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A COMPARISON OF THE EFFECTS OF LOCALLY AND SYSTEMICALLY ADMINISTERED KININS ON CORONARY BLOOD FLOW AND MYOCARDIAL METABOLISM

BY

W. LOCHNER AND J. R. PARRATT*

From the Physiologisches Institut der Medizinischen Akademie, Düsseldorf, Germany

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It has been demonstrated in a number of species that bradykinin increases coronary blood flow when injected intravenously (Grayson & Parratt, 1962; Maxwell, Elliot & Kneebone, 1962; Rowe, Afonso, Castillo, Lioy, Lugo & Crumpton, 1963). Kallidin (lys-bradykinin) has a similar action (Parratt, 1964a). Because of the rapid enzymatic destruction of the plasma kinins in the blood stream (Erdös, Renfrew, Sloane & Wohler, 1963) it is likely that only a small percentage of a dose injected intravenously could reach the coronary vascular bed. In view of this, and especially as it has been suggested that these substances may be implicated in functional vasodilatation in the heart (Parratt, 1964a), the effect of locally injected bradykinin and kallidin on coronary flow has been examined.

Eledoisin is an endecapeptide, not known to occur naturally in mammals, but having pharmacological properties similar to bradykinin and kallidin (Erspamer & Anastasi, 1962; Stürmer & Fanchamps, 1965). In view of this, Stürmer & Berde (1963) have suggested that for all practical purposes eledoisin should be regarded as belonging to the group of peptides referred to as kinins (Lewis, 1960). Recently Maxwell (1964) has reported that eledoisin decreases coronary blood flow when injected intravenously into dogs but opposite results have been obtained by Bergamaschi & Glässer (1963).

In the present study a comparison has been made of the effects of bradykinin, kallidin and eledoisin on coronary flow and myocardial metabolism when infused intravenously and when infused locally into a branch of the left coronary artery.

METHODS

Thirteen dogs (eleven male, two female) weighing between 26 and 38 kg were anaesthetized with a mixture of chloralose, 20 mg/kg (as a 2% w/v solution), and urethane, 200 mg/kg (as a 20% w/v solution) injected intravenously. Morphine hydrochloride (2 mg/kg) was then injected in divided doses subcutaneously and heparin (600 I.U./kg initially and 240 I.U./kg every 2 hr) intravenously.

Coronary sinus outflow was measured using the catheter described by Lochner & Oswald (1964), placed in the coronary sinus by way of the right external jugular vein under fluoroscopic control. Built into the head of the catheter was an electromagnetic flowmeter (carrier frequency, 400 cycles/sec) used in conjunction with a Medicon unit (Model T2004). Mean flow, determined by electrical integration, and phasic flow were simultaneously displayed on a double-beam oscilloscope. Through the catheter coronary sinus blood was continuously drawn at a rate of 10 ml./min by means of a pump (Lochner, Mercker & Schürmeyer,

* Usual address: Department of Physiology, University of Ibadan, Ibadan, Nigeria.

1956) and the oxygen tension of this blood was measured polarographically using platinum electrodes (Gleichmann & Lübbers, 1960; Schaper, Xhonneux & Bogaard, 1963). Oxygen saturation was estimated by means of the oxygen dissociation curves for dog blood obtained by Bartels & Harms (1959). Oxygen consumption was estimated from coronary sinus outflow (ml./min) multiplied by arterio-venous oxygen saturation difference, assuming the arterial saturation to be 100%. It is clear that this provides only an approximation of cardiac oxygen consumption but provided its limitations are borne in mind it nevertheless gives a useful indication of cardiac metabolic change. The control value (mean and standard error, in arbitrary units) for oxygen consumption from all the dogs studied using this expression was 10,128±231.

Systemic arterial pressure and heart rate were recorded from a femoral artery using a Statham pressure transducer (P23AC) and a heart rate meter. Respiratory rate and minute volume were recorded with a gas volume meter (Elster & Co. A.G., Mainz), and end-tidal carbon dioxide tension by infrared absorptiometry (Uras; Hartmann & Braun, Frankfurt). In two dogs left intraventricular pressure was recorded using a Statham pressure transducer, as well as the first derivative of the rate of change of this intraventricular pressure pulse, dp/dt (see Gleason & Braunwald, 1962). Each of these variables, together with electrocardiogram lead II, coronary sinus flow and oxygen tension, were recorded on an Offner polygraph using thermosensitive paper.

