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Similarity and dissimilarity of the vasoconstrictor effects of Bay K 8644 on coronary, femoral, mesenteric and renal circulations of dogs

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1 The effect of the dihydropyridine calcium agonist Bay K 8644 on the coronary, femoral, mesenteric and renal circulations was investigated and compared with that of noradrenaline in pentobarbitone-anaesthetized dogs.

2 The left anterior descending coronary, femoral, cranial mesenteric and renal arteries were cannulated and their arterial beds perfused with autologous blood at a constant pressure slightly higher than the mean systemic arterial blood pressure. Bay K 8644 (0.1–300 nmol) and noradrenaline (0.1–300 nmol) were injected intra-arterially.

3 Bay K 8644 decreased blood flow (vasoconstriction) in all 4 arterial beds. A maximum decrease was attained at 100 nmol and a further increase in dose did not appear to result in a further decrease in blood flow.

4 At maximum effects blood flow decreased to about 35% of the basal value in coronary, 30% in femoral, 20% in renal and 15% in mesenteric circulation.

5 Normalized ED_{50} values (ED_{50} divided by basal flow) of Bay K 8644 were 0.07 ± 0.02 nmol in the femoral, 0.08 ± 0.01 nmol in the coronary, 0.16 ± 0.06 nmol in the mesenteric and 0.55 ± 0.19 nmol in the renal circulation.

6 At 100 nmol, the values for the half-duration of Bay K 8644 vasoconstrictor effects were about 196 s in the renal, 78 s in the mesenteric, 84 s in the femoral and 21 s in the coronary circulation.

7 Noradrenaline produced a dose-dependent decrease in blood flow in femoral, mesenteric and renal circulations, and was about 2 times in femoral, 4 times in mesenteric and 9 times in renal circulation more potent than Bay K 8644.

8 Bay K 8644 produced slight increases in the maximum rate of rise of left ventricular pressure and intraluminal pressure of the ileum. However, the increases did not appear to impede blood flow.

9 Bay K 8644 produced slightly but significantly greater femoral vasoconstriction in normal dogs than in reserpine-pretreated dogs.

10 From these results it was concluded that differences in potency, effectiveness and duration of the vasoconstrictor effects of Bay K 8644 between the 4 arterial beds probably derive from differences in characteristics of the smooth muscle of resistance vessels there. In arterial beds where α-adrenoceptors are dominant, potentiation of the vasoconstrictor effect of endogenous catecholamines by Bay K 8644 seems to contribute to its vasoconstrictor effect.

Introduction

The dihydropyridine calcium agonist Bay K 8644 produces an increase in systemic arterial blood pressure in dogs when administered intravenously (Schramm *et al.*, 1983a,b) and a decrease in coronary blood flow in isolated hearts of the guinea-pig (Schramm *et al.*, 1983b) and also in dog isolated, blood-perfused heart preparations (Taira *et al.*, 1985; Wada *et al.*, 1985). Bay K 8644 is more potent at producing coronary vasoconstriction than inducing positive inotropic, chronotropic and dromotropic effects in dog isolated, blood-perfused heart preparations (Wada *et al.*, 1985). Interestingly, however, the coronary vasoconstrictor effect of Bay K 8644 is far more short-lived than the positive inotropic effect; the

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former had nearly worn off when the latter reached a peak (Wada *et al.*, 1985). Thus, it was of interest to see whether or not there are differences in sensitivity to Bay K 8644 and in duration of its effect between different vascular beds. To obtain such information, in the present experiments the effects of Bay K 8644 on the coronary, femoral, mesenteric and renal arterial beds were investigated in dogs. In previous experiments on the dog saphenous arterial bed (Goto *et al.*, 1985) it was found that Bay K 8644 potentiated the vasoconstrictor effects of both endogenous and exogenous noradrenaline. Therefore, in the present experiments a possible involvement of endogenous noradrenaline in the vasoconstrictor effects of Bay K 8644 was also investigated.

Methods

Twenty-four mongrel dogs of either sex weighing 10 to 16 kg were used; 5 for coronary, 7 for femoral, 6 for mesenteric and 6 for renal circulation experiments. These animals were anaesthetized with pentobarbitone sodium (30 mg kg^{-1}, i.v.). In the experiments on coronary circulation, the animals were respired artificially with room air in a tidal volume of 20 ml kg^{-1} at 18 breaths min^{-1} by use of a dog respirator (Harvard Apparatus, Model 607). The chest was opened at the 5th intracostal space on the left side. The pericardium was opened and the left anterior descending coronary artery (LAD) cannulated. To measure left ventricular pressure (LVP) a Mikro-tip catheter pressure transducer (Millar Instruments, Model PC-360) was inserted into the left ventricle via the left atrium. Its first derivative (LV dP/dt) was determined with a pulse pressure differentiator (San-ei Instrument, Type 1323). In the experiments on femoral circulation the left femoral artery was cannulated. In those on mesenteric circulation the abdominal wall was opened by a median incision and the cranial mesenteric artery cannulated. To measure intraluminal pressure of the ileum, a water-filled balloon made of thin rubber was inserted into the lumen of the ileum through a small incision made about 20 cm from its end, and this was connected to a pressure transducer (Nihon Koden, LPU-0.1). The amount of water placed in the balloon was adjusted initially to give a resting intraluminal pressure ranging from 10 to 15 cmH_2O. In the experiments on renal circulation, the abdominal wall was opened by a median incision and the right renal artery cannulated. To these cannulated arteries blood from the left common carotid artery was delivered by means of a peristaltic pump (Harvard Apparatus, Model 1200). Constant pressure perfusion was achieved by placement of a Starling pneumatic resistor through which excess blood was shunted to the right femoral vein. Perfusion pressure was initially adjusted to a value slightly higher than the mean systemic arterial blood pressure and then kept constant throughout the experiment. Blood flow through these arteries was measured with an electromagnetic flow meter (Nihon Koden, MFV-2100). Systemic arterial blood pressure was measured at the right femoral artery with a pressure transducer (Gould Statham, P23 ID). Heart rate was also measured with a cardiotachometer (San-ei Instrument, Type 1321) triggered by Lead I ECG. All recordings were made on charts by 2 rectilinear pen-recorders (San-ei Instrument, Rectiholiz 8S).

