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A COMPARISON OF THE EFFECTS OF THE PLASMA KININS, BRADYKININ AND KALLIDIN, ON MYOCARDIAL BLOOD FLOW AND METABOLISM

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Using a heated thermocouple technique it was shown that the plasma kinins, kallidin (lys-bradykinin) and bradykinin, increased myocardial blood flow, when given either by single injection or by continuous slow infusion, in the rabbit, cat, dog, monkey and chimpanzee. In every experiment systemic arterial blood pressure and myocardial vascular resistance fell by an amount related to the log of the dose of the kinin administered. These effects were seen with quite small doses of bradykinin and kallidin and demonstrate that the myocardial vascular bed is very sensitive to these plasma kinins. In larger doses, bradykinin increased "corrected temperature" —the myocardial temperature change corrected for alterations in blood flow and with heat losses controlled. This response represents a stimulation of metabolic heat production which was not observed with kallidin.

Several workers have suggested that, under certain conditions, the heart can regulate its own blood flow by the release of a vasodilator substance (see Marcou, 1939 ; Berne, Blackmon & Gardner, 1957). In recent years the nonapeptide bradykinin has been implicated in functional vasodilatation in glandular tissues (Hilton & Lewis, 1956, 1958) and in skin (Fox & Hilton, 1958) and the possibility has been raised that bradykinin might be a mediator of the vasodilatation which occurs in skeletal muscle during reactive hyperaemia, exercise and insulin hypoglycaemia (Lewis, 1960 ; Hilton, 1960).

It seemed important, therefore, to investigate the vascular effects of bradykinin in cardiac muscle and with this in view the effects of this plasma kinin, and of the related decapeptide kallidin (lys-bradykinin), on myocardial blood flow have been studied in a number of species. Preliminary notes on the effects of bradykinin on myocardial blood flow in the rabbit have been published (Grayson & Parratt, 1962 ; Parratt & Grayson, 1963).

METHODS

Rabbits were anaesthetized with urethane (1.5 g/kg, intravenously) and cats and dogs with pentobarbitone sodium (45 mg/kg, intraperitoneally). West African Green monkeys (*Cercopithecus aethiops*), Mona monkeys (*Cercopithecus mona*) and Patas monkeys (*Erythrocebus patas*) of either sex were anaesthetized with pentobarbitone sodium (40 mg/kg, intraperitoneally)

after induction with ethyl chloride. A single experiment was performed on a chimpanzee (*Pan troglodytes*), 30 kg body weight, which was anaesthetized with pentobarbitone sodium (35 mg/kg, injected into a brachial vein).

Intravenous injections and infusions. These were made through a polyethylene cannula in a femoral vein. For the infusions, a constant speed continuous injection apparatus was used which delivered 0.5 ml./min from either of two 50 ml. syringes: one contained 0.9% saline, the other the plasma kinin solution. Initial values of blood pressure and flow were obtained during continuous infusions of 0.9% saline. The solution of bradykinin or kallidin was then infused for 10 min after which the infusion was changed to 0.9% saline.

Blood pressure recording. Systemic arterial blood pressure was recorded from a polyethylene cannula in a femoral artery using a mercury manometer or a Shillingford-Muller transducer with one of two oscillator channels of a Cambridge recording camera.

Blood pressure compensation. In a few of the infusion experiments the systemic arterial blood pressure was prevented from falling by means of the compensator described by Grayson & Mendel (1961).

Measurement of myocardial blood flow. The method used was that of Grayson (1952) as modified by Grayson & Mendel (1961), for the measurement of myocardial blood flow; it depends upon the thermoelectric measurement of thermal conductivity. It has been shown for a variety of tissues, for example, liver (Grayson, 1952), brain (Carlyle & Grayson, 1956), skeletal muscle (Graf & Rosell, 1958) and thyroid (Mowbray, 1959), that the difference in thermal conductivities of living and dead tissues (termed the "conductivity increment," ΔK) is approximately a linear function of blood flow. That this relationship applies also to cardiac muscle was first demonstrated by Kiese & Lange (1957) who showed that flow values obtained using this calorimetric technique corresponded well to those obtained with the nitrous oxide method. A linear relationship between myocardial thermal conductivity and blood flow has also been observed in hearts, perfused through the coronary arteries, under conditions in which the temperature is rigidly controlled (Grayson & Parratt, unpublished).

The recording instrument was that described by Grayson & Mendel (1961). Insertion of the recording thermocouple (which was usually complete within 3 min of opening the chest) produced a transient drop in blood pressure (averaging 16%) and a slight alteration in pulse form during the next beat. The insertion of the recording thermocouple thus had little effect on the performance of the heart and also produced little trauma, as evidenced by histological examination of the left myocardium.