Under fluoroscopic control, a steel catheter was introduced by way of the right carotid artery, into either the circumflex or the descending branch of the left coronary artery (West, Kobayashi & Guzman, 1958). Intracoronary infusions were given at a rate of 0.5, 1.0 or 2.0 ml./min for a period of 2 min using a constant-speed infusion pump. Intravenous infusions were given into a femoral vein.

The drugs used were synthetic bradykinin, kallidin and eledoisin (Sandoz), dipyridamole (Persantin; Thomae) and propranolol (Inderal; I.C.I.).

RESULTS

Effects of intracoronary infusions

The results for the three peptides are summarized in Table 1. In doses of up to 0.2 μg/kg/min, neither bradykinin nor kallidin had any significant effect on mean blood pressure. In most experiments pressure did not change or fell only very slightly, but in two dogs intracoronary infusions of both substances increased mean pressure by up to 7 mm Hg. Coronary sinus outflow was greatly increased from control levels and these increases were accompanied by increases in coronary sinus oxygen tension. The result from one experiment

TABLE 1

THE EFFECTS OF INTRACORONARY INFUSIONS OF BRADYKININ, KALLIDIN AND ELEDOISIN ON BLOOD PRESSURE, HEART RATE, CARDIAC OXYGEN CONSUMPTION AND ON CORONARY SINUS OUTFLOW AND OXYGEN TENSION

Results are means and standard errors. * Significantly different from controls at $P<0.05$; † at $P<0.005$

Drug	Dose (μg/kg/min)	No. of expts.	Mean blood pressure (mm Hg)	Heart rate (beats/min)	Coronary sinus		Cardiac oxygen consumption (% control)
					Outflow (ml./min)	Oxygen tension (mm Hg)	
Controls		—	145±3·1	140±5·5	156± 4·3	21·2±0·4	—
Bradykinin	0·025	7	145±1·6	141±4·1	193± 4·7†	24·6±0·6†	+12·2±2·9†
	0·05	21	145±0·4	144±1·4	205± 4·7†	26·9±0·5†	+15·9±2·7†
	0·1	16	145±1·4	152±4·2*	227± 6·2†	28·2±0·8†	+25 ±3·1†
	0·2	9	142±3·0	157±7·3*	246±10·9†	26·8±0·8†	+34 ±6·8†
Kallidin	0·025	9	145±0·5	141±2·2	190± 5·9†	23·2±0·2†	+18 ±4·5†
	0·05	13	145±0·1	142±1·4	203± 5·4†	25·6±0·5†	+15 ±3·2†
	0·1	14	145±1·4	150±2·9	228± 8·5†	27·6±1·0†	+30 ±5·3†
	0·2	9	142±2·9	163±5·9†	255±13·2†	27·8±1·2†	+44 ±8·0†
Eledoisin	0·008	5	141±1·6	142±1·1	190± 3·6†	23·2±0·3†	+11·7±4·2†
	0·017	7	138±2·1*	152±2·1*	188± 9·4†	24·7±0·8†	+12 ±4·8†
	0·035	8	133±1·1†	153±3·1*	212± 8·6†	25·3±0·9†	+22 ±5·3†