In order to investigate the involvement of endogenous catecholamines in the vasoconstrictor effects of Bay K 8644, the effect of intra-arterial (i.a.) administration of Bay K 8644 on femoral blood flow was also examined in 6 dogs (10–12.5 kg) which had been pretreated with reserpine and this effect was compared with that of normal dogs. Reserpine, 0.3 mg kg^{-1} s.c., was given for 3 consecutive days. Experiments were performed on the 3rd day of reserpine-pretreatment.

The drugs used were Bay K 8644 (methyl 1,4-dihydro - 2,6 - dimethyl - 3 - nitro - 4 - (2 - trifluorometh-ylphenyl)-pyridine-5-carboxylate; Bayer), (−)-noradrenaline base (Fluka), acetylcholine chloride (Daiichi), tyramine hydrochloride (Wako). Bay K 8644 was dissolved in 99.5% ethanol at a concentration of 3 μmol ml^{-1} or in 99% dimethyl sulphoxide (Wako) at a concentration of 30 μmol ml^{-1}. (−)-Noradrenaline base was dissolved in 0.34 N HCl to give a concentration of 100 μmol ml^{-1}. The stock solutions of Bay K 8644 and noradrenaline were diluted with 0.9% w/v NaCl solution (saline) to give the desired concentrations. Acetylcholine chloride and tyramine hydrochloride were dissolved in saline at a concentration of 100 μmol ml^{-1}. The Bay K 8644 dissolved in dimethyl sulphoxide was used only in the experiments on the LAD bed since LAD flow was markedly affected by ethanol (a decrease in flow followed by an increase). Drug solutions were injected into the femoral, renal and mesenteric arties in a volume of 100 or 300 μl over a period of 10 or 30 s. Drug solutions were injected into the LAD in a constant volume of 100 μl over a period of 10 s, because the duration of the effect of Bay K 8644 on LAD flow was very short and a 30 s injection was too long to determine the effect of Bay K 8644 correctly.

Experimental values were expressed as means ± s.e.mean. In the 4 vascular beds ED_{50} values (the doses required to produce 50% of the maximum effect) of Bay K 8644 and noradrenaline were obtained from the Hill plot ($\log[E/(E_{max} - E)]$ vs. log(dose), where E is the effect and E_{max} is the maximum effect) in individual experiments. Since we have commonly observed that ED_{50} values for a given drug depend greatly on the basal blood flow, even in a given vascular bed, and the basal blood flows were greatly

different among the 4 vascular beds, ED_{50} values were divided by the respective basal blood flow to be compared with each other (normalized ED_{50}). In general we have found that, the greater the blood flow, the larger the ED_{50}; this may be due to differences in drug concentrations at its sites of action. Analysis of variance was used for statistical analysis of mean values, and the profiles of the dose-response curves for Bay K 8644 in normal and reserpine-pretreated dogs were analysed by use of analysis of variance for repeated measurements (Morrison, 1976). Dose-response curves for the vasoconstrictor effects of Bay K 8644 and noradrenaline were approximated by linear regressions and their slopes in the text refer to those of the regression lines. Parallelism of these dose-response curves was analysed by use of analysis of covariance techniques described by Snedecor & Cochran (1967). The criterion for significance was P values less than 0.05.

Results

In the 24 normal dogs used the basal values of mean systemic arterial blood pressure and heart rate were 126 ± 5 mm Hg and 167 ± 5 beats min^{-1}, respectively. In 6 reserpine-pretreated dogs the basal values of these variables were 93 ± 5 mm Hg and 101 ± 7 beats-min^{-1}, respectively.

