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A COMPARATIVE STUDY OF THE EFFECTS OF BRADYKININ, KALLIDIN II AND ELEDOISIN ON SEGMENTAL SUPERIOR MESENTERIC RESISTANCE

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The kinins are polypeptides of small molecular weight which have a profound effect on smooth muscle but whose physiological role is insufficiently understood (Erdös, 1963). Bradykinin and kallidin II are respectively, a nona- and a deca-peptide, which occur in man and in other species. Eledoisin is an unrelated endecapeptide found by Erspamer (1949) in the posterior salivary glands of two molluscs; because of its similar pharmacological activity Stürmer & Berde (1963*a*) have suggested that it should be considered with bradykinin and kallidin II as a kinin. All three polypeptides have now been synthesized (Nicolaides, Dewald & McCarthy, 1961; Boissonnas, Guttmann, Jacquenod, Konzett & Stürmer, 1960; Sandrin & Boissonnas, 1962). Kallidin II (hereafter referred to as kallidin), which is converted from kallidinogen by the enzyme kallikrein, appears to be the immediate precursor of bradykinin (Elliot, 1963).

Bradykinin increases cardiac output and decreases total peripheral resistance (Olmsted & Page, 1962; Montague, Rosas & Bohr, 1963). There have been reports that it increases the blood flow in skin and in skeletal muscle (Hilton, 1960; Elliot, Horton & Lewis, 1960; Paldino, Hyman & Lenthall, 1962), in the coronary (Antonio & Rocha e Silva, 1962; Maxwell, Elliot & Kneebone, 1962; Rowe, Afonso, Castillo, Lioy, Lugo & Crumpton, 1963), cerebral (Carpi & Corrado, 1961) and in the isolated pulmonary circulations (Waaler, 1961). On the other hand, bradykinin decreases blood flow in the rabbit ear (Guth, Cano & Jaramillo, 1963) and lung (Lecomte & Troquet, 1960) and in the human finger (Burch & DePasquale, 1962). Much less is known about the haemodynamic effects of kallidin and eledoisin (Olmsted & Page, 1962; Erspamer & Anastasi, 1962; Erspamer & Glaesser, 1963; Sicuteri, Fanciullacci, Franchi & Michelacci, 1963). The present investigation was designed to assess the effects of these kinins on

the segmental resistance of the superior mesenteric circulation. A preliminary account of this work has been published (Chou, Frohlich & Texter, 1963).

METHODS

Twenty-seven dogs weighing 14–18 kg were anaesthetized with pentobarbital sodium (30 mg/kg) I.V. An endotracheal tube was inserted. The femoral arteries and veins were exposed, as also the superior mesenteric artery near its origin. After injection of heparin sodium (5 mg/kg) I.V., the aorta was cannulated through one femoral artery. A pump (Sigmamotor model 142X) was interposed between the other femoral artery and the distal portion of the superior mesenteric artery with polyethylene tubing and a right-angled stainless-steel cannula. Blood flow was adjusted so that the mesenteric perfusion pressure equalled the systemic arterial pressure. A small mesenteric artery was ligated and cannulated in a distal direction with a fine polyethylene catheter (O.D. 0·582 mm) inserted until the tip was 5 cm from the intestinal margin. A small mesenteric vein was cannulated so that the tip of the tubing was 1 cm from the intestine. A side branch of the portal vein was cannulated by inserting a right-angled 18-gauge needle which had been connected with a fine polyethylene catheter. An 18-gauge needle, which had been connected with a fine polyethylene catheter, was inserted into the inflow perfusion tubing to measure the perfusion pressure. Intravascular pressures of the aorta, the mesenteric small artery and vein, large vein (a branch of the portal vein) and perfusion tubing (large artery) were measured with three pressure transducers (Statham P 23Gb) using two multiple stopcock devices (Corein-Farnsworth) and recorded with a direct-writing amplifier-recorder (Sanborn Polyviso). The intraluminal pressure in the small intestine was recorded by another pressure transducer attached to polyethylene tubing inserted into the intestinal lumen.