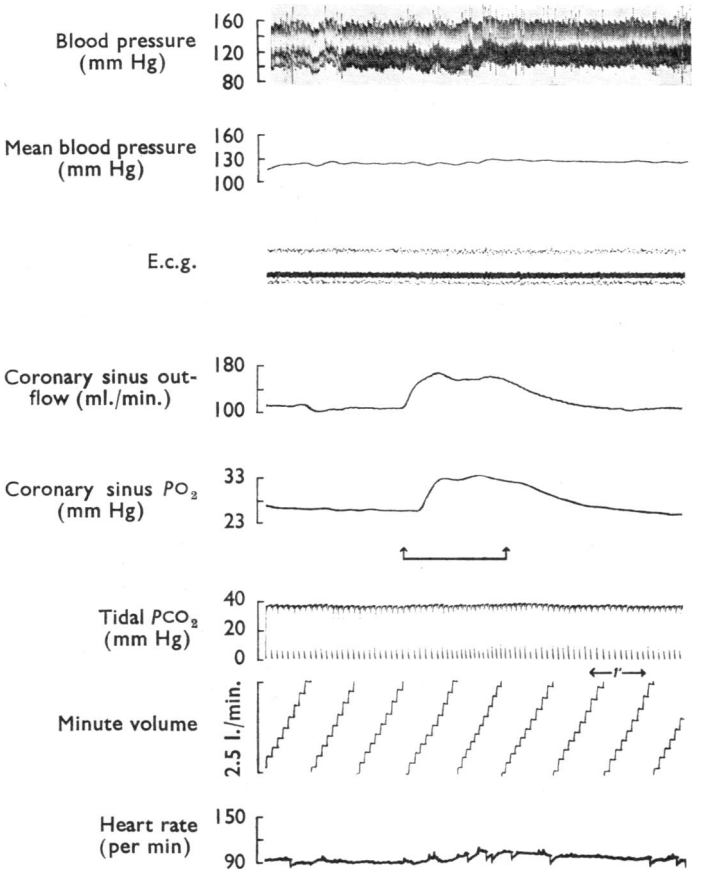

Fig. 1. The effect of an intracoronary infusion of bradykinin (0.025 μg/kg/min, between arrows) on blood pressure, the electrocardiogram (lead II), coronary sinus outflow and oxygen tension (Po_2), end-tidal carbon dioxide tension (Pco_2), respiratory minute volume and heart rate in an anaesthetized dog.

is illustrated in Fig. 1, where it can be seen that with intracoronary infusions of bradykinin flow rose to a maximum and remained at this steady state until the infusion was switched off. From Fig. 1 it appears that the coronary sinus oxygen tension begins to increase after the commencement of the flow increase. This is probably not so, since the difference can be accounted for by the time taken for the blood to reach the platinum electrodes from the coronary sinus and by the inherent delay in recording by the electrodes themselves.

With the lowest doses used (0.025 and 0.05 μg/kg/min) the increases in flow and oxygen tension occurred without changes in heart rate or respiratory minute volume but with higher doses significant increases in heart rate occurred, up to 16% with the highest dose of kallidin. In addition, with these high doses (0.1 and 0.2 μg/kg/min) increases in cardiac oxygen consumption and in respiratory minute volume could be demonstrated. Thus bradykinin in a dose of 0.2 μg/kg/min increased minute volume by 22%, and kallidin in the

same dose by 29%, without an effect on respiratory rate. The control respiratory minute volume in these experiments was 3.8±0.1 l./min and the rate 7.8±0.2 breaths/min (means and standard errors).

Eledoisin was more active in increasing coronary flow, doses as low as 0.005 μg/kg/min being effective. These flow changes were accompanied by significant reductions in arterial blood pressure presumably because, unlike bradykinin and kallidin, eledoisin is only slowly destroyed in the blood and lungs. These results indicate that all three peptides decrease resistance to flow in the coronary vascular bed (calculated as arterial pressure divided by coronary flow), and that this is dose-related is clearly demonstrated in Fig. 2.

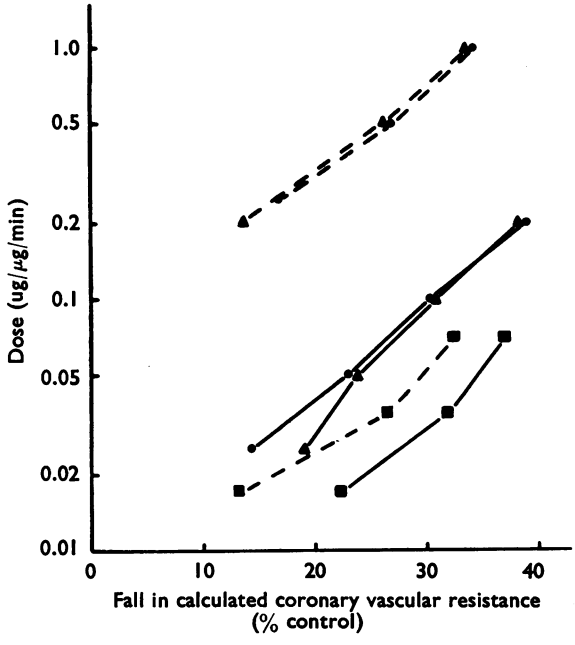

Fig. 2. Comparison of the effects of 2-min intracoronary infusions of bradykinin ●——●, kallidin ▲——▲ and eledoisin ■——■ with intravenous infusions (●- - - -●, ▲- - - -▲, ■- - - -■) on calculated coronary vascular resistance (abscissa). Ordinate, dose on log scale.