Effects of Bay K 8644 and noradrenaline on coronary blood flow, LVP and LV dP/dt *in normal dogs*

Coronary blood flow The basal LAD flow in 5 dogs was 17.0 ± 3.2 ml min^{-1}. Single injections of Bay K 8644 (0.1–100 nmol) into the LAD produced dose-dependent decreases in LAD flow (Figure 1a). The dose-response curve for the decrease in LAD flow to

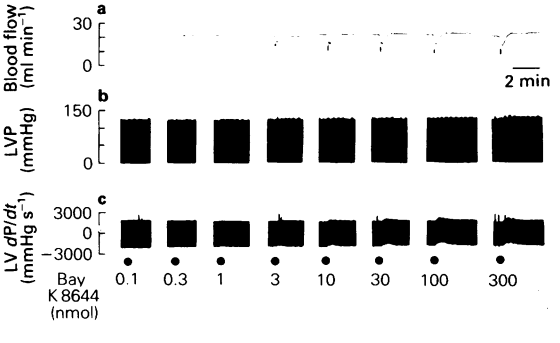

Figure 1 Effects of Bay K 8644 injected into the left anterior descending coronary artery (LAD) on blood flow through the LAD (a), left ventricular pressure (LVP) (b) and its first derivative (LV dP/dt) (c) in a normal dog.

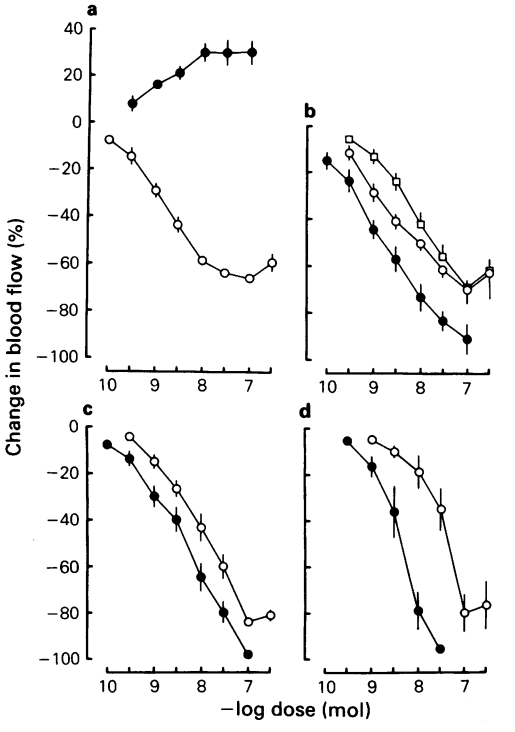

Figure 2 Dose-response curves for changes in blood flow through (a) the left anterior descending coronary artery (LAD) (n = 5), (b) the left femoral artery (n = 7), (c) the cranial mesenteric artery (n = 6) and (d) the right renal artery (n = 6) to Bay K 8644 (○) and noradrenaline (●) injected into the respective arteries in normal dogs. The dose-response curve for the changes in blood flow through the left femoral artery in reserpine-pretreated dogs to Bay K 8644 injected into the same artery is also represented in (b) (□, n = 6). Vertical lines represent s.e.mean.

Bay K 8644 is shown in Figure 2a. The decrease in LAD flow attained a maximum, 34% of the basal flow (Table 1), at 100 nmol, and the decrease at 300 nmol appeared slightly smaller (about 7%) than that at 100 nmol (Figure 2a), although the difference was insignificant. The dose-response curve for the decrease in LAD flow had a slope of 28.8 (Table 1). The ED_{50} of Bay K 8644 in the LAD bed was 1.29 ± 0.23 nmol. The normalized ED_{50} of Bay K 8644 in the coronary circulation was 0.08 ± 0.01 nmol (Table 1). Dimethyl sulphoxide (the solvent for Bay K 8644) injected into the LAD scarcely affected LAD flow. With medium and high doses of Bay K 8644 (3–300 nmol) the decrease in LAD flow occurred promptly and was followed by a rather slowly decaying decrease (Figure 1a). The vasoconstrictor effect of the highest dose of Bay K 8644 attained a peak about 11 s after the

Table 1 A comparison of the dose-response curve parameters (normalized ED_{50}, maximum effect and slope) for the vasoconstrictor effects of Bay K 8644 and the half-duration of the vasoconstrictor effect of 100 nmol Bay K 8644 in 4 arterial beds

Arterial bed	*Normalized ED_{50}* (nmol)	*Maximum effect* (%)	*Slope* (% (log mol)$^{-1}$)	*Half-duration* (s)
Coronary	0.08 ± 0.01 (5)	65.9 ± 1.0 (5)	28.8	20.6 ± 4.7 (5)
Femoral	0.07 ± 0.02 (7)	69.7 ± 6.4 (7)	22.7	83.5 ± 15.3 (7)
Mesenteric	0.16 ± 0.06 (6)	83.5 ± 2.8 (6)	34.2	77.5 ± 17.8 (6)
Renal	0.55 ± 0.19 (6)	79.6 ± 8.3 (6)	61.5	195.5 ± 56.7 (6)

Values are means ± s.e.mean (*n*).

injection (Table 2). This effect was so short-lived that it wore off within 2 min (Figure 1a). The half-duration of the vasoconstrictor effect of Bay K 8644, the time from the point of half the peak effect to the point of the half recovery, was about 21 s at 100 nmol (Table 1).

Single injections of noradrenaline (0.3–10 nmol) into the LAD increased LAD flow in a dose-dependent manner up to about 30% of the basal flow at 10 nmol, and no further increase occurred at higher doses (30 and 100 nmol) (Figure 2a). The increase in LAD flow occurred slowly and at 1 nmol it attained a peak about 30 s after the injection (Table 2).