In order to determine the dose–response curves of the mesenteric vessels, isotonic saline (0·9 % NaCl) solutions containing synthetic bradykinin (0·05 μg/ml. Sandoz), kallidin (0·05 μg/ml. Parke-Davis) and eledoisin (0·005 μg/ml. Sandoz) were infused in a randomized sequence upstream to the perfusion pump at sequentially increasing rates (0·12–4·96 ml./min) with an infusion–withdrawal pump (Harvard). Each infusion was continued for 30 sec after which the infusion was increased to the next higher rate. The response to each agent was studied in ten dogs. Before infusing another agent, the infusion catheter and syringe were changed and the pressures in the perfused vessels were allowed to return to control levels. Heparin dissolved in 0·9 % NaCl solution was infused from a pressurized bottle through the catheters and needles between pressure recordings.

Three dogs were used to study the local and systemic effects of larger doses of each agent. Bradykinin (5 μg/kg), kallidin (10 μg/kg) and eledoisin (0·5 μg/kg) were injected as a single dose upstream to the perfusion pump. The effects of blocking agents on the actions of these polypeptides were determined by pretreatment with phenoxybenzamine hydrochloride (10 mg/kg, I.V.), dichloro*iso*propyl noradrenaline (3 mg/kg, I.A.) and pentolinium tartrate (3 mg/kg, I.A.). Phenoxybenzamine blocks vasoconstricting action of sympathomimetic amines, dichloro*iso*propyl noradrenaline blocks inhibitory action (vasodilating action) of sympathomimetic amines and pentolinium blocks autonomic ganglia. Two dogs were studied with each agent.

The results are expressed as changes in segmental intravascular pressure and resistance. Total (R_T), small vessel (R_{SV}), arterial (R_A) and venous (R_V) resistances were calculated by dividing the pressure gradient of each segment by the blood flow (Haddy, 1960). Since blood flow was kept constant, changes in the calculated resistances represent not only the geometric changes in the calibre of the vessels, but also the changes in the active tension of the vascular smooth muscle (Burton & Stinson, 1960). The results were analysed using paired comparison analysis (Hill, 1961) and a four-point assay (British Pharmacopoeia, 1953).

RESULTS

Dose–response effects

The mean changes in pressure in successive segments of the mesenteric vascular bed after local intra-arterial infusion of small doses of bradykinin, kallidin and eledoisin at sequentially increasing rates, are shown in Fig. 1. The pressure falls in the small and large artery paralleled each other,

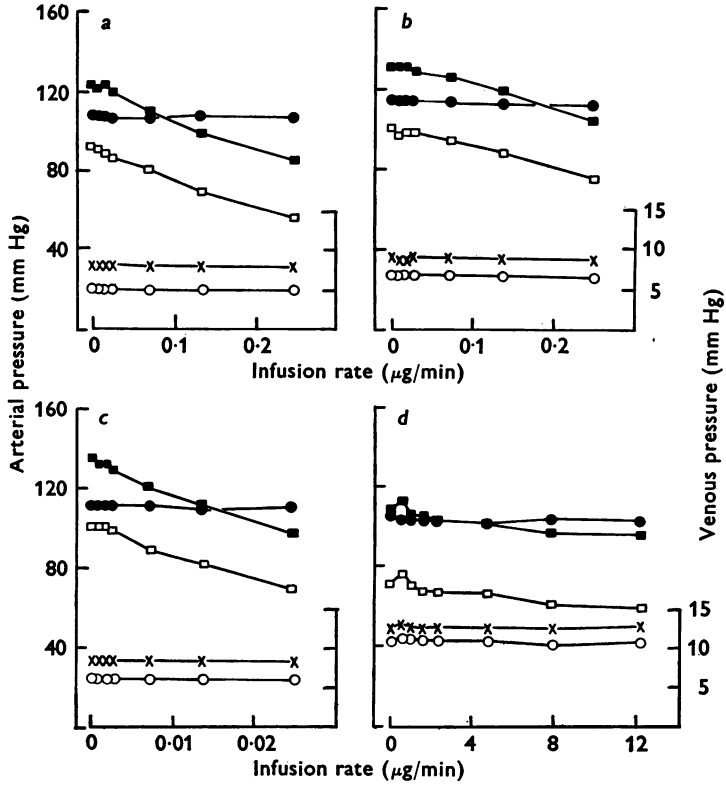

Fig. 1. Effects of increasing infusion rates of *a*, bradykinin; *b*, kallidin; *c*, eledoisin; and *d*, histamine on aortic (●—●,) large (■—■) and small (□—□) mesenteric artery and vein (large, ○—○; small × — ×) pressures. Mean blood flows (ml./min): *a*, *c*, 175; *b*, 170; *d*, 184. Ten dogs studied in each case.

whilst pressures in the large and small veins did not change. Systemic blood pressure (aorta) remained constant, confirming the restriction of the vaso-active response to the mesenteric circulation. The actions of bradykinin, kallidin and eledoisin were similar. The effect of histamine (Texter, Chou & Frohlich, 1963) is shown here to compare its effect with those of the kinins. The average blood flows of the superior mesenteric circulations

during the experiments were 175 for bradykinin and eledoisin, 170 for kallidin and 184 ml./min for histamine.

