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HYPOTENSIVE AND VASODILATOR ACTIONS OF SK&F 24260, A NEW DIHYDROPYRIDINE DERIVATIVE

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1 The blood pressure of conscious normotensive, Goldblatt-hypertensive and genetic-hypertensive rats and normotensive dogs was lowered by SK&F 24260 (1,4-dihydro-2,6-dimethyl-4-(2-trifluormethylphenyl)-3,5-pyridinedicarboxylic acid diethyl ester).

2 Tachycardia always accompanied the hypotension. In rats propranolol abolished the tachycardia but in dogs there was only a small reduction in the heart rate response.

3 In conscious dogs there was an increase in left ventricular output and a marked fall in total peripheral resistance.

4 SK&F 24260 dilated resistance vessels in rat hindquarters. Dilatation was caused by doses of SK&F 24260 some 50 times smaller than those of hydrallazine.

5 In preparations of cat skeletal muscle and intestinal vascular beds SK&F 24260 selectively dilated resistance vessels in preference to capacitance vessels and resembled hydrallazine rather than papaverine which has no such selectivity.

6 Pre-capillary sphincter vessels were also dilated by SK&F 24260. Changes in fluid equilibrium caused by SK&F 24260 were consistent with selective dilatation of resistance vessels.

Introduction

SK&F 24260 (1,4-dihydro-2,6-dimethyl-4-(2-trifluormethylphenyl)-3,5-pyridinedicarboxylic acid diethyl ester) is a potent hypotensive drug thought to act by direct vasodilatation (Loev, Ehrreich & Tedeschi, 1972). In anaesthetized dogs hypotension was caused by intravenous doses of 10 μg/kg while hypotension and tachycardia persisted for 4-8 h following the oral administration of doses of 1 mg/kg to hypertensive conscious dogs. The results described in this paper confirm previous observations in conscious animals and show that the hypotension is due to a decrease in total peripheral resistance. We have used perfusion techniques to show that the decrease in total peripheral resistance is a result of selective dilatation of pre-capillary resistance vessels. This selectivity was determined by comparison with the vascular effects of hydrallazine, a vasodilator known to have selective effects on the same vessels (Ablad & Mellander, 1963), and papaverine, a non-selective vasodilator.

Methods

Conscious rats

Experiments were carried out on male normotensive and Goldblatt-hypertensive rats (ICI-Wistar strain) and female genetic hypertensive rats of the strain developed in New Zealand (Smirk & Hall, 1958), and maintained at the Wellcome Research Laboratories, Beckenham. Blood pressure (1 mmHg = 1.33 mbar) was recorded from aortic catheters implanted, under halothane anaesthesia, by the techniques of Popovic & Popovic (1960) or Weeks & Jones (1960). Experiments were done not less than 24 h after surgery. The rats were starved overnight, placed in individual boxes providing minimal restraint and the catheters connected to low displacement pressure transducers.

In some experiments heart rate only was measured. Rats were trained to stand quietly in Perspex tubes with a flat floor on which were four stainless steel plates. After a few periods of training the rats would remain in these holders, with their feet on the metal plates, for 3 h or more. Lead I electrocardiograms were detected from the plates and recorded on an 8-channel recorder. Heart rates were determined at intervals by counting the R-wave from the ECG records.

To prepare Goldblatt-hypertensive animals, weanling rats (70 g) were anaesthetized with halothane and oxygen, and, using antiseptic precautions, the left renal artery was exposed and a silver clip (0.25 mm) placed around the artery.

One week later the contralateral kidney was removed. The rats were used for experiment about six weeks later.

Conscious dogs

Male, normotensive Beagle dogs (10-15 kg) were selected for their quiet temperament. Under halothane anaesthesia and using aseptic precautions the left omocervical artery was exposed and a catheter introduced and manipulated until the tip lay in the descending aorta. The end was brought to the surface at the back of the neck and connected to a ball valve (Day & Whiting, 1972) fixed subcutaneously. The catheters were flushed daily with sterile 0.9% w/v NaCl solution (saline) containing heparin (500 units/ml). Experiments were begun not less than one week after surgery.

The dogs were starved overnight, but allowed free access to water. In the morning the dogs were taken to a quiet experimental room, allowed about 30 min to settle and fitted with a harness supporting a blood pressure transducer which was connected to the aortic catheter. When blood pressure and heart rate had become stable drugs were administered and blood pressure and heart rate continuously monitored for 5-6 hours.

Rat hindquarters

Male rats (250 g) were starved overnight and anaesthetized with Dial-urethane (Allobarbitone, 100 mg/kg; urethane, 400 mg/kg, i.p.). The abdominal aorta was exposed ventrally just above the bifurcation and cannulated in both directions. Blood from the central part of the aorta was pumped distally to perfuse the hindquarters. A servo-controlled roller pump maintained a constant perfusion pressure at or about the level of the systemic blood pressure. Vasodilatation increased hindquarters blood flow which was recorded as a change in pump speed. SK&F 24260 and hydrallazine were administered by intravenous injection into a jugular vein. Only one dose of compound was given to any one preparation.