LVP and LV dP/dt The basal values of LVP, LV *dP/dt max* and LV *dP/dt-max*, a maximum rate of fall in left ventricular pressure, were 108 ± 8 mm Hg, 1732 ± 87 mm Hg s^{-1} and −1616 ± 169 mmHg s^{-1}, respectively. With Bay K 8644 (10–300 nmol) LV *dP/dt max* increased and absolute values of LV *dP/dt-max* decreased in a dose-dependent manner (Figures 1c and 3). The maximum increase in LV *dP/dt max* attained at 300 nmol was 494 ± 54 mm Hg s^{-1} and the maximum decrease in the absolute value of LV *dP/dt-max* attained at 100 nmol was 348 ± 123 mm Hg s^{-1}. The increase in LV *dP/dt max* occurred more slowly than the decrease in LAD flow; at 300 nmol the former reached a peak about 30 s after the injection, whereas the latter took about 11 s (Table 2). With all the doses of Bay K 8644 examined LVP remained virtually unchanged (Figure 1b).

After injections of noradrenaline (1–300 nmol) into the LAD both LV *dP/dt max* and absolute values of LV *dP/dt-max* increased in a dose-dependent manner (Figure 3). The maximum increases in LV *dP/dt max* and absolute values of LV *dP/dt-max* attained with 300 nmol were 4032 ± 806 mm Hg s^{-1} and 2732 ± 558 mm Hg s^{-1}, respectively. The increase in LV *dP/dt max* attained with 1 nmol noradrenaline was 552 ± 22.5 mm Hg s^{-1}, which was nearly equal to the maximum increase produced by 300 nmol Bay K 8644. The increase in LV *dP/dt max* occurred faster with noradrenaline than with Bay K 8644; the time to peak effect was about 16 s with 1 nmol noradrenaline as

Table 2 The difference in the time to peak effect of 1 nmol noradrenaline and 300 nmol Bay K 8644 at increasing left ventricular (LV) *dP/dt max* and decreasing left anterior descending coronary artery (LAD) flow

	Time to peak effect (s) *Noradrenaline*	*Bay K 8644*
LV *dP/dt max*	16.2 ± 1.6 (5)	29.6 ± 1.4 (5)
LAD flow	29.9 ± 4.6 (5)	10.8 ± 0.7 (5)

Results are mean ± s.e.mean (*n*).

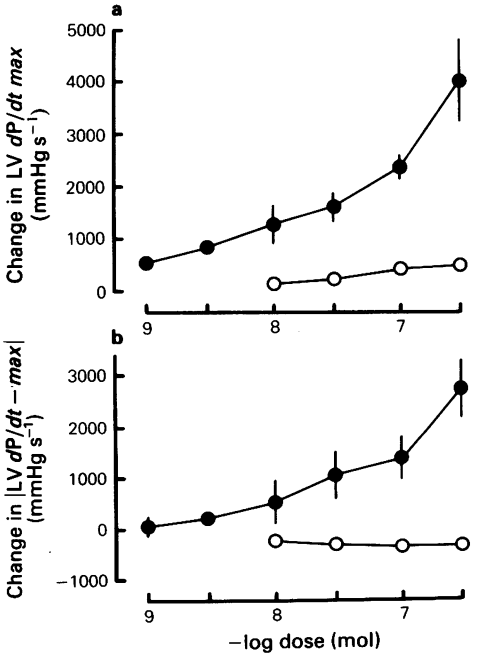

Figure 3 Dose-response curves for changes in (a) left ventricular (LV) *dP/dt max* and (b) absolute values of LV *dP/dt-max* to Bay K 8644 (○) and noradrenaline (●) injected into the left anterior descending coronary artery (LAD) in normal dogs ($n = 5$).

against about 30 s with 300 nmol Bay K 8644 (Table 2). The increase in LV dP/dt *max* occurred faster than the increase in LAD flow with noradrenaline; the time to peak effect of 1 nmol noradrenaline was about 16 s for LV dP/dt as against about 30 s for LAD flow (Table 2). LVP was increased by noradrenaline (1–300 nmol) in a dose-dependent manner and the increase at 300 nmol was 121 ± 33 mm Hg (data not shown).

Effects of Bay K 8644 and noradrenaline on femoral blood flow in normal dogs

The basal blood flow through the left femoral artery in 7 dogs was 33.7 ± 2.2 ml min^{-1}. Injections of Bay K 8644 (0.3–100 nmol, i.a.) caused a dose-dependent decrease in femoral blood flow down to about 30% of the basal value at 100 nmol (Table 1). The decrease tended to diminish slightly (about 7%) at 300 nmol (Figures 2b and 4a), although there was no significant difference. The slope of the dose-response curve for the decrease in femoral blood flow to Bay K 8644 was 22.7 (Table 1) and in 2 of the 7 dogs, the decrease in femoral blood flow was followed by an increase at doses above 1 nmol. The ED_{50} of Bay K 8644 in the femoral arterial bed was 2.48 ± 0.51 nmol and its normalized value was 0.07 ± 0.02 nmol (Table 1). Ethanol (the solvent for Bay K 8644), at the amounts required to dissolve 100 and 300 nmol Bay K 8644, increased femoral blood flow up to about 18% and 31% of the basal value, respectively. With Bay K 8644 the decrease in femoral blood flow occurred slowly and the effect was long-lasting at higher doses (100 and 300 nmol; Figure 4a). The half-duration of the vasoconstrictor effect of 100 nmol Bay K 8644 was about 84 s (Table 1).