The operation was completed as follows. The chest wall was closed with thick thread sutures and the leads from the recorder, emerging from the chest wall, were soldered to the heating or thermocouple circuits. The reference cold-junction (mounted in a fine polyethylene tube) was inserted through the left carotid artery (in the rabbit experiments) or the left brachial artery (in the other species) so that the tip lay in the arch of the aorta.

Assessment of metabolic heat production. Photographic records of blood flow were analysed to obtain indications of local metabolic heat production as described in detail by Dosekun, Grayson & Mendel (1960). In the present experiments the cold-junction (temperature reference point) was situated in the aorta and, being thus in the stream of afferent blood, changes in blood temperature were automatically compensated. Since the animals were in a constant temperature room and had controlled positive pressure ventilation, heat losses were assumed to be constant. Alterations in the temperature recorded from the heated thermocouple could thus have been due to changes in blood flow or to changes in local heat production. Using the calculation described by Dosekun *et al.* (1960), temperature changes due to blood flow were determined; the change remaining (termed by these authors "corrected temperature") was probably related to local metabolic heat production.

In a few experiments absolute temperatures were recorded directly from the left myocardium, from the blood in the arch of the aorta and from the mediastinal tissue adjacent to the heart, using simple unheated thermocouples as described by Parratt & Grayson (1963).

Drugs. These were synthetic kallidin-10 (lys-bradykinin), bradykinin (B.R.S. 640) and hog pancreatic kallikrein (Glumorin, Bayer).

RESULTS

The effects of single intravenous injections of bradykinin on myocardial blood flow, vascular resistance and metabolic heat production

Results obtained in rabbits, monkeys and dogs are summarized in Table 1. In all experiments, bradykinin produced a transient fall in blood pressure, the size of which depended upon the dose. These falls in blood pressure were accompanied

TABLE 1

EFFECTS OF INTRAVENOUS INJECTIONS OF BRADYKININ ON BLOOD PRESSURE, HEART RATE, MYOCARDIAL BLOOD FLOW AND CALCULATED MYOCARDIAL VASCULAR RESISTANCE IN RABBITS, MONKEYS AND DOGS

Values are expressed as percentages of controls and also included are values for "corrected temperature," a measure of myocardial metabolic heat production

Dose (μg/kg)	No. of observations	Percentage change from controls for: Blood pressure	Blood flow	Vascular resistance	Heart rate	Corrected temperature (°C)
Rabbits						
0·05	4	−7	+6	−9	—	+0·04
0·1	6	−14	+9	−16	—	+0·01
0·2	7	−21	+7	−21	—	+0·05
0·5	8	−37	+9	−39	—	+0·15
1·0	6	−48	0	−47	—	+0·09
Monkeys						
0·25	2	−18	−4	−18	+3	+0·07
0·5	5	−13	+5	−15	0	+0·07
1·0	7	−27	+7	−28	+4	+0·08
2·0	5	−35	+10	−39	0	+0·16
3·0	1	−51	+57	−58	0	+0·23
Dogs						
0·25	1	−19	+31	−38	+1	+0·03
0·5	3	−26	+70	−45	+3	+0·05
1·0	3	−34	+62	−50	+4	no change
2·0	1	−41	+121	−67	+9	+0·07

by increases in myocardial blood flow (Fig. 1) which were particularly conspicuous in the dogs. These results indicate that bradykinin decreased the myocardial vascular resistance. This fall in resistance was related linearly to the log of the dose of bradykinin injected (Fig. 2).

Similar results were obtained in the experiment with the chimpanzee. Doses of 0.5, 1.0 and 1.5 μg/kg lowered blood pressure by 16, 25 and 28% respectively with slight increases in heart rate (maximal increase 11%) and blood flow (up to 24%). The cats were much less sensitive to injected bradykinin, a dose of 2 μg/kg being needed to lower the blood pressure by 18%. In two out of the three experiments with cats, increases in myocardial flow were observed with doses of 5 and 10 μg/kg, in one instance amounting to over 25%. The average fall in blood pressure with a dose of 10 μg/kg was 55%, and with 20 μg/kg was 66%. With both these doses heart rate fell to a level 20% below the control.