Changes in segmental resistances are shown in Fig. 2. Arterial and venous resistances did not change significantly; the decreases in total and small vessel resistance were parallel. The values were statistically significant using paired comparison analysis at doses above 0·06 μg/min for

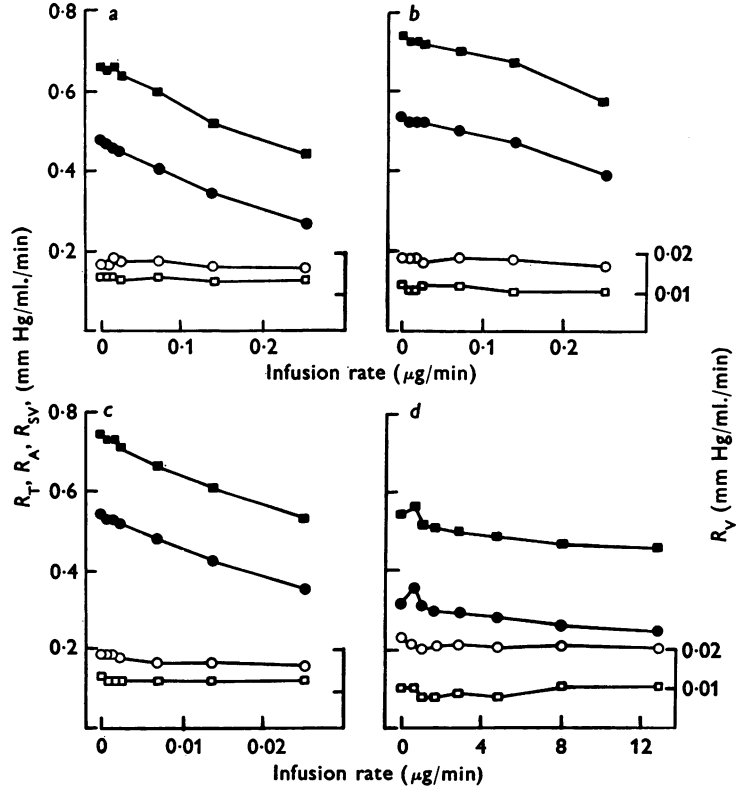

Fig. 2. Effects of increasing infusion rates of *a*, bradykinin; *b*, kallidin; *c*, eledoisin and *d*, histamine on the segmental resistances of the superior mesenteric vascular bed. R_T (■—■) = total, R_A'(○—○) = arterial, R_{SV} (●—●) = small vessel and R_V(□—□) = venous resistances. Ten dogs studied for each graph. Blood flows as for Fig. 1.

bradykinin, 0·12 μg/min for kallidin and 0·006 μg/min for eledoisin (Table 1). Assuming the absence of other active forms of these agents in the circulation, the blood levels required to produce significant vasodilatation were 0·35 ng/ml. for bradykinin, 0·75 ng/ml. for kallidin and 0·035 ng/ml. for eledoisin.

The changes in resistance were consistent with dilatation of vessels with

diameter less than 0·5 mm (the vessels between the small arteries and small veins). The vasodilator action was much greater than that of histamine, serotonin and acetylcholine administered in similar fashion (see Fig. 3). By comparing the dose–response curves on the basis of weight which resulted in approximately the same degree of decrease in R_{SV}, eledoisin was 300 times more potent than serotonin and 400 times more potent than histamine and acetylcholine (Texter *et al.* 1963).