Noradrenaline (0.1–100 nmol, i.a.) produced a dose-dependent decrease in femoral blood flow down to about 10% of the basal value at 100 nmol (Figure 2b). In 3 of the 7 dogs, the decrease in femoral blood

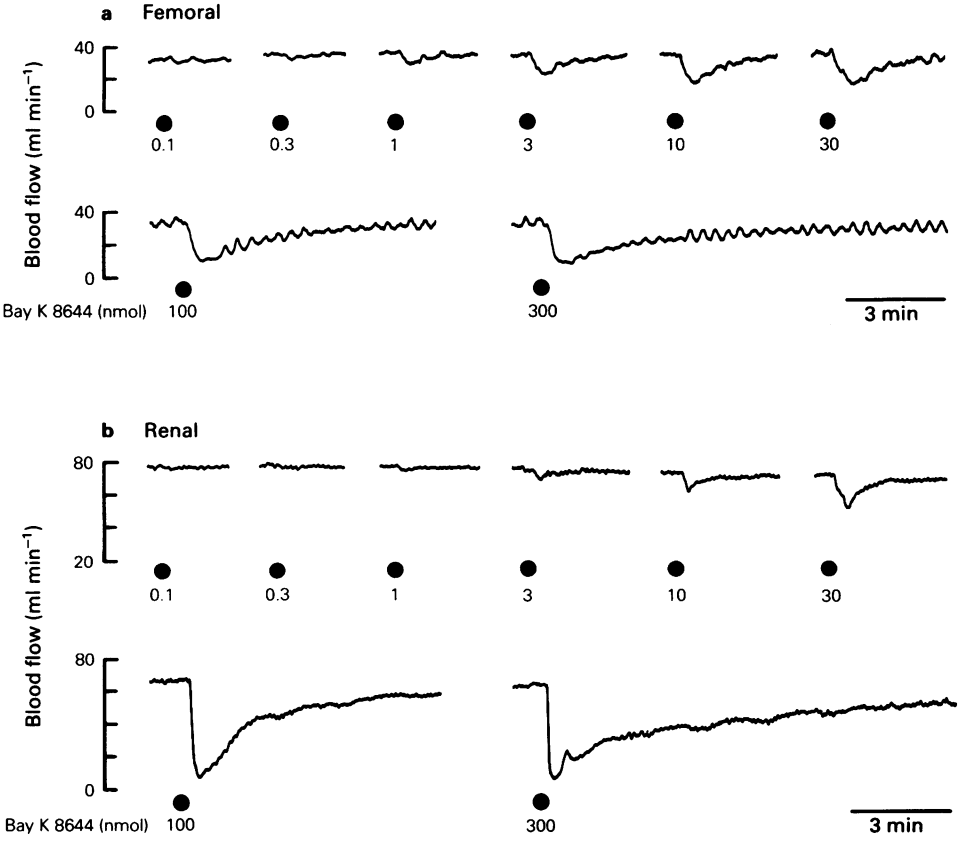

Figure 4 Effects of Bay K 8644 injected into the left femoral artery (a) and the right renal artery (b) on blood flow through the respective arteries in two normal dogs.

flow was followed by an increase at doses from 1 to 30 nmol. The ED_{50} of noradrenaline in the femoral arterial bed was 3.65 ± 2.06 nmol and its normalized value was 0.12 ± 0.05 nmol. The dose-response curve for the decrease in femoral blood flow to noradrenaline had a slope of 26.8 and was parallel with that of Bay K 8644 (Figure 2b).

Effects of Bay K 8644 on femoral blood flow in reserpine-pretreated dogs

In 6 reserpine-pretreated dogs the basal blood flow through the left femoral artery was 39 ± 1.3 ml min^{-1}. In these dogs i.a. injections of tyramine (30 μmol) decreased femoral blood flow down to 58.5 ± 9.9% of the basal value. In 5 of these 6 dogs this decrease was followed by an increase (by about 50% of the basal value). By contrast, in 3 normal dogs i.a. tyramine (30 μmol) decreased femoral blood flow down to about 8% of the basal flow. In the reserpine-pretreated dogs under these conditions i.a. injections of Bay K 8644 (0.1–100 nmol) produced a dose-dependent decrease in femoral blood flow down to about 30% of the basal flow at 100 nmol, and the decrease appeared to diminish slightly (about 7%) at 300 nmol (Figure 2b), although there was no significant difference. The normalized ED_{50} of Bay K 8644 was 0.34 ± 0.20 nmol. The decrease in femoral blood flow was significantly smaller in the reserpine-pretreated dogs than in the 7 normal dogs (Figure 2b).