In rabbits, monkeys and dogs higher doses of bradykinin produced increases in " corrected temperature " (Table 1) which lasted for about 10 min after the injection

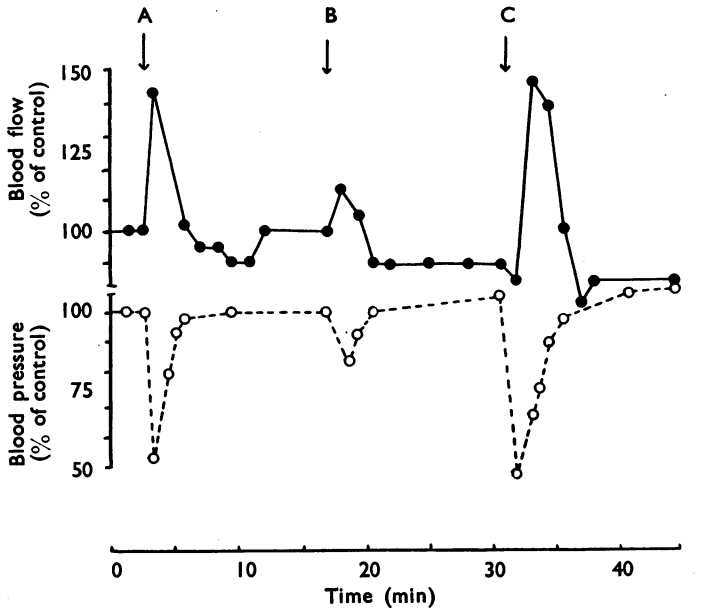

Fig. 1. The effect of three successive intravenous injections of bradykinin (2.0 μg/kg at A, 1.0 μg/kg at B and 3.0 μg/kg at C) on myocardial blood flow (● —— ●) and blood pressure (○ – – ○) in a West African Green monkey. Blood pressure and flow are expressed as percentages of control values.

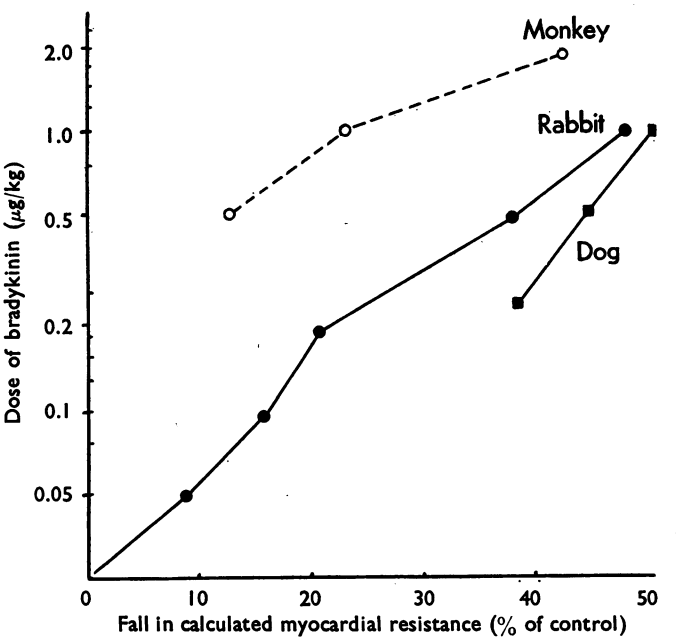

Fig. 2. Comparison of the effects of single intravenous injections of synthetic bradykinin (ordinate, dose on log scale) on fall in calculated myocardial vascular resistance (abscissa, percentage of controls) in monkeys (○ —— ○), rabbits (● —— ●) and dogs (■ —— ■). Values are means from results given in Table 1.

(Fig. 3). In a few of the rabbit experiments absolute temperatures were recorded from the myocardium of the left ventricle, from the blood in the arch of the aorta and from the mediastinum next to the heart. The myocardium was hotter than the blood flowing to it by an average of 0.7° C, presumably an indication of heat production as a result of myocardial metabolism. In confirmation of previous findings (Parratt & Grayson, 1963) injections of bradykinin in doses of 0.5 μg/kg increased this temperature differential by values ranging from 0.06 to 0.38° C.

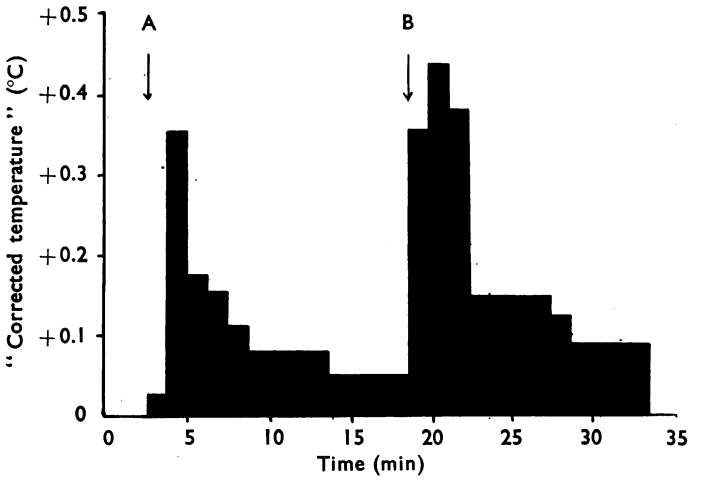

Fig. 3. The effect of two single intravenous injections of bradykinin (0·5 μg/kg at A and 1.0 μg/kg at B) on the "corrected temperature" (ordinate, °C) of a rabbit myocardium.