Effects of intravenous infusions

The results are summarized in Table 2. Infusions of each of the three peptides lowered blood pressure, increased coronary sinus outflow and, in addition, greatly increased heart rate. This explains the fact that in most experiments coronary venous oxygen tension remained virtually unchanged—indicating an increase in oxygen consumption. Respiratory minute volume was greatly increased by intravenous infusions of each of the three peptides. Thus bradykinin in a dose of 0.5 μg/kg/min increased minute volume by 25% and in a dose of 1.0 μg/kg/min by 47%. The corresponding results for kallidin were 23 and 80% respectively. With kallidin there were also increases in respiratory rate (up to 30%).

TABLE 2

THE EFFECTS OF INTRAVENOUS INFUSIONS OF BRADYKININ, KALLIDIN AND ELEDOISIN ON BLOOD PRESSURE, HEART RATE, CARDIAC OXYGEN CONSUMPTION AND ON CORONARY SINUS OUTFLOW AND OXYGEN TENSION

Results are means and standard errors. * Significantly different from controls at $P<0.05$; † at $P<0.005$

Drug	Dose (μg/kg/min)	No. of expts.	Mean blood pressure (mm Hg)	Heart rate (beats/min)	Coronary sinus Outflow (ml./min)	Coronary sinus Oxygen tension (mm Hg)	Cardiac oxygen consumption (% control)
Controls			145±3·1	140± 5·5	156± 4·3	21·2±0·4	
Bradykinin	0·25	5	136±2·4*	153± 4·3*	175± 3·9†	21·9±0·1*	
	0·5	9	132±2·6†	181± 8·8†	195± 7·9†	22·0±0·6	+23·2± 5·7†
	1·0	5	125±5·2†	212±31·2	212±30·2*	23·4±1·5	+32·3±15·4*
Kallidin	0·2	5	139±1·4*	142± 1·0	158± 6·4	20·9±0·6	+ 4·8± 1·1*
	0·5	7	132±2·6†	177± 9·5†	194± 7·3†	21·9±1·1	+25·3± 5·3†
	1·0	4	125±5·2†	212±23·4†	213±22·1†	24·3±1·0*	+28·2±12*
Eledoisin	0·017	4	140±1·7	149± 5·7	173±11·3	21·1±0·5	+10 ± 3·4†
	0·035	5	132±1·2†	195± 9·8†	194± 8·7†	23·2±1·0	+14 ± 3·8†
	0·07	2	122	166	185		17

Effects of plasma kinins after sympathetic β-receptor blockade and after administration of dipyridamole

In three experiments the effects of β-receptor blockade with propranolol, 0.25 mg/kg intravenously (Black, Crowther, Shanks, Smith & Dornhorst, 1964), on the response of the coronary circulation to bradykinin and kallidin were examined. These experiments were undertaken because these substances (and also eledoisin) can release catechol amines from the adrenal medulla (Feldberg & Lewis, 1963; Parratt, 1964b). It was conceivable therefore that the local injection of these peptides into the coronary circulation might release adrenaline and noradrenaline from cardiac stores, with subsequent effects on coronary vascular resistance. Because β-receptor blockade in dogs prevents the decrease in coronary resistance which results from infusions of adrenaline (Parratt, 1965) it was believed that these experiments would demonstrate whether the decrease in vascular resistance resulting from infusions of bradykinin, kallidin and eledoisin was mediated in part through adrenaline release. All three peptides increased coronary flow and decreased resistance after β-receptor blockade, although on two occasions the effects were slightly reduced. The increases in heart rate observed after intravenous infusions of the peptides were also unaffected by β-receptor blockade.

In three other dogs the effects of bradykinin and kallidin were studied before and after dipyridamole, a substance which potentiates the effects of injections of the adenosine derivatives (Bretschneider, 1964). No such potentiation was observed with the peptides.