Effects of Bay K 8644 and noradrenaline on mesenteric blood flow and intraluminal pressure of the ileum in normal dogs

Mesenteric blood flow The basal blood flow through the cranial mesenteric artery in 6 dogs was 64.0 ± 6.5 ml min^{-1}. Bay K 8644 (0.3–100 nmol, i.a.) produced a dose-dependent decrease in mesenteric blood flow down to about 16% of the basal level at 100 nmol (Table 1), and the decrease appeared to diminish slightly (about 3%) at 300 nmol (Figures 2c and 5), although the difference was insignificant. The slope of the dose-response curve for the decrease in mesenteric blood flow to Bay K 8644 was 34.2 (Table 1). The ED_{50} of Bay K 8644 in the mesenteric arterial bed was 8.61 ± 2.26 nmol and its normalized value was 0.16 ± 0.06 nmol (Table 1). Ethanol, at the

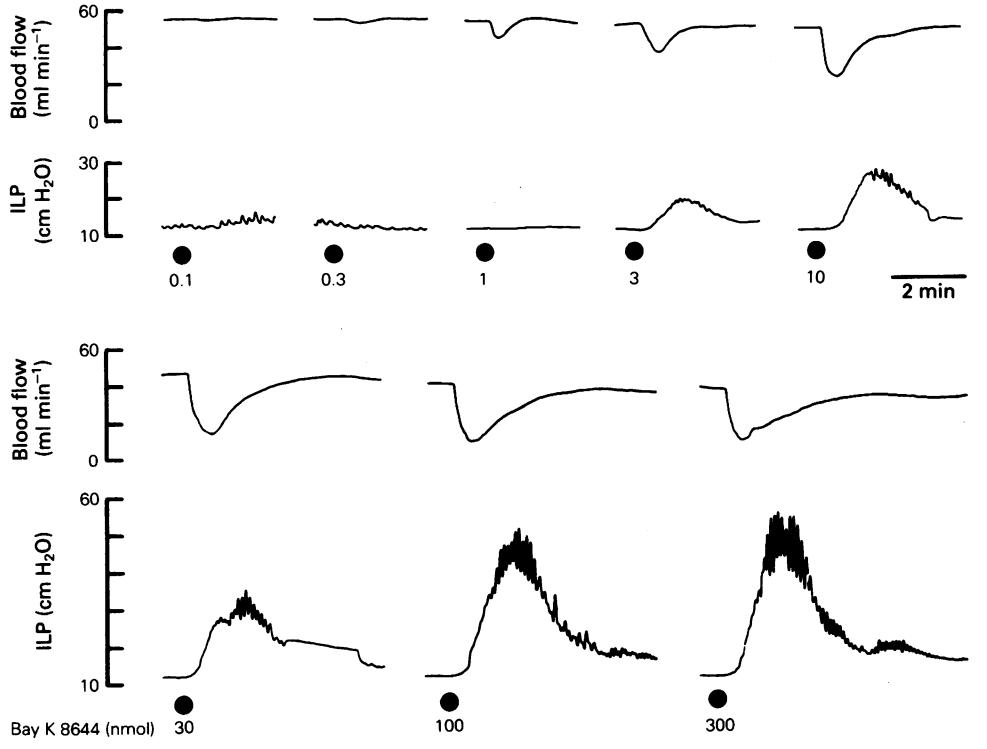

Figure 5 Effects of Bay K 8644 injected into the cranial mesenteric artery on blood flow through the same artery and intraluminal pressure of the ileum (ILP) in a normal dog.

amounts required to dissolve high doses of Bay K 8644, scarcely affected mesenteric blood flow. The decrease in mesenteric blood flow occurred slowly, and the effect lasted rather longer at higher doses (100 and 300 nmol; Figure 5). The half-duration of the vasoconstrictor effect of Bay K 8644 was about 78 s at 100 nmol (Table 1).

With noradrenaline (0.1–100 nmol, i.a.) mesenteric blood flow decreased in a dose-dependent manner down to about 2% of the basal flow at 100 nmol (Figure 2c). The decrease was followed by an increase at doses above 1 nmol. The ED_{50} of noradrenaline in the mesenteric arterial bed was 5.19 ± 1.76 nmol and its normalized value was 0.10 ± 0.03 nmol. The dose-response curve for the noradrenaline-induced decrease in mesenteric blood flow had a slope of 33.3 and was parallel with that for Bay K 8644 (Figure 2c).

Intraluminal pressure of the ileum The basal intraluminal pressure of the ileum was 13.6 ± 3.5 cmH_2O. Bay K 8644 (3–300 nmol) injected into the cranial mesenteric artery produced a dose-dependent increase in intraluminal pressure (Figure 6) and oscillatory contractions (Figure 5). However, the increase in intraluminal pressure produced by the highest dose (300 nmol) of Bay K 8644 remained only 20% of that produced by 1 μmol acetylcholine (nearly maximum contractions). The increase in intraluminal pressure by Bay K 8644 occurred more slowly than the decrease in mesenteric blood flow and the former reached a peak later than the latter (Figure 5).

Noradrenaline (3–100 nmol) injected into this artery also produced a dose-dependent increase in intraluminal pressure by about 8% (expressed as above) at 100 nmol (Figure 6).