TABLE 2

EFFECT OF 10 MIN INTRAVENOUS INFUSIONS OF BRADYKININ ON BLOOD PRESSURE, MYOCARDIAL BLOOD FLOW AND CALCULATED MYOCARDIAL VASCULAR RESISTANCE IN RABBITS

Values indicate maximal responses during infusion, expressed as percentages of controls, and also included are values for "corrected temperature," a measure of myocardial metabolic heat production.
*Blood pressure compensated

Dose (μg/kg/min)	Percentage change from controls for: Blood pressure	Blood flow	Vascular resistance	Corrected temperature (°C)
0·1	−23	−10	−27	−0·11
0·1	−5	−21→+32	−25	+0·29
0·2	−10	+18	−16	0
0·2	−13	0	−14	—
0·35	−23	+10	−24	+0·11
0·5	−26	−14→+7	−23	0
0·5	−11	+23	−14	−0·44
0·5	0*	+35	−27	+0·80
0·5	—	−22	—	−0·30
0·5	−25	−11	−16	−0·20
1·0	−43	−19→+10	−32	+0·11
1·0	−23	−29	−19	−0·44→+0·26
1·0	0*	+52	−21	−0·25
1·0	—	+4→−22	—	—
1·0	−23	−7→+42	−32	+0·10
1·5	−42	0	−42	+0·09
1·5	−17	+65	−38	+0·38
2·0	−50	+28→−24	−45	+0·47→0·3
3·5	−23	−22	−15	0

The effects of continuous intravenous infusions of bradykinin on myocardial blood flow, vascular resistance and metabolic heat production

Results obtained for rabbits and monkeys are given in Tables 2 and 3. In both species a consistent finding was the partial recovery of the blood pressure during the period of the infusion (Fig. 4). In the monkeys, myocardial blood flow was

TABLE 3

EFFECT OF 10 MIN INTRAVENOUS INFUSIONS OF BRADYKININ ON BLOOD PRESSURE, HEART RATE, MYOCARDIAL BLOOD FLOW AND CALCULATED MYOCARDIAL VASCULAR RESISTANCE IN MONKEYS

Values indicate maximal responses at any time during the infusion period expressed as percentages of controls, and also included are values for "corrected temperature," a measure of myocardial metabolic heat production

Dose (μg/kg/min)	Percentage change from controls for: Blood pressure	Heart rate	Blood flow	Vascular resistance	Corrected temperature (°C)
0·25	−5	—	+16	−16	+0·05
0·5	−17	+5	+42	−39	0
0·5	−8	—	+28	−26	+0·07
0·5	−29	0	+16	−22	+0·07→−0·23
0·5	−14	+11	0	−12	0
1·0	−41	+18	+48	−53	+0·17
1·0	−41	0	+21	−39	0
1·0	−20	—	+41	−56	+0·11
1·0	−35	0	+24	−42	+0·15
1·0	−34	0	+25	−38	+0·02→−0·23
1·0	−26	+20	0	−27	0
1·0	−29	+17	−12→+15	−37	0
2·0	−58	−5→+3	+111	−77	+0·39→−0·17
2·0	−31	—	+44	−43	+0·12
2·0	−12	+16	+26	−42	+0·17
3·0	−36	—	+81	−72	+0·21

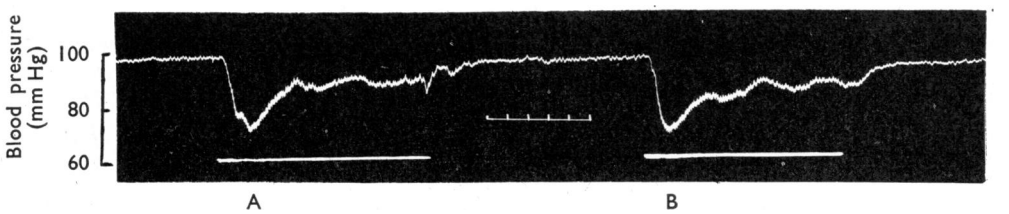

Fig. 4. Monkey, 6 kg. The effect of two intravenous infusions of bradykinin (1.0 μg/kg/min at A and 2.0 μg/kg/min at B, during periods indicated by white lines) on systemic arterial blood pressure. Note that partial recovery of pressure takes place during the period of infusion. Time marks, minutes.

increased during the whole of the infusion period but was greatest during the first few minutes (Fig. 5). These increases in flow were accompanied by slight (up to 20%) increases in heart rate. The blood flow responses to infused bradykinin were more variable in the rabbits (Table 2). Where increases did occur, they were most conspicuous during the first 2 min of the infusion. In all experiments there was a considerable reduction in calculated myocardial vascular resistance.