Cat skeletal muscle

Cats (2.5-3.0 kg) were starved overnight and anaesthetized with pentobarbitone sodium (60 mg/kg, i.p.). The calf muscle of the right leg was prepared as described by Mellander (1966) modified so that the arterial pressure was kept constant at 120 mmHg with a servo-controlled roller pump. Changes in tone of resistance vessels, capacitance vessels and changes in transcapillary fluid movement were calculated from changes of blood flow, rapid changes of limb volume and slow changes of limb volume, respectively; capillary filtration coefficients were calculated from the changes in limb volume in response to increases of venous hydrostatic pressure caused by raising the level of the venous outflow (Mellander, 1960). Drugs were usually injected intra-arterially close to the calf muscle vascular bed to produce large local vascular responses with minimal systemic effects. SK&F 24260 or hydrallazine were given as single injections in a volume of 0.05-0.25 ml, papaverine was infused at a rate of 0.2 ml/minute. Doses were calculated per kg of calf muscle, assuming the calf muscles of one leg comprise 1.7% of total body weight (Mellander, personal communication). In experiments with SK&F 24260 and hydrallazine only one or two doses were administered to any one cat, but repeated doses of papaverine were given to one preparation.

Cat mesenteric vasculature

The effects of drugs on the resistance vessels and capacitance vessels of the cat mesenteric vasculature were studied by the method of Taylor (1973). Cats (2.5-3.0 kg) of either sex were starved overnight and anaesthetized with pentobarbitone sodium (45 mg/kg, i.p.). The abdomen was opened along the mid-line, the duodenum and rectum tied and the posterior mesenteric artery ligated. One carotid artery and the anterior mesenteric artery were cannulated and connected to a constant-flow roller pump so that blood could be pumped from the carotid artery through the intestinal vascular bed. The arterial perfusion pressure (Pa) was recorded. One femoral vein and the anterior mesenteric vein were cannulated and connected by a second constant-flow roller pump so that blood was returned from the intestines to the systemic circulation. The pressure (Pv) in the anterior mesenteric vein was recorded. The sympathetic nerves surrounding the mesenteric artery were cut. Systemic blood pressure was recorded from the second femoral artery. Clotting was prevented by pretreatment with heparin. The outputs of the two pumps were adjusted and balanced so that blood was supplied to and removed from the intestinal vascular bed at the same flow rate and the pressures Pa and Pv remained stable. Changes in the pressure Pa were proportional to changes in resistance while changes in the pressure Pv were inversely proportional to changes in capacitance.

SK&F 24260 was injected intravenously to minimize effects from the vehicle, the other drugs were given intra-arterially close to the vascular bed in a maximum volume of 0.1 ml. Only one or two doses of SK&F 24260 or hydrallazine were given to any one cat, but complete dose-response curves to papaverine were obtained for each animal.

Drugs

SK&F 24260 was prepared in the Research and Development Division of Smith Kline and French Laboratories, Philadelphia. Because of its extremely poor aqueous solubility, SK&F 24260 was administered parenterally as a solution in polyethylene glycol-300 (PEG-300) diluted with an equal volume of saline. For oral administration the drug was sometimes dissolved in 100% Tween-80, but otherwise given as powdered drug, either suspended in 0.35% Keltrol (A.B.A. Industrial Products Ltd) for the rats, or mixed with a small amount of meat for the dogs. The crystalline material (particle size (Fisher sub-sieve sizer) 10.8 μm) sometimes gave irregular results so in most experiments the crystalline material milled to smaller more uniform particles (4.7 μm) was used.

Hydrallazine (Ciba), papaverine hydrochloride (BDH), isoprenaline and propranolol (ICI) were dissolved in saline. Nitroglycerine (BPC) was dissolved in 90% ethanol.

Results

Effects of SK&F 24260 on conscious animals

Rats. SK&F 24260 administered subcutaneously caused dose-dependent falls in mean blood pressure and increases in heart rate. The hypotension was greater in Goldblatt and spontaneously hypertensive rats than in normotensive ones (Table 1). The fall in blood pressure was rapid and was well maintained for 2-4 hours. Although the falls in blood pressure were dose-related the tachycardia caused by SK&F 24260 was not so well related to dose. Sometimes the heart rate had returned to pre-drug levels, or sometimes less, while the blood pressure remained low.