DISCUSSION

Increases in coronary flow which occur after the local administration of substances into a branch of the left coronary artery might be the result of an effect on vascular smooth muscle, or indirectly through changes in the metabolic requirements of the myocardium. One of the main factors regulating flow through the myocardial vascular bed is the oxygen requirement of the myocardium (Eckenhoff, Hafkenschiel, Landmesser & Harmel, 1947; Foltz, Page, Sheldon, Wong, Tuddenham & Weiss, 1950). The experiments reported here

show that bradykinin, kallidin and eledoisin each exerts its effect on coronary flow by means of an action on the vessels themselves. Clear increases in flow occurred with doses which had no significant effect on heart rate and furthermore these flow changes were accompanied by increases in coronary venous oxygen tension. Changes in contractile force were not measured but local infusions of the peptides into the coronary circulation, in doses which increased flow and coronary sinus oxygen tension, had no effect on intraventricular pressure or on the rate of change of intraventricular pressure. Together these would be expected to give an indication of changes in contractile force and extravascular support. A similar result has been obtained by Bergamaschi & Glässer (1963). These workers found that increases in flow could be obtained with eledoisin in doses which had no effect on myocardial contractility, as measured by a strain gauge.

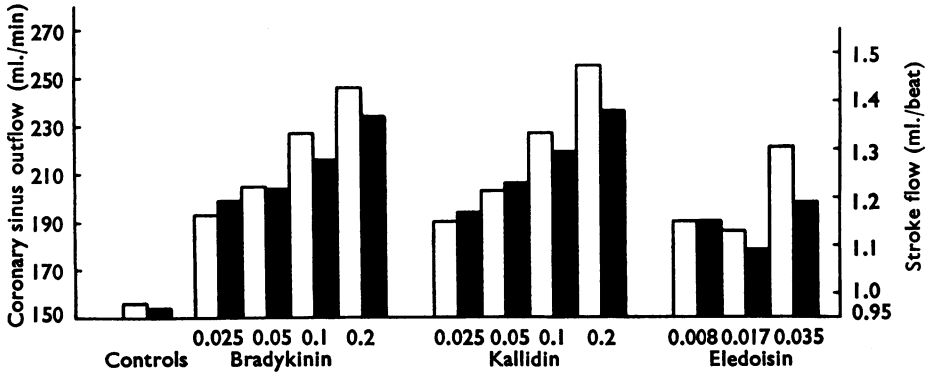

Fig. 3. Comparison of the effects of intracoronary infusions of bradykinin, kallidin and eledoisin (all doses in μg/kg/min) on coronary sinus outflow (open columns) and coronary sinus outflow per heart beat (filled columns).

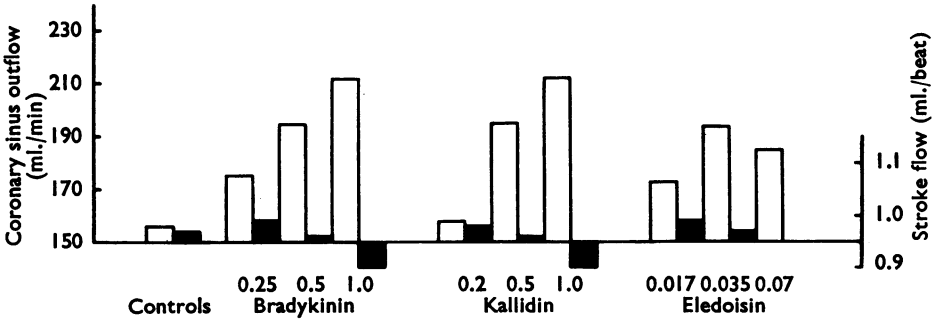

Fig. 4. Comparison of the effects of intravenous infusions of bradykinin, kallidin and eledoisin (all doses in μg/kg/min) on coronary sinus outflow (open columns) and coronary sinus outflow per heart beat (filled columns).