Bradykinin infusions were also given (in doses ranging from 0.1 to 1.0 μg/kg/min) to dogs; in each of six experiments increases in myocardial blood flow were observed together with slight increases in heart rate (never more than 10%) and

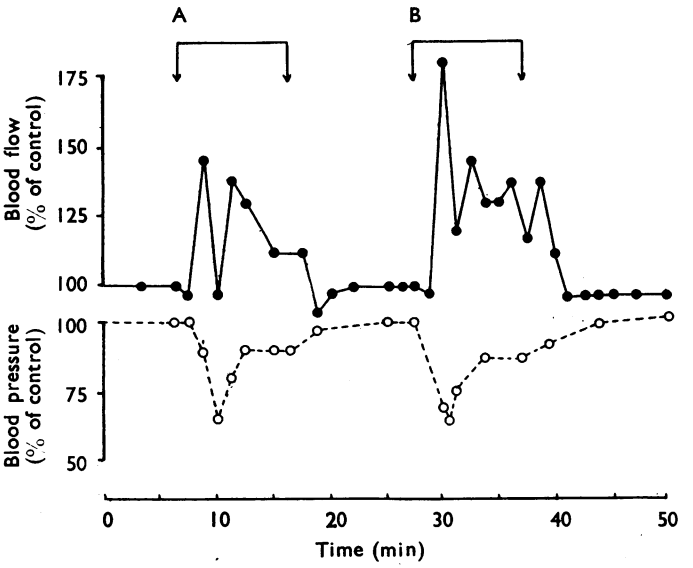

Fig. 5. The effect of two 10 min intravenous infusions of bradykinin (2.0 μg/kg/min at A and 3.0 μg/kg/min at B) on myocardial blood flow (● —— ●) and on systemic arterial blood pressure (○ - - - - ○) in a West African Green monkey. Myocardial blood flow and systemic blood pressure are expressed as percentages of control values.

in "corrected temperature." Larger doses (1.0 to 4.0 μg/kg/min) were needed to produce comparable decreases in blood pressure in cats, where again increases in myocardial blood flow occurred. An exception occurred in one experiment performed on a pregnant cat where bradykinin, in three dose levels, increased systemic blood pressure and myocardial vascular resistance. This animal also responded differently to bradykinin in regard to metabolic heat production, which was raised in normal female cats but markedly depressed in the pregnant animal.

The effects of single intravenous injections of kallidin on myocardial blood flow, vascular resistance and metabolic heat production

In all the species studied, injections of kallidin decreased blood pressure; the rabbits were by far the most sensitive, doses as low as 0.05 μg/kg depressing blood pressure by an average of 16% (Table 4). In dogs (Table 4) and monkeys larger doses (0.2 μg/kg) had to be used to produce similar falls in blood pressure and, in contrast to rabbits, there appeared to be no consistent relationship between dose and response. This result agrees with those of Stürmer & Berde (1962). There were no great (over 5%) increases in heart rate after kallidin in rabbits, dogs or the chimpanzee, but large doses (2 μg/kg) did increase heart rate in the two monkeys, in one instance by as much as 24%.

Blood flow responses after intravenous injections of kallidin were variable and depended largely upon the extent of the blood pressure fall. When increases did occur (for example in the chimpanzee and in the dogs after injections of up to

TABLE 4

EFFECTS OF INTRAVENOUS INJECTIONS OF KALLIDIN ON BLOOD PRESSURE, HEART RATE, MYOCARDIAL BLOOD FLOW AND CALCULATED MYOCARDIAL VASCULAR RESISTANCE

Values are expressed as percentages of controls, and also included are values for "corrected temperature," a measure of myocardial metabolic heat production

Dose (μg/kg)	No. of observations	Percentage change from controls for: Blood pressure	Heart rate	Blood flow	Vascular resistance	Corrected temperature (°C)
Rabbits						
0·05	4	−16	+2	+10	−21	−0·09
0·1	3	−18	+2	+10	−21	−0·10
0·2	2	−22	+7	+21	−29	−0·23
Dogs						
0·1	2	−15	0	0	−16	—
0·2	2	−17	0	+17	−24	−0·09
0·5	4	−22	+3	+42	−33	−0·15
1·0	3	−23	+4	+65	−40	−0·21

1.0 μg/kg) they were transient, the maximal increase often corresponding in time to the maximal decrease in blood pressure (Fig. 6). This response resulted in a considerable fall in calculated myocardial vascular resistance and this fall, since there was no change in heart rate, can probably be attributed to active vasodilatation.