Oral administration of SK&F 24260 also lowered blood pressure and increased heart rate. The degree of the hypotension, its duration and the rapidity of the initial fall were dependent on the drug formulation. Figure 1 summarizes some of these results and shows the hypotension in Goldblatt-hypertensive rats caused by doses of 2.5 or 5.0 mg/kg of SK&F 24260 in solution in Tween-80, or as crystalline or milled material suspended in Keltrol. A dose of 5 mg/kg of the crystalline drug lowered blood pressure slowly over a period of 2 h by about 25 mmHg. In contrast, half that dose when in solution with Tween-80 had lowered blood pressure maximally (by about 70 mmHg) within 15 minutes. Recovery was also rapid, about 50% in 2 hours. The milled

Table 1 Effect of SK&F 24260 subcutaneously on mean blood pressure and heart rate of conscious normotensive and hypertensive rats

	0.1 mg/kg				*0.2 mg/kg*			
	Normotensive	*Hypertensive*		*Normotensive*	*Hypertensive*			
	(n = 3)	*Goldblatt (n = 7)*	*Genetic (n = 4)*	*(n = 3)*	*Goldblatt (n = 15)*	*Genetic (n = 9)*
Blood pressure before drug	149	184 ± 10.4	180 ± 13.7	149	177 ± 12.0	163 ± 9.0
Blood pressure after drug	131	148 ± 7.4	141 ± 4.7	128	119 ± 5.0	120 ± 5.7
Difference (*P*)	–	<0.05	0.05	–	<0.001	<0.001
Heart rate before drug	383	434 ± 18.5	399 ± 24.4	390	431 ± 11.7	414 ± 9.9
Heart rate after drug	433	472 ± 10.2	420 ± 17.8	503	478 ± 7.3	452 ± 4.6
Difference (*P*)	–	NS	NS	–	<0.01	<0.01

Values shown are mean with s.e. mean blood pressure (mmHg) and heart rate (beats/min) before drug and at the maximum hypotensive response.
NS, not significant ($P > 0.05$).

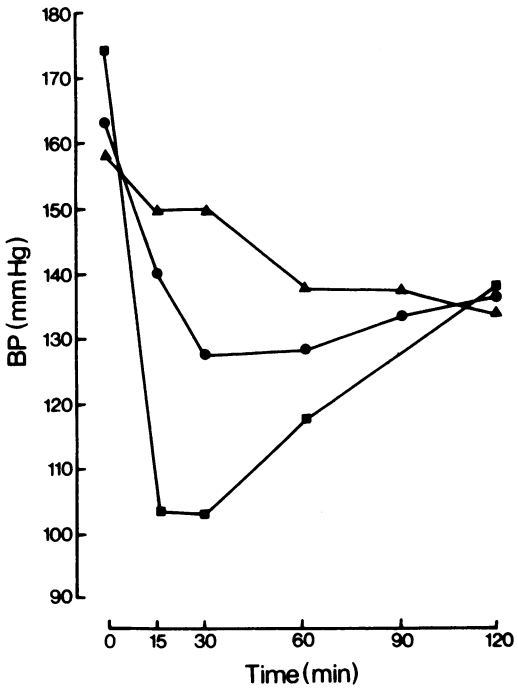

Figure 1 Mean blood pressures of groups of conscious Goldblatt hypertensive rats before and for 2 h after the oral administration of different preparations of SK&F 24260. (■) Drug (2.5 mg/kg) as a solution in Tween-80; (▲) crystalline drug (5.0 mg/kg) suspended in Keltrol; (●) milled drug (5.0 mg/kg) suspended in Keltrol.

drug at a dose of 5 mg/kg caused a fall in blood pressure intermediate between those caused by the solution or the crystalline material, reaching a maximum effect after about 30 minutes.

Dogs. Oral administration of SK&F 24260 to normotensive dogs either as milled drug or as a Tween-80 solution lowered blood pressure and increased heart rate. Figure 2 summarizes the results from dogs given 10, 20 or 40 mg of milled drug. The time-courses of the two responses were very similar, and degree and duration of response were dose-dependent. Experiments were carried out in four dogs in which as well as blood pressure and heart rate, left ventricular output was also measured with an electromagnetic flow probe implanted round the ascending aorta. SK&F 24260 (1 mg/kg of the Tween-80 solution p.o.) caused a fall in blood pressure accompanied by a large fall in total peripheral resistance and large increases in heart rate and cardiac output. There was little change in stroke volume and left ventricular work was increased in three dogs but decreased in the fourth. The results are illustrated in Figure 3.

Effects of propranolol

Rats. The mean blood pressure of a group of 10 genetic hypertensive rats fell after SK&F 24260 (0.4 mg/kg, s.c.) by 56 mmHg and heart rate increased by 42 beats/minute. When this treatment was repeated in five rats pretreated 30 min earlier with propranolol (5 mg/kg, s.c.) blood pressure fell by 71 mmHg but heart rate ' now fell by 39 beats/min (Table 2). Propranolol (5 mg/kg, s.c.)

Table 2 Blood pressure and heart rates of conscious genetic hypertensive rats and heart rates of normotensive rats before and 30 min after SK&F 24260 subcutaneously and the effect of pretreatment 30 min earlier with propranolol (5 mg/kg s.c.)

