	>0.9
10	1	7	7.4 ± 0.3	6.8 ± 0.4	6.9 ± 0.4	0.6 ± 0.4	0.5 ± 0.4		
50	0	10	6.8 ± 0.3	4.4 ± 0.3*	4.7 ± 0.4*	2.4 ± 0.2	2.1 ± 0.3		
								>0.1	>0.1
50	1	9	7.5 ± 0.5	5.8 ± 0.5*	6.2 ± 0.5*	1.7 ± 0.4	1.3 ± 0.4		
100	0	10	7.3 ± 0.4	4.6 ± 0.4*	4.9 ± 0.4*	2.7 ± 0.2	2.4 ± 0.2		
								<0.005	<0.001
100	1	7	7.6 ± 0.6	6.2 ± 0.6*	6.5 ± 0.6*	1.4 ± 0.3	1.1 ± 0.3		

Data are expressed as means ± s.e.; n = number of kidneys.
Comparison of IPP before and during infusion of Bk (paired Student's t test): *$P < 0.01$.

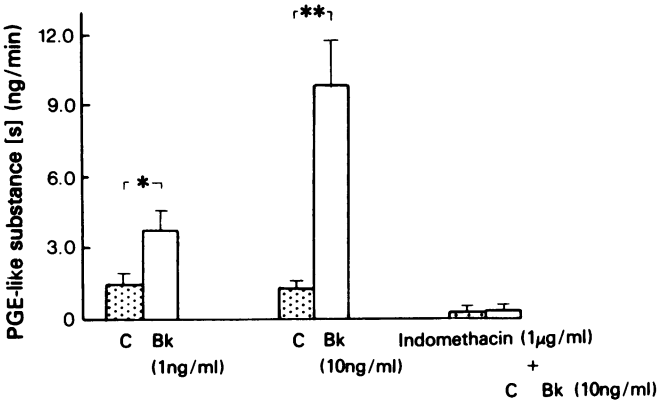

Figure 2 Venous output of a prostaglandin E-like substance from the isolated kidney of rabbit before (C-stippled column) ($n = 6$) and during infusion of bradykinin (Bk-open column) ($n = 6$) in the absence and presence of indomethacin. Vertical bars indicate the s.e. mean. Probability level (non-paired Student's t test): $^{*}P < 0.01$, $^{**}P < 0.001$.

The effect of sympathetic nerve stimulation on the venous output of prostaglandin E-like substance in the presence and absence of bradykinin

Bradykinin, in concentrations of 1 and 10 ng/ml, increased the output of PGE-like substance from the perfused rabbit kidney by about 2.5 and 7.7 fold, respectively (Figure 2). Addition of indomethacin to the perfusion medium suppressed both the basal and the bradykinin-evoked prostaglandin output (Figure 2). Stimulation of sympathetic nerves increased the output of PGE-like substance both in the absence as well as during infusion of bradykinin (Table 3). However, the absolute increment in prostaglandin release evoked by nerve stimulation was significantly greater in the presence than in the absence of bradykinin.

Discussion

The present study demonstrates that bradykinin reduces the vasoconstriction evoked by sympathetic nerve stimulation and by exogenous noradrenaline in the isolated kidney of the rabbit perfused with Tyrode solution. The results obtained following addition of indomethacin to the perfusion medium suggest that the action of bradykinin in reducing the renal vasoconstriction induced by sympathetic nerve stimulation depends, in part, upon the biosynthesis of renal prostaglandins. Bradykinin increased the output of a PGE-like substance from the perfused kidney and augmented further the release of prostaglandin evoked by electrical stimulation of the renal nerves. Indomethacin suppressed both the basal and the bradykinin-evoked output of a PGE-like substance(s), and diminished the associated effect of the kinin in reducing the renal vasoconstriction evoked by nerve stimulation. However, only the reduction in noradrenaline-induced renal vasoconstriction effected by bradykinin at 100 ng/ml was minimized by indomethacin. Two major conclusions emerge from these observations. First, bradykinin stimulates production by the kidney of a product of prostaglandin synthe-

Table 3 The effect of sympathetic nerve stimulation on the venous output of prostaglandin E (PGE)-like substance from the perfused rabbit kidney in the presence and absence of bradykinin

	PGE-like substance (ng/min)	
	Control	*Nerve stimulation*
Without bradykinin ($n = 4$)	1.35 ± 0.23	4.75 ± 1.10*
Bradykinin 10 ng/ml	12.00 ± 2.30	22.10 ± 4.27**

Values are mean ± s.e.; n = number of experiments.
Significance of difference from control: $^{*}P < 0.05$; $^{**}P < 0.01$.