In contrast to bradykinin, no dose level of kallidin increased metabolic heat production. Indeed in most experiments there were decreases. This result seems to be a major point of distinction between the two plasma kinins.

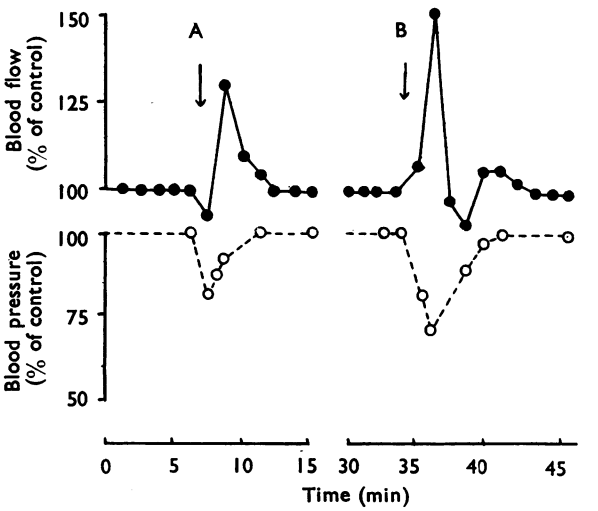

Fig. 6. Chimpanzee, female, 30 kg. The effect of intravenous injections of kallidin (0.33 μg/kg at A and 1.0 μg/kg at B) on myocardial blood flow (●——●) and on systemic arterial blood pressure (○- - - -○), expressed as percentages of controls. There are transient increases in flow despite the falls in blood pressure.

The effects of continuous intravenous infusions of kallidin on myocardial blood flow, vascular resistance and metabolic heat production

The results are presented in Table 5. In all species kallidin lowered blood pressure, the minimal effective dose being 0.1 μg/kg/min for rabbits and 0.5 μg/kg/min for dogs and monkeys. Partial recovery of blood pressure took place during the infusion (Fig. 7) but this effect was by no means as conspicuous as with bradykinin infusions.

TABLE 5

EFFECTS OF 10 MIN INTRAVENOUS INFUSIONS OF KALLIDIN ON BLOOD PRESS URE HEART RATE, MYOCARDIAL BLOOD FLOW AND CALCULATED MYOCARDIAL VASCULAR RESISTANCE

Values indicate maximal responses during infusion, expressed as percentages of controls, and also included are values for "corrected temperature," a measure of myocardial metabolic heat production.
*Blood pressure compensated

Dose (μg/kg/min)	No. of observations	Percentage change from controls for: Blood pressure	Heart rate	Blood flow	Vascular resistance	Corrected temperature (°C)
Rabbits						
0·1	4	−15	0	+12	−18	−0·11
0·2	5	−16	0	+14	−25	−0·14
0·5	7	−39	+5	+12	−41	−0·12
0·75	1	−63	+5	+4	−57	−0·11
Monkeys						
0·1	2	0	0	0	0	—
0·2	1	−7	0	+22	−19	—
0·5	3	−8	+3	+8	−12	—
1·0	3	−11	+5	+40	−24	—
2·25	2	−22	+9	+56	−45	—
2·25	1	0*	+7	+229	−62	—
Dogs						
0·1	2	−2	0	+13	−8	—
0·2	3	−2	0	+10	−7	−0·13
0·5	8	−14	0	+20	−15	−0·16
1·0	6	−21	+4	+45	−32	—
2·0	1	−16	+5	+57	−45	−0·12

In most experiments, except where the blood pressure fall was large, increases in blood flow to the myocardium could be demonstrated (Fig. 7) especially in dogs and monkeys with doses of 1.0 μg/kg/min and above. These increases in flow were accompanied by only slight increases (less than 10%) in heart rate. It seems that the increases in blood flow during kallidin infusions were due to vasodilatation of the myocardial vessels so that flow could increase in spite of falls in blood pressure. This conclusion is supported by the fact that when the pressure was prevented from falling, increases in myocardial flow were even greater (Table 5). It is considered doubtful that changes in heart rate (which in any case never exceeded 10%) or in extravascular support *alone* could have produced such increases in myocardial blood flow.

Kallidin infusions had very little effect on metabolic heat production in any of the species studied. The usual response, especially in rabbits, was a slight fall; this contrasts with the response to bradykinin.