		Control		*Propranolol-treated*	
Animal	*Treatment*	*Blood pressure*	*Heart rate*	*Blood pressure*	*Heart rate*
Genetic hypertensive	–	154 ± 13.7	416 ± 11.8	156 ± 11.1	276 ± 12.1*
Genetic hypertensive	SK&F 24260 (0.4 mg/kg)	98 ± 9.9	458 ± 14.4	85 ± 5.4	237 ± 22.9
Difference (*P*)		<0.01	<0.05	<0.001	NS
Normotensive	–	–	395 ± 15.0	–	338 ± 11.7*
Normotensive	SK&F 24260 (0.2 mg/kg)	–	463 ± 21.7	–	343 ± 15.0
Difference (*P*)			<0.05		NS

Shown are mean values with s.e. (mmHg and beats/min respectively).
* Significantly different from control ($P = <0.001$).
NS, not significant.

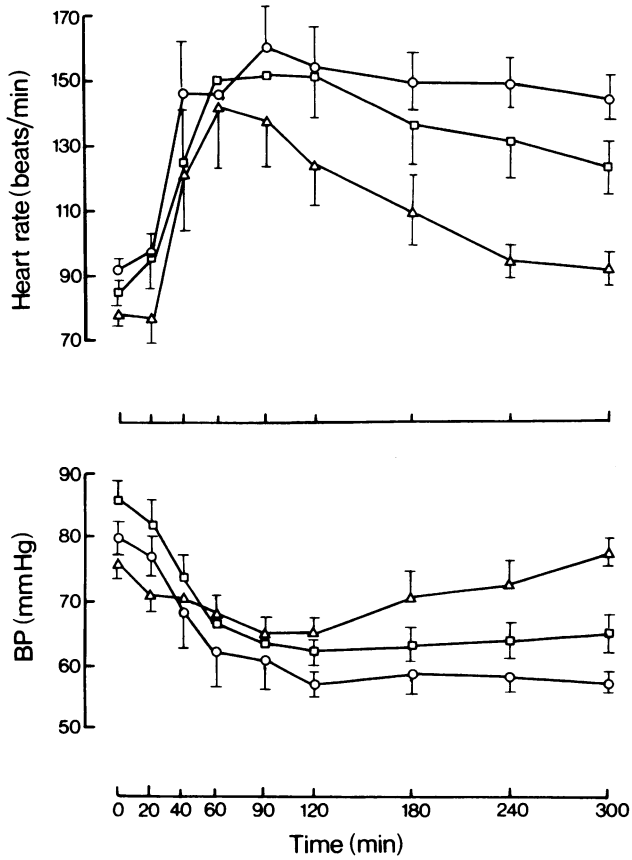

Figure 2 Mean diastolic blood pressures and heart rates of conscious dogs before and after the oral administration of SK&F 24260 (milled drug), (△) 10 mg (n = 9); (□) 20 mg (n = 8); (○) 40 mg (n = 8). Vertical bars indicate s.e. mean.

also reduced resting heart rate and abolished the tachycardia caused by SK&F 24260 (0.2 mg/kg, s.c.) in intact normotensive rats (Table 2).

Dogs. In untreated dogs oral administration of SK&F 24260 (10 mg) as a solution in Tween-80 increased heart rate by 97 beats/minute. Propranolol treatment, 10 min beforehand with doses of 1 and 5 mg/kg (i.v.), reduced this tachycardia to 61 and 56 beats/min respectively. Resting heart rates were reduced to about the same level (77 beats/min) by both doses. The responses after

Table 3 Effect of SK&F 24260 and hydrallazine on blood flow through the rat hindquarters

SK&F 24260			*Hydrallazine*		
Dose (μg/kg)	*Control blood flow (ml/min)*	*Post drug flow (ml/min)*	*Dose (mg/kg)*	*Control blood flow (ml/min)*	*Post drug flow (ml/min)*
5	2.6 ± 0.19	2.9 ± 0.2	0.2	2.7 ± 0.07	3.4 ± 0.12
10	2.7 ± 0.21	3.5 ± 0.35	0.4	2.7 ± 0.12	3.6 ± 0.29
20	3.2 ± 0.09	4.4 ± 0.12	0.8	2.6 ± 0.13	3.4 ± 0.13
40	2.6 ± 0.16	4.5 ± 0.33	1.6	2.7 ± 0.05	4.0 ± 0.19
			3.2	2.6 ± 0.1	4.1 ± 0.13
			6.4	2.5 ± 0.08	4.0 ± 0.22

Values are means with s.e. of five or six experiments.