TABLE 1. Effect of bradykinin, kallidin II and eledoisin on the total resistance (R_T) and the small vessel resistance (R_{SV}) (mm Hg/ml./min). Ten dogs were studied for each agent infused at sequentially increasing rates. The control R_T and R_{SV} and their S.E. were respectively bradykinin (R_T: 0·704 ± 0·066, R_{SV}: 0·521 ± 0·066), kallidin II (R_T: 0·776 ± 0·060, R_{SV}: 0·570 ± 0·060) and eledoisin (R_T: 0·771 ± 0·066, R_{SV}: 0·572 ± 0·057)

Agent	Infusion rate (μg/min)	Mean of the decrease in R_T and R_{SV} after infusion (mean ± S.E.) (control R_T or R_{SV} – expt. R_T or R_{SV})	
		ΔR_T	ΔR_{SV}
Bradykinin	0·006	0·012 ± 0·010	0·010 ± 0·006
	0·012	0·021 ± 0·009	0·031 ± 0·016
	0·024	0·025 ± 0·012	0·042 ± 0·016
	0·062	0·071 ± 0·019*	0·078 ± 0·019*
	0·124	0·143 ± 0·029*	0·146 ± 0·028*
	0·247	0·226 ± 0·035*	0·223 ± 0·037*
Kallidin II	0·006	0·011 ± 0·007	0·011 ± 0·008
	0·012	0·006 ± 0·005	0·006 ± 0·006
	0·024	0·015 ± 0·010	0·008 ± 0·007
	0·062	0·026 ± 0·012	0·024 ± 0·011
	0·124	0·071 ± 0·020*	0·064 ± 0·017*
	0·247	0·167 ± 0·028*	0·149 ± 0·029*
Eledoisin	0·0006	0·008 ± 0·002*	0·012 ± 0·003*
	0·0012	0·014 ± 0·005	0·009 ± 0·007
	0·0025	0·028 ± 0·012	0·023 ± 0·011
	0·0062	0·084 ± 0·017*	0·073 ± 0·018*
	0·0124	0·138 ± 0·023*	0·115 ± 0·024*
	0·0247	0·222 ± 0·031*	0·200 ± 0·026*

* Indicates the change being statistically significant at P value below 1 %. The paired comparison method (Hill, 1961) was used for the statistical analysis $n = 10$.

For quantitative analysis of the relative potency of bradykinin, kallidin and eledoisin, paired comparison analysis and four-point assays (or two and two dose assays) were employed. The paired comparison method, a less sensitive technique, indicated that eledoisin was 5–10 times more potent than bradykinin, and 10–20 times more potent than kallidin. Bradykinin was 1–2 times more potent than kallidin. Since bradykinin, kallidin and eledoisin produced qualitatively identical vasodilator responses and since the slopes of the dose–response curves with 0·125–0·250 μg/min for bradykinin and kallidin and with 0·0125–0·025 μg/min for eledoisin did not yield statistically significant differences four-point assays were employed to evaluate the relative potency of bradykinin and

kallidin in terms of eledoisin or bradykinin as a reference. This analysis revealed that eledoisin had 6·3 times the potency of bradykinin and 15·3 times the potency of kallidin; bradykinin had 1·4 times the potency of kallidin.

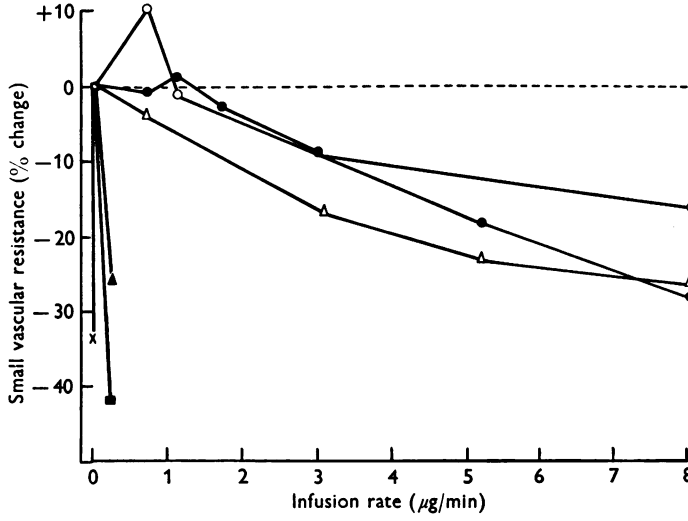

Fig. 3. Comparison of the effects of kinins, histamine, acetylcholine and serotonin on the small vessel resistance (R_{SV}) of the superior mesenteric vascular bed. The ordinate is the percentage changes from their respective control R_{SV}. Each curve represents the average obtained from ten animals. ○, histamine; ●, acetylcholine; △, serotonin; ▲, kallidin; ■, bradykinin; ×, eledoisin.