The effects of single intravenous injections of hog pancreatic kallikrein on myocardial blood flow, vascular resistance and metabolic heat production

In view of the effects of kallidin on the myocardial circulation, it was decided to attempt to release this plasma kinin *in vivo* by kallikrein. This experiment is of particular interest since kallikrein preparations have been used to treat angina pectoris. In twenty experiments hog pancreatic kallikrein (0.02 to 0.5 U/kg) was

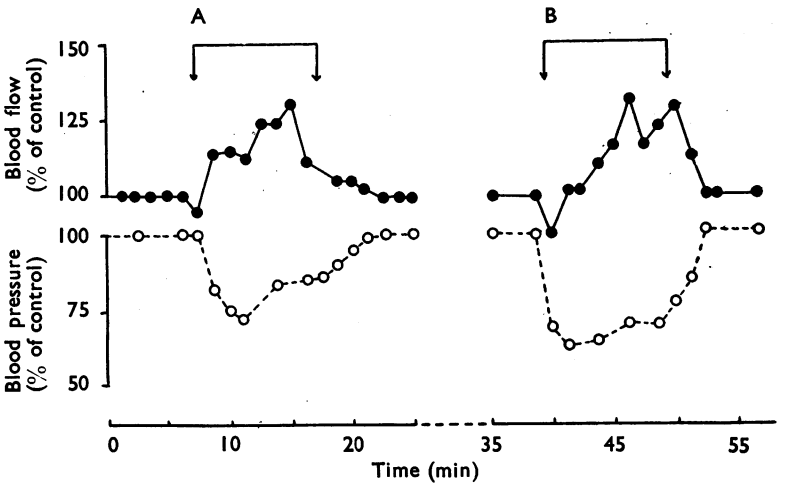

Fig. 7. Rabbit, male, 2.3 kg. The effect of two 10 min infusions of kallidin (0.2 μg/kg/min at A and 0.5 μg/kg/min at B) on myocardial blood flow (● —— ●) and on systemic arterial blood pressure (○ - - - - ○), both expressed as percentages of the control levels before the kallidin infusions.

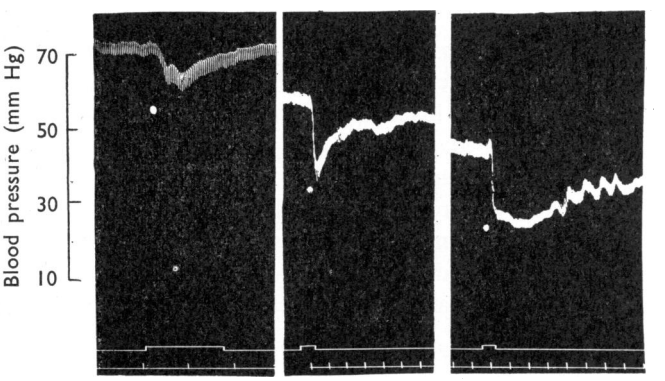

Fig. 8. The effect of hog pancreatic kallikrein on the blood pressure of a rabbit anaesthetized with urethane. From left to right, 0.05, 0.125 and 0.25 U of kallikrein. Time marks, minutes.

injected into rabbits but in no experiment was there an increase in myocardial blood flow, although decreases in systemic blood pressure were consistently observed (Fig. 8).

DISCUSSION

Plasma kinins and blood pressure. The blood pressure of all the mammals investigated fell in response to intravenous injections of bradykinin and kallidin.

The rabbits were the most sensitive—doses as low as 0.05 μg/kg injected into the femoral vein being sufficient to produce a detectable fall in blood pressure. Kallidin was slightly more active in this respect than bradykinin, a finding which agrees with previous work (Stürmer & Berde, 1962). The effects on blood pressure of the plasma kinins were transient and, provided the interval between doses exceeded 10 min, there was no tachyphylaxis. The results for rabbits, cats and dogs accord with those of Konzett & Stürmer (1960) and Stürmer & Berde (1962). With intravenous infusions of the plasma kinins, a consistent finding was the partial recovery of blood pressure during the period of the infusion (Figs. 4, 5 and 7). This recovery also occurs with intravenous infusions of vasoactive substances such as acetylcholine and adrenaline but has not been previously reported with bradykinin or with kallidin. In fact, Saameli & Eskes (1962) could find no evidence of recovery of blood pressure during infusions of bradykinin into women.