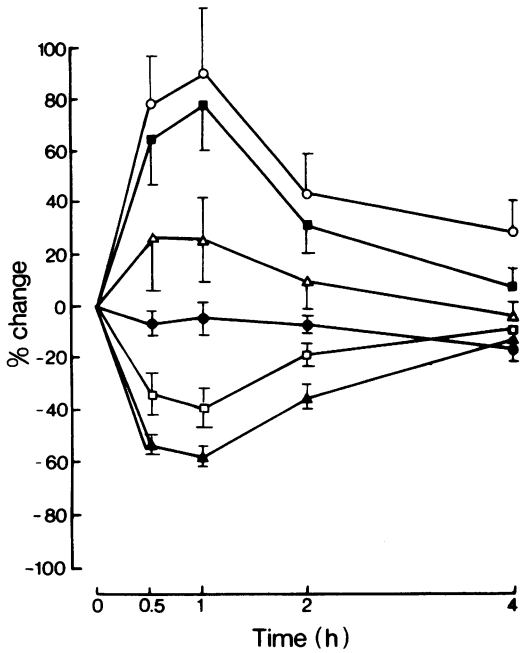

Figure 3 Effect of SK&F 24260 (1.0 mg/kg orally dissolved in Tween-80) on the haemodynamics of four conscious dogs in which aortic blood flow was measured with an electromagnetic flow meter. The results are shown as the mean percentage change from the pre-drug value. Vertical bars show s.e. mean. (□) Diastolic blood pressure (pre-drug value 87 mmHg); (○) heart rate (100 beats/min); (■) cardiac output (2.9 litres/min); (●) stroke volume (ml/min); (△) left ventricular work (4.06 kg M/min); (▲) total peripheral resistance (2995 absolute units).

both doses of propranolol were significantly less than in untreated animals ($P < 0.05$) but the large dose of propranolol had no more effect than the small dose. The hypotensive response was unchanged by either dose of propranolol.

Nitroglycerine (200 or 300 μg) intravenously also caused a marked reflex increase in heart rate of about 90 beats/minute. Pretreatment with propranolol (1 mg/kg, i.v.) had little effect on this response and in three experiments the mean reduction was only 16%. In contrast the tachycardia (90 beats/min) in response to intravenous isoprenaline (2.0 μg) was abolished by treatment with propranolol (1.0 mg/kg, i.v.).

Effects of SK&F 24260 on perfused vascular beds

Rat hindquarters. Blood flow through the hindquarters increased in a dose-related manner following the intravenous injection of SK&F 24260 or hydrallazine (Table 3). SK&F 24260

Table 4 Effect of SK&F 24260, hydrallazine and papaverine on the consecutive sections of cat skeletal muscle vasculature

Drug	*Dose (μg/kg)*	n	*Resistance vessel dilatation. (Resistance as % of control value)*	*Capacitance vessel dilatation (ml/100 g muscle)*	*Capillary filtration coefficient (% of control value)*	*Fluid movement (ml min^{-1} 100g^{-1})*
SK&F 24260	0.2	2	99	0	103	0
	1.0	4	88 ± 2.2	0	106 ± 6.6	0
	5.0	5	74 ± 4.8	0.07 ± 0.03	112.6 ± 8.2	0.25 ± 0.02
	25	4	58.8 ± 6.7	0.26 ± 0.09	131.5 ± 9.5	0.13 ± 0.04
	125	4	49.3 ± 11.0	0.47 ± 0.14	134.0 ± 12.0	0.74 ± 0.28
	625	4	51.8 ± 6.3	0.42 ± 0.06	164.7 ± 21.8	0.57 ± 0.09
Hydrallazine	100	2	97.5	0	82.5	0
	500	4	77.5 ± 1.7	0.05 ± 0.02	116.7 ± 16.7	0.03 ± 0.01
	2500	2	55	0.21	133	0.13
Papaverine	0.04*	3	87.7 ± 6.7	0.05 ± 0.05	131.7 ± 15.3	0
	0.2*	3	73.3 ± 10.4	0.27 ± 0.09	138.0 ± 12.5	0
	1.0*	3	61.7 ± 10.4	0.44 ± 0.1	169.0 ± 16.3	0.2 ± 0.12
	5.0*	3	41.0 ± 8.5	0.62 ± 0.12	197.7 ± 11.3	0.32 ± 0.12
	25.0*	3	33.7 ± 9.2	0.76 ± 0.1	197.7 ± 11.3	0.41 ± 0.13

Figures shown are mean with s.e.
* μg kg^{-1} min^{-1}.