Local and systemic effects of larger doses

After a single-dose injection of these polypeptides, a triphasic effect on blood pressure resulted. A typical response to eledoisin is shown in Fig. 4. Pressures in the large and small arteries fell sharply during the first 10 sec, after which pressures in the large and small artery promptly rose for the next 20 sec; pressures then gradually fell to approximately control levels. Venous pressure rose during the first minute and then gradually returned to control levels. The pressure changes in the mesenteric vascular beds with all three polypeptides were qualitatively similar; however, whereas a triphasic effect on systemic pressure was observed following administration of bradykinin and kallidin, the response to eledoisin was biphasic. After injection of bradykinin or kallidin, systemic pressure fell sharply during the first 15 sec, rose briefly to or above control levels, and gradually fell to below that of the control period.

Intraluminal pressures in the small intestine did not change during infusion of small amounts of these agents; however, with the use of the

larger amounts, the intraluminal pressure rose and fell concurrently with the abrupt rise and fall in mesenteric arterial pressure. Intraluminal pressure increased by 60 mm Hg at the height of the intestinal contraction. Marked blanching of the intestine could be observed during the period of tonic contraction; blanching was not observed during infusion of the smaller amounts of the polypeptides over the entire dosage range.

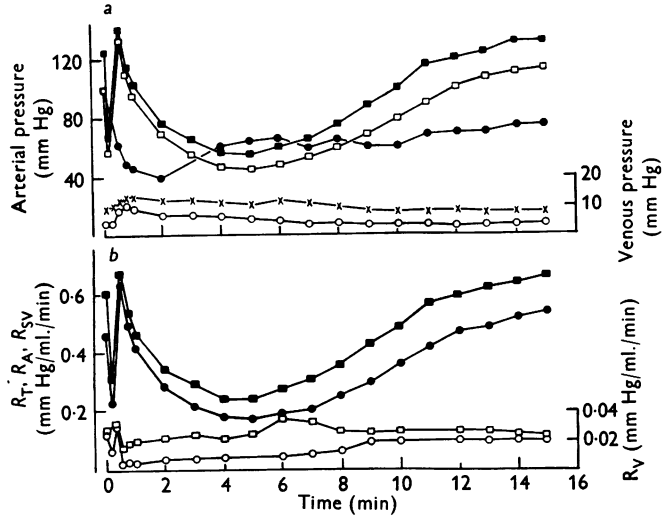

Fig. 4. Changes in the pressures (*a*) and resistance (*b*) within the successive vascular segments of the superior mesenteric bed after a single intra-arterial injection of 0·5 μg/kg eledoisin at zero time. The abscissa is the time after the injection. *a*, Symbols as Fig. 1: *b*, symbols as Fig. 2. Mean blood flow, 196 ml./min.

Effects of blocking agents

Dichloroisopropyl noradrenaline, a known beta adrenergic receptor blocking agent, which blocked the vasodilator response to *iso*propyl noradrenaline and small doses of adrenaline, did not interfere with the vasodilator action of the polypeptides. The triphasic response to larger doses of the polypeptides was not altered by prior administration of dichloro*iso*propyl noradrenaline. Prior administration of phenoxybenzamine or pentolinium did not alter the triphasic response to administration of larger doses of these agents, although the systemic hypotension was accentuated.

Relation between the vasodilator response and initial vascular tone

The response of a vascular bed to various vaso-active substances is influenced, in part, by its initial vascular tone. When the changes in small vessel resistance (R_{SV}) at the maximum infusion rate (0·25 μg/min for bradykinin and kallidin and 0·025 μg/min for eledoisin) were compared with the respective control R_{SV}, the correlation coefficients were as follows: bradykinin 0·944 ($P < 0·02$); kallidin 0·692 ($P < 0·1$); and eledoisin 0·742 ($P < 0·05$). A great dilator response was observed when the initial small vessel resistance was greater.

DISCUSSION

Our observations concerning the relative potency of bradykinin, kallidin and eledoisin are in accord with those of Olmsted & Page (1962). Most studies of bradykinin, kallidin and eledoisin have been carried out on the systemic arterial pressure. Eledoisin was found to be the most potent vasodepressor, 5–100 times more active than bradykinin and kallidin (Stürmer & Berde, 1963*a*, *b*; Olmsted & Page, 1962; Erspamer & Glaesser, 1963; Sicuteri *et al.* 1963). However, because of the positive inotropic and chronotropic cardiac action of bradykinin (Montague *et al.* 1963), changes in systemic arterial pressures are not a reliable index for comparing the vasodilating activity of these polypeptides.