tase activity that mediates, in part, the inhibitory action of the peptide on the adrenergically-induced renal vasoconstriction. Second, an important component in the reduction by bradykinin of the vascular response to sympathetic nerve stimulation and particularly to exogenous noradrenaline is not affected by indomethacin and, consequently, appears to be independent of prostaglandin synthesis. PGE_2 inhibits the release of noradrenaline evoked by stimulation of sympathetic nerves and reduces noradrenaline-evoked vasoconstriction in the rabbit kidney (Malik & McGiff, 1975; Frame & Hedqvist, 1975). Furthermore, PGE_2 is the major product of arachidonic acid metabolism released from the perfused kidney by bradykinin (Needleman *et al.*, 1978). It follows that PGE_2 may be the putative mediator of the effect of bradykinin in reducing adrenergically-induced renal vasoconstriction which is sensitive to prostaglandin synthesis blockade by indomethacin. The relative importance of the PGE_2-mediated inhibition of the vascular responses to renal nerve stimulation during bradykinin infusion may decline with time. This is inferred from (1) our finding that the inhibitory action of bradykinin at 50 and 100 ng/ml on the vasoconstriction evoked by nerve stimulation waned, despite continuous infusion of the peptide and from (2) a report that the effectiveness of bradykinin in releasing prostaglandin-like material from the kidney subsides during prolonged infusion of the kinin (McGiff *et al.*, 1972; Isakson, Raz, Denny, Wyche & Needleman, 1977). Also, the possibility must be considered that the effect of bradykinin on the vasoconstrictor responses to adrenergic stimuli, particularly that component of the effect which is related to prostaglandin synthesis, varies among different tissues and animal species. This possibility is suggested by (1) the finding that the action of PGE_2 on the adrenergic neuroeffector junction is organ- and species-dependent (Malik & McGiff, 1975; Malik, 1978) and by (2) a recent study showing that bradykinin enhances the vasoconstriction evoked by adrenergic stimuli in the isolated perfused kidney of the rat (Malik & Nasjletti, 1977b).

Our study did not consider a possible involvement of products of arachidonic acid metabolism other than PGE_2, e.g., PGI_2 and $PGF_{2\alpha}$, in the action of bradykinin on adrenergically evoked renal vasoconstriction. PGI_2, the major prostaglandin produced by blood vessels (Moncada, Higgs & Vane, 1977), reduces the vasoconstrictor responses to sympathetic nerve stimulation and to injected noradrenaline in the perfused rabbit kidney (unpublished observations). In contrast, $PGF_{2\alpha}$ enhances the vasoconstrictor responses of the renal vasculature to adrenergic stimuli (Malik & McGiff, 1975). However, neither PGI_2 nor $PGF_{2\alpha}$ is released from the perfused rabbit kidney by bradykinin (Needleman *et al.*, 1978).

Information on the effects of kinins on the adrenergic neuroeffector junction is scanty. Bradykinin stimulates the autonomic ganglia (Lewis & Reit, 1965) and liberates catecholamines from the adrenal gland of the cat and dog (Feldberg & Lewis, 1964; Staszewska-Barczak & Vane, 1967). There are reports suggesting that the action of bradykinin in causing relaxation of non vascular smooth muscle is mediated by noradrenaline released from sympathetic nerves by the kinin (Türker, Kiran & Kaymakcalan, 1964). This view conflicts with studies that show failure of catecholamine depletion or of α- and β-adrenoceptor blockade to affect the bradykinin-induced relaxation of intestinal smooth muscle (Antonio, 1968, Ufkes & Van Der Meer, 1975). In the isolated, perfused spleen of the dog bradykinin affected neither the basal output nor the release of noradrenaline evoked by sympathetic nerve stimulation (Moerman, Scapagnini & de Schaepdryver, 1969). However, the recent work of Starke, Peskar, Schumacher & Tauba (1977) suggested that bradykinin, by stimulating prostaglandin biosynthesis, inhibits the nerve impulse-evoked release of noradrenaline from the perfused heart and the superfused pulmonary artery of the rabbit. Our studies on the effect of bradykinin on vascular reactivity to exogenous noradrenaline suggest that the kinin attenuates adrenergically-induced vasoconstriction by interfering with events at postsynaptic sites. However, the possibility of an additional effect at presynaptic sites inhibiting sympathetic transmission in the kidney could not be excluded. Indeed, such a possibility is compatible with the observation that bradykinin at 1 ng/ml brings about reduction of the vasoconstriction evoked by nerve stimulation but not that produced by noradrenaline.

The present studies suggest an influence of bradykinin on events at the vascular adrenergic neuroeffector junction in the rabbit kidney. However, only tentative conclusions can be drawn about the physiological significance of such an influence. A kallikrein that cleaves the decapeptide lysyl-bradykinin from a protein substrate occurs in the renal cortex (Erdös, 1976). Kinins are generated continuously within the kidney and stimulate renal prostaglandin production (Nasjletti & Colina-Chourio, 1976; Nasjletti *et al.*, 1978). Hence, the results of this study raise the possibility that kinins formed intrarenally contribute to modulate events at adrenergic neuroeffector junctions within the kidney.

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