The experiment in which infusions of bradykinin raised the blood pressure of a pregnant cat suggests that its action is like that of oxytocin—a vasodilator action being converted into constrictor action during late pregnancy. Lloyd (1959) has reported that the usual vasodilator action of oxytocin in the rat could be reversed during the last half of pregnancy and also by oestrogen administration. Although Lloyd (1962) has more recently reported that administration of stilboestrol does not convert the usual depressor action of bradykinin to a pressor one in female rats, even in this species bradykinin can cause hypertension under certain conditions (Croxatto & Belmar, 1961). For example, a pressor response to bradykinin can be consistently demonstrated in rats of either sex when the blood pressure is lowered to 30 to 50 mm Hg (Parratt, unpublished), and this response is abolished by acute adrenalectomy. It is a further possibility, therefore, that the pressor responses with bradykinin in the pregnant cat may be mediated through the adrenal medulla.

Plasma kinins and myocardial blood flow. In most experiments, provided the fall in blood pressure was not excessive, both bradykinin and kallidin increased myocardial blood flow. In every instance they also decreased the resistance to flow in the myocardial vascular bed. In dogs, the increase in flow following intravenous injection of bradykinin has been attributed to an increase in heart rate by Maxwell, Elliot & Kneebone (1962), who reported a good correlation between these parameters. There was no such correlation in the present experiments. In the dogs and monkeys, for example, increases in blood flow occurred with no accompanying increases in heart rate, and in the cats increases in flow were observed despite decreases in rate.

Intravenous infusions of bradykinin often produced initial large but transient increases in myocardial flow followed by smaller but more sustained increases, reminiscent of the effects of adrenaline on skeletal muscle blood flow (Barcroft & Swan, 1953). This pattern of response is well seen in Fig. 5. The initial transient increase in flow corresponds in time to the maximal effect on blood pressure and, likewise, the partial recovery of blood pressure corresponds to the secondary, more sustained, flow increase. This result must mean that during this phase there is a progressive return of vascular resistance towards initial levels. It is tempting to link the initial, greater increase in flow with stimulation of metabolic heat production, which is often greatly increased during the early stages of a bradykinin infusion and

then returns towards control levels during the remainder of the infusion period. A point in favour of this explanation is the fact that these initial transient increases in myocardial flow seldom occur with kallidin infusions which have no stimulant action on myocardial metabolic heat production.

The later decrease in myocardial vascular resistance and increase in myocardial blood flow are probably due to a direct vasodilator action of bradykinin and kallidin. Effects on extravascular resistance have not been excluded in the present work but are probably unlikely to be sufficient to account for such great and sustained changes in flow or resistance. Certainly, the plasma kinins are active vasodilators in most other parts of the body and there seems no need to propose an alternative explanation for the increased blood flow to heart muscle. This view receives support from the recent experiments on isolated hearts by Antonio & Rocha e Silva (1962), who showed that bradykinin is a very potent coronary vasodilator in a number of isolated mammalian hearts and that there is no relationship between this response and effects on the frequency and amplitude of contraction of the heart.

Attempts were made in rabbits to release kallidin *in vivo* by injections of hog pancreatic kallikrein. Although kallikrein regularly lowered the blood pressure in these experiments, in no instance was an increase in myocardial blood flow observed. This result was unexpected since, if the fall in blood pressure were the result of kallidin formation (or release) we would have expected increases in myocardial blood flow such as occur when kallidin itself is injected into rabbits. Schachter (1956), however, has pointed out that hog pancreatic kallikrein (Padutin or Glumorin) cannot release kallidin from either rabbit or human serum *in vitro*, although it can release this kinin from guinea-pig serum under similar conditions. It is possible therefore that the hypotensive action of this kallikrein preparation in rabbits is not due to the release of kallidin but to a direct action of this plasma-kinin forming enzyme. The possibility that kallikrein has actions of its own, quite apart from its ability to release a plasma kinin, has been discussed by Lewis (1960).

Plasma kinins and metabolic heat production. In a large number of experiments, bradykinin produced considerable increases in " corrected temperature "—tissue temperature compensated for blood flow changes and with heat losses controlled. Bradykinin also increased the temperature differential between the left myocardium and the blood in the arch of the aorta, which presumably has approximately the same temperature as that in the coronary arteries. It is difficult to explain either of these findings other than by a considerable increase in local heat production resulting from a stimulation of myocardial metabolism by bradykinin. Increase in heat production could presumably result from an increase in heart rate but this could not be the explanation in the present experiments since increases in heart rate resulting from the administration of bradykinin never exceeded 10% and increases in " corrected temperature " occurred without any effect on heart rate. In the nonpregnant female cats bradykinin increased metabolic heat production despite decreases in heart rate.

In none of the experiments did kallidin increase " corrected temperature " and this absence of a stimulant action on myocardial metabolism is an interesting point of difference between the two plasma kinins.

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