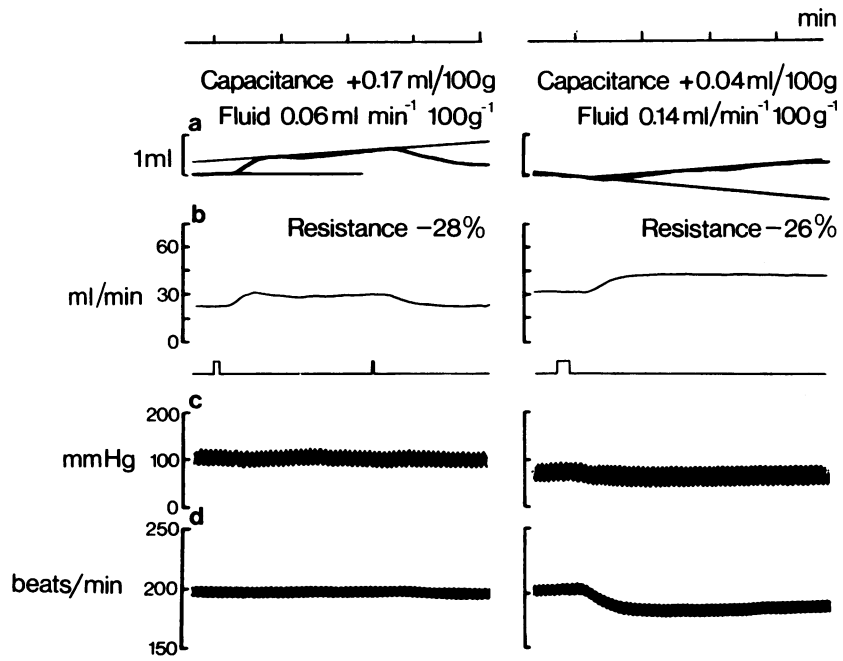

Figure 4 Mellander preparation of cat skeletal muscle, showing changes in (a) limb volume (b) blood flow (c) systemic blood pressure and (d) heart rate in response to papaverine, 50 μg kg^{-1} min^{-1}, intra-arterially (left hand panel) and SK&F 24260, 5.0 μg/kg intravenously (right hand panel). Both drugs increased blood flow and decreased resistance equally. Only papaverine caused a rapid increase in limb volume indicating dilatation of capacitance vessels. Shifts in fluid equilibrium were calculated from the lines drawn to indicate slow mean changes in volume. There was a greater loss of fluid from blood to extra vascular tissue with SK&F 24260 than with papaverine.

Table 5 Effect of SK&F 24260, hydrallazine and papaverine on the arterial perfusion pressure (Pa) and venous pressure (Pv) of the isovolaemic preparation of the cat intestinal vascular bed showing effects on resistance and capacitance vessels

Drug	*Dose (μg)*	n	*Reduction in Pa (mmHg)*	*Reduction in Pv (mmHg)*
SK&F 24260 (i.v.)	0.2	4	12.7 ± 2.95	0
	0.5	4	30.8 ± 0.92	0
	1.0	6	50.6 ± 2.17	0.88 ± 0.44
	2.0	5	62.6 ± 6.74	0.4 ± 0.31
	5.0	5	69.1 ± 2.58	0.3 ± 0.23
	10.0	5	83.2 ± 4.42	1.69 ± 0.38
Hydrallazine (i.a.)	20	5	10.5 ± 0.5	0
	40	5	30.8 ± 7.2	0
	80	5	47.6 ± 6.3	0.28 ± 0.17
	160	5	67.1 ± 6.7	0.76 ± 0.22
	320	5	73.0 ± 6.3	0.82 ± 0.17
	640	5	80.2 ± 4.7	1.04 ± 0.25
Papaverine (i.a.)	2.5	22	13.0 ± 0.67	0.43 ± 0.05
	10	22	30.2 ± 0.85	1.10 ± 0.09
	40	22	50.3 ± 1.29	2.31 ± 0.13
	160	22	67.1 ± 1.46	3.99 ± 0.16
	640	22	80.7 ± 1.51	5.64 ± 0.19

Values shown are mean with s.e.

was, very approximately, 50 times more active than hydrallazine as a vasodilator.

Cat skeletal muscle vasculature. SK&F 24260 caused dose-dependent increases in blood flow through the cat skeletal muscle vasculature when given at doses over the range 0.2 to 125 μg/kg of calf muscle (Table 4). During a maximal response, blood flow doubled and, since perfusion pressure was constant, resistance to flow was halved. Thus, SK&F 24260 had a graded and marked vasodilator action on the resistance vessels of the cat calf muscle. Capacitance vessels were also dilated, but only at the higher dose levels (5.0 to 625 μg/kg of muscle); the lower doses which caused dilatation of resistance vessels had little or no effect on capacitance vessels. Pre-capillary sphincter vessels were also dilated since the capillary filtration coefficient was increased. Finally, there was a net transcapillary fluid shift into the extra-vascular space.

Papaverine also increased blood flow through the calf muscle vascular bed when infused at rates of 0.04 to 25 μg/kg of calf muscle per minute. At the highest dose level blood flow was trebled. Capacitance vessels and pre-capillary sphincter vessels were also dilated by all the doses of papaverine used, and there was also at the higher dose levels a shift of fluid into the extra-vascular space (Table 4). But papaverine, for a given increase in blood flow, dilated capacitance vessels and pre-capillary sphincter vessels to a greater extent than did SK&F 24260. These actions of the two drugs are shown in Figure 4. In this experiment the SK&F 24260 was given intravenously and there were small falls in systemic blood pressure and heart rate, but for the same degree of dilatation of resistance vessels (increase in flow) there was a four-fold difference in dilatation of the capacitance vessels (rapid increase in limb volume) between papaverine and SK&F 24260. Only a few experiments were done with hydrallazine, but resistance vessels were readily dilated with little simultaneous dilatation of capacitance vessels at doses of 0.1 to 2.5 mg/kg of muscle (Table 4).