The conclusion that bradykinin, kallidin and eledoisin exert their effect on coronary flow by a direct action on the vessels confirms that reached in previous experiments in which these substances were infused intravenously (Parratt, 1964a). Other workers (Maxwell *et al.*, 1962; Rowe *et al.*, 1963), on the basis solely of intravenous or intra-atrial infusions

of relatively large amounts of bradykinin, have argued that this substance cannot be classified as a potent coronary dilator since it does not (like other coronary dilators) increase coronary sinus oxygen content. In their experiments coronary sinus oxygen saturation actually decreased after bradykinin administration; the increases in coronary flow observed were linked with increases in heart rate. Somewhat similar results are recorded in Table 2—unchanged oxygen tension, decreased flow per beat (stroke flow) and increased absolute flow and heart rate. Very different effects are, however, seen after local infusions (Table 1). Thus increases occur not only in absolute flow but also in stroke flow and in coronary sinus oxygen tension and these changes occur without effects on heart rate or contractile force. The difference between locally and systemically infused peptides is most strikingly seen when stroke flow is calculated (compare Figs. 3 and 4) and illustrates the considerable dilatation which occurs in the coronary vascular bed after local infusion of the peptides. The experiments also illustrate the danger of drawing conclusions about the action of substances on coronary vascular tone simply from the intravenous administration of large amounts. There may be secondary effects produced which may completely mask the true action of the substance on the coronary vessels themselves. Thus the finding that eledoisin actually decreases coronary flow (Maxwell, 1964), which is in sharp contradiction to the results reported here and also to those of other workers (Bergamaschi & Glässer, 1963), can perhaps be accounted for by the considerable hypotension which resulted from the relatively large doses administered.

Attention has been drawn by previous workers (Rowe *et al.*, 1963) to the similarities which exist between some of the effects of intravenous injections of bradykinin on the heart and coronary circulation and those of the catechol amines. These include increase in cardiac output, coronary flow and myocardial oxygen consumption and also of arterial haemoglobin content. Very small amounts of the plasma kinins are able to release adrenaline and noradrenaline from the adrenal medulla (Feldberg & Lewis, 1963) and it is conceivable that this might also occur in cardiac tissue and that the released catechol amines might contribute to the flow increase. The experiments recorded here in which sympathetic β-receptor blockade failed to prevent the increases in flow which follow local infusions of the kinins indicate that this is unlikely. A similar conclusion was reached by Rowe *et al.* (1963) who depleted the cardiac catechol amine stores with reserpine and found that the haemodynamic effects of bradykinin were basically the same as in normal dogs. It also seems that the stimulant action of the kinins on heart rate, especially seen after intravenous infusions, is not mediated through adrenaline release because intravenous kallidin increased heart rate even after β-receptor blockade. Rowe *et al.* (1963) also observed that bradykinin increased heart rate when cardiac catechol amine stores had been depleted with reserpine. These effects of the plasma kinins are probably therefore the result of a direct action on the pacemaker. It is still, however, possible that the slight hypertensive effects sometimes seen after intracoronary infusions of bradykinin and kallidin, and which can also be demonstrated after intravenous injections of these substances in rats (Parratt, 1964b), art mediated through adrenaline release.

It is likely that in the coronary vascular bed bradykinin, kallidin and eledoisin act on a similar receptor. The log dose/response curves are parallel (Fig. 2), and the fact thae eledoisin is the most active of the three peptides can probably be accounted for by the relatively slow rate of breakdown of this substance in mammalian blood compared to that

of bradykinin and kallidin (Stürmer & Berde, 1963). Furthermore, intravenous infusions of eledoisin were almost as effective in decreasing coronary vascular resistance as were intracoronary infusions. This is in marked contrast to bradykinin and kallidin, which were much less effective by the intravenous route, presumably because of the degree of breakdown of these substances that occurs between the site of infusion and the coronary vascular bed. Thus the values in Tables 1 and 2 indicate that only about 10% of the plasma kinins infused into the femoral vein reaches the coronary vascular bed.