Comparisons of these polypeptides with other vaso-active materials have given variable results, depending upon the species studied and the method. Fox, Goldsmith, Kidd & Lewis (1961) found bradykinin to be as potent as histamine in dilating the vessels of the human finger; similar findings were made on cat skin (Elliot *et al.* 1960) and dog brain (Carpi & Corrado, 1961). As a vasodilator acetylcholine was equal in activity to bradykinin on the vessels of the cat's hind limb (Lewis, 1962), but was 5 times more potent on the vascular bed of cat's skin (Elliot *et al.* 1960), and 10–100 times less potent on the vessels of the human finger (Fox *et al.* 1961). Eledoisin was 3–5 times as active as histamine in man (Sicuteri *et al.* 1963). The present results indicate that eledoisin is about 400 and bradykinin about 50 times more potent than histamine and acetylcholine in the dog's mesenteric circulation.

The responsiveness of the superior mesenteric vascular bed to these kinins cannot be satisfactorily compared to that of other vascular beds because of differences in method. The responsiveness of the superior mesenteric vessels was approximately the same as that of the isolated coronary bed of the dog and of the guinea-pig (Antonio *et al.* 1962); the latter is comparable in sensitivity to the rat uterus or duodenum, the two most sensitive preparations to bradykinin.

Lewis (1962) has suggested that the plasma kinins may mediate digestive tract function by altering blood flow. Bradykinin plays a role in salivary and pancreatic secretion; it may be involved in the physiological regulation of the mesenteric vascular bed.

The depressor phases of the triphasic pressure response after administration of larger amounts of these kinins are consistent with a direct vasodilator action on the small blood vessels. The second pressor phase was most likely produced by the mechanical effect of intestinal smooth muscle contraction upon intramural vessels (Mohamed & Bean, 1951; Sidky & Bean, 1958; Boatman & Brody, 1963). Compression of the vessels would produce: (*a*) a blanched appearance of the intestine, (*b*) a decrease in calibre of the intramural vessels, as reflected by an increase in small vessel resistance with increases in the small arterial and venous pressures, (*c*) passive distension of the arterial and venous segments outside the intestine owing to the obstruction of the blood flow to and from the intestine, as reflected by the decreases in arterial and venous resistance along with increases in the pressures in the large artery and vein. The cessation of blood flow through the intestine as the result of the violent contraction is reflected by the decrease in pressure gradient between the intra- and extra-mural arteries to zero.

This triphasic pressure response is similar to that occurring following local administration of endotoxin into the superior mesenteric bed (Meyer & Visscher, 1962; Texter, 1963). Kinin-like vaso-active materials are present during endotoxin shock (Kobold, Prett & Thal, 1962), during intestinal ischemia (Kobold & Thal, 1963) and in acute pancreatitis (Thal, Kobold & Hollenberg, 1963).

SUMMARY

1. Local and systemic effects of synthetic bradykinin, eledoisin and kallidin II were studied in anaesthetized dogs by infusing these kinins into a constantly perfused superior mesenteric circulation. Pressures in the aorta, large and small mesenteric arteries and veins, and small intestinal lumen were measured. The average blood flow was 173 ml./min.

2. With small doses, these kinins decreased total and small vessel resistances without affecting arterial and venous resistances and intestinal intraluminal pressure. The degree of dilatation was a function of the dosage. In a dose 10^{-8} to 10^{-9} mg/min, a detectable vasodilatation was observed. Eledoisin was found to be 6·3 times more potent than bradykinin, and 15·3 times more potent than kallidin; bradykinin was 1·4 times more potent than kallidin.

3. These kinins are the most potent vasodilators so far studied in the superior mesenteric vascular bed.

4. With large doses, a triphasic response was obtained. The second pressor phase was produced by the violent contraction of the intestinal smooth muscle produced by these kinins. This triphasic response is not unlike the response of this vascular bed to endotoxin.

5. Dichloro*iso*propyl noradrenaline did not alter the vasodilator action of these kinins. Phenoxybenzamine hydrochloride and pentolinium accelerated the systemic hypotension.

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