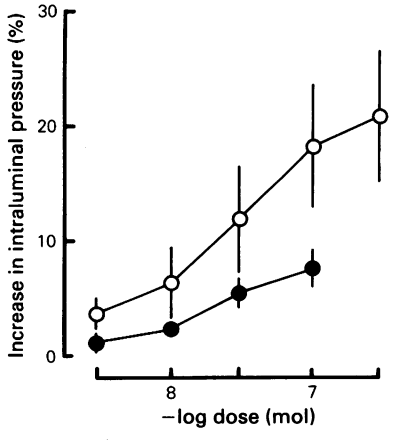

Figure 6 Dose-response curves for changes in intraluminal pressure of the ileum to Bay K 8644 (○) and noradrenaline (●) injected into the cranial mesenteric artery in normal dogs ($n = 6$).

Effects of Bay K 8644 and noradrenaline on renal blood flow in normal dogs

The basal blood flow through the right renal artery in 6 dogs was 70.7 ± 6.9 ml min^{-1}. After i.a. injections of Bay K 8644 (1–100 nmol) renal blood flow decreased in a dose-dependent manner (Figures 2d and 4b). At 100 nmol the flow decreased down to about 20% of the basal one (Table 1), and the decrease appeared to diminish slightly (about 3%) at 300 nmol (Figure 2d), although the reduction was insignificant. The slope of the dose-response curve for the decrease in renal blood flow to Bay K 8644 was 61.5 (Table 1). The ED_{50} of Bay K 8644 was 32.9 ± 8.9 nmol and its normalized value was 0.55 ± 0.19 nmol (Table 1). In 2 of the 6 dogs, ethanol decreased renal blood flow; the mean decreases in the 2 dogs were about 6% with the amount required to dissolve 100 nmol Bay K 8644 and about 31% of the basal flow for the amount required to dissolve 300 nmol Bay K 8644. The decrease in renal blood flow occurred immediately but lasted longer with higher doses of Bay K 8644 (Figure 4b). The half-duration of the vasoconstrictor effect of 100 nmol Bay K 8644 was about 196 s (Table 1).

Renal blood flow was also decreased by noradrenaline (0.3–30 nmol, i.a.) and, at the maximum effect attained by 30 nmol, the flow remained only 5% of the basal flow (Figure 2d). The ED_{50} of noradrenaline in the renal arterial bed was 3.71 ± 1.07 nmol, and its normalized value was 0.05 ± 0.01 nmol. The dose-response curve for the decrease in renal blood flow to noradrenaline had a slope of 62.4 and was parallel with that for Bay K 8644 (Figure 2d).

Discussion

In the present experiments Bay K 8644 produced vasoconstriction in the coronary, femoral, mesenteric and renal arterial beds. In all these arterial beds the vasoconstrictor effect of Bay K 8644 reached a maximum at 100 nmol, but the details of this effect of Bay K 8644 were not the same in the different circulations. There was a significant difference between the normalized ED_{50} values of Bay K 8644 in the 4 arterial beds. The potency of Bay K 8644 was of the following order: femoral > coronary > mesenteric > renal arterial bed. There was about a 7.5 fold difference in potency between the femoral and the renal arterial bed. When comparing the maximum vasoconstrictor effects that were attained at 100 nmol in these arterial beds, the order of effectiveness was as follows: mesenteric > renal > femoral > coronary arterial bed; the maximum decrease in blood flow as a percentage of the respective basal blood flow was about 84% in the mesenteric, 80% in the renal, 70% in the femoral and 66% in the coronary arterial bed. The

steepness of the slopes of the dose-response curves for the vasoconstrictor effect of Bay K 8644 were of the following order: renal>mesenteric>coronary>femoral arterial bed (Table 1). Furthermore, when comparing the half-duration of the vasoconstrictor effect of 100 nmol Bay K 8644, the order of length was as follows: renal, > mesenteric ≒ femoral > coronary arterial beds.

When the fact that the basal LAD flow was about 1/4 the basal renal flow is taken into consideration, the short life of the coronary vasoconstrictor effect of Bay K 8644, together with its being least effective on the coronary arterial bed, deserves attention. That Bay K 8644 was least effective at reducing coronary blood flow and that it had a short duration of action are compatible with results obtained in previous experiments using dog isolated, blood-perfused heart preparations (Wada *et al.*, 1985). These authors (Wada *et al.*, 1985) discussed the possibility that a metabolic link might be responsible for the diminished effectiveness and short duration of action of Bay K 8644 in the coronary arterial bed. In their experiments the vasoconstrictor effect had worn off when the positive inotropic effect of Bay K 8644 reached a peak in the isolated, blood-perfused papillary muscle preparation. Thus, it appeared that the increase in cardiac metabolism caused by the positive inotropic action of Bay K 8644 might reduce the vasoconstrictor effect. However, this possibility was ruled out since the vasoconstrictor effect of Bay K 8644 in the artery supplying the papillary muscle was as short-lived as that seen in the arteries supplying the SA node and the AV node, where the positive inotropic effect of Bay K 8644 was not so prominent as in the papillary muscle. In the present experiments, the maximum increase in LV dP/dt *max* produced by Bay K 8644 (300 nmol) was only about 1/8 the maximum increase produced by noradrenaline (300 nmol). With 1 nmol noradrenaline, which was equieffective with 300 nmol Bay K 8644 in producing a positive inotropic effect, coronary blood flow increased by about 16% of the basal value. Furthermore, the vasodilator effect, induced by this dose of noradrenaline, developed more slowly than the positive inotropic effect so that coronary blood flow had increased only by about 1/3 its maximum effect when the positive inotropic effect reached a peak. In other words, the increase in coronary blood flow at the peak positive inotropic effect of 1 nmol noradrenaline was about 5% of the basal flow. Therefore, taking into consideration the above finding together with the fact that the positive inotropic effect of Bay K 8644 reached a maximum about 10 s after its vasoconstrictor effect had reached a peak, it is unlikely that a metabolic link contributes much to the diminished effectiveness of Bay K 8644 in producing coronary vasoconstriction at its peak effect. The short duration of the vasoconstrictor action of Bay K 8644 in the coronary arterial bed, however, could possibly be attributed to a metabolic link.