The high vasodilator activity of the plasma kinins in a number of tissues has stimulated considerable interest in the possibility that they play a role in the local regulation of blood flow. This is true in a number of glandular tissues such as the pancreas and the lachrymal, salivary and sweat glands (for references see Lewis, 1960), although attempts to demonstrate the presence of bradykinin in the venous effluent from contracting skeletal muscles have been unsuccessful (Hilton & Lewis, 1958). The sensitivity of the coronary vascular bed to the plasma kinins is such that it is conceivable that the local production of such vasodilator polypeptides (perhaps by way of the release of kallikrein from contracting cardiac muscle cells) might contribute to the regulation of flow through this vascular bed. It has been suggested that in the heart this local regulation of blood flow is mediated through the release of adenosine (Berne, 1963) but it is worth pointing out that the plasma kinins are considerably more active in increasing coronary flow than are the adenosine derivatives. Thus under similar experimental conditions to those reported here adenosine was about a hundred times less active (on a molar basis) than either bradykinin or kallidin; a dose of 0.002 μmoles/kg/min of adenosine were needed to decrease coronary vascular resistance by 25% (J. Scholtholt, personal communication). Although it is conceivable that plasma kinins play a role in functional vasodilatation in the coronary vascular bed, it would be difficult to demonstrate this using available methods of detecting plasma kinins in blood, particularly as their destruction in coronary venous blood is presumably rapid.

When infused either locally into the coronary circulation, or intravenously, each of the three peptides stimulated respiration. With local infusions the threshold dose needed to produce this effect (0.1 μg/kg/min) was about ten times higher than that needed to increase coronary sinus outflow. With intravenous infusions this stimulation of respiration (as evidenced by increase in minute volume) was particularly strong. It is interesting that the three kinins have this dual property of stimulating respiration as well as of increasing coronary blood flow because it has been pointed out that all drugs known to increase coronary flow also stimulate the chemoreceptors of the carotid body (Lochner & Hirche, 1962; Lochner, 1964). It is now clear that bradykinin, kallidin and eledoisin must be added to this list.

In agreement with previous workers (Maxwell *et al.*, 1962; Rowe *et al.*, 1963) it has been found that bradykinin increases myocardial oxygen consumption. This has now been shown also for kallidin and eledoisin. The method used to estimate oxygen consumption is only approximate. It takes no account of changes in arterial oxygen tension or of arterial haemoglobin concentration, both of which are increased after large doses of bradykinin (Rowe *et al.*, 1963). However, even if such increases occurred after local infusions of small amounts of the kinins (for example doses which had no effect on respiration) the method would underestimate rather than overestimate changes in oxygen consumption. It is apparent from Table 1 that after local administration increases in calculated cardiac oxygen

consumption occurred without very great changes in heart rate. In fact, these increases were more than those that occurred after much higher intravenous doses which had strong stimulant effects on heart rate (Table 2). The apparent increase in cardiac oxygen consumption after the local infusion of the peptides without an increase in heart rate or contractile force (or of calculated external work) perhaps indicates an increase in local metabolic heat production by the myocardium. A similar conclusion has also been reached using direct measurement of intramyocardial temperature by Parratt & Grayson (1963).

SUMMARY

1. A comparison has been made of the effects of intravenous and intracoronary infusions of synthetic bradykinin, kallidin and eledoisin on the coronary circulation in anaesthetized closed-chest dogs with an electromagnetic flowmeter placed in the coronary sinus.

2. Each of the three peptides infused locally into a branch of the left coronary artery in doses as low as 0.025 μg/kg/min (bradykinin and kallidin) or 0.008 μg/kg/min (eledoisin) greatly increased coronary sinus outflow, coronary sinus oxygen tension and stroke flow without affecting blood pressure or heart rate. The changes were accompanied by increased cardiac oxygen consumption which was attributed to increased myocardial metabolic heat production.

3. Intravenous infusions of larger doses also increased coronary outflow and oxygen consumption but coronary stroke flow and sinus oxygen tension remained almost unchanged. With these doses large increases in heart rate and respiratory minute volume occurred.

4. The increase in blood flow by the local infusion of these peptides is attributed to coronary vasodilatation as a result of a direct effect on the myocardial vessels, and was unaffected by sympathetic β-receptor blockade or by injection of dipyridamole. The fact that the plasma kinins are the most active naturally occurring coronary vasodilators makes it conceivable that their local production within the coronary vascular bed plays a role in functional vasodilatation in cardiac tissue.

We are grateful to Drs A. Fanchamps and W. v. Orelli of Sandoz (Basel) for generous supplies of synthetic bradykinin, kallidin and eledoisin; to Dr R. G. Shanks of I.C.I. for the propranolol and to Dr Ihrig of Thomae (Biberach) for the dipyridamole. One of us (J. R. P.) would also like to thank Drs H. Hirche and J. Scholtholt for their contributions to the experiments and for their help in many other matters during his stay in Düsseldorf.

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