Cat mesenteric vasculature. SK&F 24260 at doses of 0.2 to 10 μg/kg, intravenously, reduced the arterial perfusion pressure (Pa) but there was little consistent effect on intestinal venous pressure (Pv); there was no reduction of Pv with a dose of 0.5 μg/kg, although Pa fell by 30 mmHg (Table 5). The decrease in perfusion pressure was dose-dependent. Following intravenous administration the onset of the response was rapid, reaching a peak within 2 minutes. The duration depended on dose, but was usually less than 30 minutes. Responses to hydrallazine were more

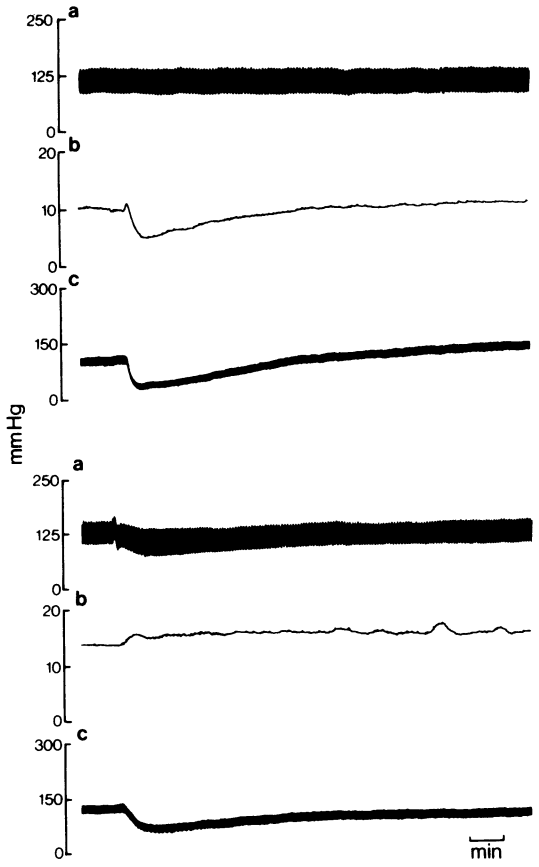

Figure 5 Perfused isovolaemic cat intestinal vascular bed preparation, showing (a) systemic blood pressure, and (b) arterial (Pa) and (c) venous (Pv) perfusion pressures. Papaverine (250 μg/kg, i.a., upper panel) reduced both Pa and Pv but SK&F 24260 (2.0 μg/kg, i.v., lower panel) reduced only Pa.

prolonged (60 min) while those to papaverine were much briefer (5 minutes). Figure 5 illustrates the responses of Pa, Pv and systemic blood pressure to SK&F 24260 (2.0 μg, i.v.) and papaverine (250 μg, i.a.). Papaverine lowered both arterial and venous pressures. SK&F 24260 reduced only arterial perfusion pressure. This difference between the drugs extends over a wide dose range (Table 5). Hydrallazine, like SK&F 24260, reduced perfusion pressure (Pa) in a dose-related manner over the dose range 20 to 640 μg but had little effect on venous pressure.

Discussion

SK&F 24260 lowers arterial blood pressure in conscious rats and dogs. Substantial and prolonged

falls in blood pressure are caused by doses of 0.2 mg/kg, subcutaneously. Larger reductions in blood pressure occur in hypertensive animals (either spontaneously occurring or experimentally induced) than in normotensive ones, but nevertheless blood pressure of normotensive animals is lowered by SK&F 24260. SK&F 24260 is also active orally. Extreme insolubility precluded the administration of aqueous solutions, but solutions in Tween-80 or powdered drugs, either free or in suspension, were used. The hypotension is greatest and most rapid in onset with the solution in Tween-80 and slowest with the crystalline or unmilled drug. The milled drug gave intermediate responses. Thus, activity increases as the particle size of the drug decreases, possibly because of better absorption.

SK&F 24260 has vasodilator activity and decreases resistance to blood flow in the vascular beds of the rat hindquarters and cat skeletal muscle when perfused at constant pressure, and of the cat intestine perfused at constant flow. The hypotension in conscious dogs with implanted aortic flow probes and in anaesthetized dogs (unpublished observations) and in anaesthetized rabbits (B. Johnston, unpublished observations) is a result of a reduction in total peripheral resistance and not a decreased cardiac output. This reduction in total peripheral resistance can be accounted for by the vasodilator action at peripheral blood vessels. Thus, the hypotensive action of SK&F 24260 is due to peripheral vasodilatation.