Conversely, the greater effectiveness and the longer duration of action of Bay K 8644 in other arterial beds should be discussed. In the mesenteric arterial bed contractions of intestinal smooth muscle might have exerted vascular compression so as to decrease mesenteric blood flow. Indeed Bay K 8644 produced a slightly larger increase in intraluminal pressure of the ileum than that induced by noradrenaline at all doses examined. However, the difference in potency between Bay K 8644 and noradrenaline in producing a reduction of blood flow in the mesenteric arterial bed was comparable with that observed in the femoral arterial bed where no extravascular smooth muscle impedes arterial blood flow. Therefore, the contribution of contractions of extravascular smooth muscle to the greater effectiveness of Bay K 8644 on the mesenteric arterial bed can be ruled out. Thus, the differences in potency of Bay K 8644 and in its effectiveness as a vasoconstrictor in the 4 arterial beds would be due mainly to differences in the characteristics of the smooth muscle of resistance vessels there.

However, an involvement of endogenous catecholamines in the greater effectiveness and longer duration of action of Bay K 8644 in the renal, mesenteric and femoral arterial beds where α-adrenoceptors are dominant is possible, since a previous study (Goto *et al.*, 1985) has shown that, in the dog saphenous arterial bed, Bay K 8644 augments the vasoconstrictor effects on resistance vessels of endogenous and exogenous noradrenaline. In the present experiments the effect of Bay K 8644 in decreasing femoral blood flow was slightly but significantly smaller in reserpine-pretreated dogs than in normal dogs. This indicates that in normal dogs augmentation by Bay K 8644 of the constrictor effect of endogenous catecholamines on resistance vessels could contribute to the greater vasoconstrictor effect of Bay K 8644.

In the present experiments the vasoconstrictor effect of Bay K 8644 on all the 4 arterial beds reached a maximum at 100 nmol and did not appear to become greater with increasing doses. It has been shown that Bay K 8644 is less effective at high concentrations than at medium concentrations in producing both contractions of K^+-depolarized rabbit aortic strips (Schramm *et al.*, 1983a,b) and a positive inotropic effect on guinea-pig isolated heart preparations (Schramm *et al.*, 1983a,b). Similar phenomena have been observed in porcine isolated coronary arteries and rat hearts, and taken to indicate its partial agonistic property (Grupp *et al.*, 1984). The diminished effectiveness of Bay K 8644 in producing a positive inotropic effect at high concentrations compared to medium concentrations has also been observed in canine isolated ventricular muscle (Ishii *et al.*, 1985). However, this has

been attributed to the negative inotropic effect of the solvent used for Bay K 8644 (Ishii *et al.*, 1985). Therefore, a possible involvement of the solvents of Bay K 8644 in the effects of high doses of Bay K 8644 in the present experiments should be considered. In the LAD bed the solvent for Bay K 8644, dimethyl sulphoxide, exerted virtually no effect. In the mesenteric arterial bed the solvent for Bay K 8644, ethanol, had no effect. In the femoral arterial bed the solvent for Bay K 8644, ethanol, increased femoral blood flow at amounts required to dissolve 100 and 300 nmol Bay K 8644. Therefore, it is difficult to discern whether the diminished effectiveness of Bay K 8644 at high doses in producing vasoconstriction is due to the solvent effect or a partial agonistic property of Bay K 8644. In the renal arterial bed, however, the solvent at amounts required to dissolve 100 and 300 nmol Bay K 8644 decreased renal blood flow in some dogs but not in others. Therefore, the reduced effectiveness of high doses of Bay K 8644 may reflect the action of Bay K 8644 as a partial agonist.

Noradrenaline injected into the coronary artery increased both LV dP/dt *max* and the absolute value of LV dP/dt-*max*, whereas Bay K 8644 increased LV dP/dt *max* and decreased the absolute value of LV dP/dt-*max*. This may indicate that Bay K 8644, unlike noradrenaline, produces a positive inotropic effect only by increasing calcium influx without promoting calcium uptake by sarcoplasmic reticulum. Noradrenaline promotes calcium uptake by sarcoplasmic reticulum, causing the acceleration of relaxation (Katz, 1979).

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