The separate responses of resistance and capacitance vessels of cat skeletal muscle to hydrallazine and sodium nitrite were studied by Ablad & Mellander (1963) who showed that selective dilatation was possible, and that hydrallazine predominantly dilated resistance vessels whereas sodium nitrite predominantly dilated capacitance vessels. Using the same technique as these authors we have confirmed the pattern of activity for hydrallazine. SK&F 24260 also dilates resistance vessels in preference to capacitance vessels and so has the same selectivity as hydrallazine. Papaverine behaves differently, lacks selectivity, and dilates both resistance and capacitance vessels. The isovolaemic perfusion technique using the cat intestinal vascular bed also differentiates the action of drugs on resistance and capacitance vessels (Taylor, 1973). By this method too, papaverine displays no selective action and dilates resistance and capacitance vessels equally well. Hydrallazine and SK&F 24260 in contrast show marked selectivity for resistance vessels and both drugs are again able to cause marked dilatation of resistance vessels without affecting capacitance vessels.

Thus, SK&F 24260 is a selective dilator of pre-capillary resistance vessels in both skeletal muscle and intestine. The drug is extremely potent showing vasodilator activity at doses of 200 ng/kg. No accurate quantitative estimates of relative activity have been made, but in the rat perfused hindquarters, where both hydrallazine and SK&F 24260 were given by the same route, SK&F 24260 is about 50 times more active. The dilatation is due presumably to a direct effect on the vascular smooth muscle since the intestinal and skeletal muscle preparations were sympathetically denervated. A more detailed investigation of the action on blood vessels has not been carried out. Such a study would be complicated by the almost complete insolubility of the drug in aqueous solutions (<1.0 μg/litre).

The effects of SK&F 24260 and papaverine on capillary function were also determined on the cat skeletal muscle vascular bed. Both drugs increased in a dose-dependent manner, the capillary filtration coefficient. This is an index of the functional capillary surface area which is determined by the tone of the pre-capillary sphincter vessels. Pre-capillary sphincters are, therefore, dilated by both papaverine and SK&F 24260, but relative to an increase in blood flow, or decrease in resistance, papaverine has a larger effect on the pre-capillary sphincters than SK&F 24260. Pre-capillary sphincters, as the smallest resistance vessels, are always dilated when there is a reduction in regional vascular resistance (Mellander & Johansson, 1968).

The equilibrium of transcapillary fluid movements is also changed by SK&F 24260 and papaverine, so that there is a net transfer of fluid from the capillaries into the extra-vascular spaces. Relative to the degree of dilatation of resistance vessels the loss of fluid is greater with SK&F 24260 than with papaverine, and this difference is well illustrated in Figure 4. This loss of fluid from the capillaries is a complex function of an increase in functional capillary surface area and an increase of capillary hydrostatic pressure from the change of the pre- to post-capillary resistance ratio. Because of the selective pre-capillary dilatation caused by SK&F 24260 capillary hydrostatic pressure will be increased more by this than by papaverine and so a greater transfer of fluid to the extra-vascular spaces will take place. However, papaverine has more effect on the functional capillary surface area and this response may tend to minimize differences in overall fluid transfer between the two drugs. Hydrallazine also dilated pre-capillary sphincters and caused a transfer of fluid from the capillaries, effects described earlier by Ablad & Mellander (1963).

In conscious animals hypotension was always accompanied by tachycardia and, in all four

experiments when it was measured, also by an increase in left ventricular output. SK&F 24260 has no direct effect on the heart (unpublished data) and these responses are probably due, at least in part, to reflexes following the reduction of carotid sinus pressure. The heart rates of anaesthetized animals, in contrast, are not increased by SK&F 24260, and usually bradycardia occurs. This presumably is a result of the anaesthetic inhibiting the reflexes.

In rats, propranolol can prevent or abolish the tachycardia caused by SK&F 24260 without affecting the hypotension, so that in this species the tachycardia is due entirely to increased sympathetic nervous activity. In the dog, however, the mechanism of the tachycardia is more complex. Here, the tachycardia evoked by SK&F 24260 is reduced by only 40% by β-adrenoceptor blockade. This incomplete blockade cannot be due to inadequate doses of propranolol since increasing the dose from 1 mg/kg to 5 mg/kg caused no further reduction of the heart rate responses and responses to isoprenaline were abolished. Nor is it specific for SK&F 24260 since the reflex tachycardia in response to the hypotension caused by nitroglycerin is also only slightly reduced by propranolol. Thus, in contrast to rats, in dogs only part of the tachycardia is due to increased sympathetic activity. To sustain an increased cardiac output, venous return must also be increased. The maintenance or elevation of venous return during hypotension and vasodilatation is possible because of the selective dilatation of resistance vessels. Blood pressure and peripheral resistance are lowered, but because the capacitance vessels are unaffected there is no increase in venous pooling, and, as SK&F 24260 has no sympathetic blocking action, the heart and veins are able to respond normally to reflex stimulation. The increase in venous return may also contribute to the tachycardia by stimulating atrial stretch receptors (Bainbridge, 1915; Ledsome & Linden, 1967; Linden, 1973). The total tachycardia consists, therefore, of at least two components; but as yet no attempt has been made to determine their relative roles.

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