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DRUG-INDUCED CHANGES IN CAPILLARY FILTRATION COEFFICIENT AND BLOOD FLOW IN THE INNERVATED SMALL INTESTINE OF THE ANAESTHETIZED CAT

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1 A modification of the Folkow Technique for simultaneous measurement of blood flow and capillary filtration coefficient (CFC) in the cat jejunum is described. The modification retained the sympathetic innervation of the preparation, and in the present experiments, drugs were administered intravenously.

2 There is evidence that CFC is a cardiovascular quantity independent of blood flow or regional vascular resistance in these preparations. Low doses of drugs may affect CFC without altering the blood pressure, blood flow, or heart rate.

3 Under control conditions the CFC, a measure of functional exchange vessel area, was lower than previously reported for similar, but denervated preparations.

4 α-Adrenoceptor stimulation with phenylephrine (1.0 μg kg^{-1} min^{-1}, i.v.) caused a fall of 75-85% from control values of CFC with concomitant rises in blood pressure of 0-15% and falls in blood flow of 10-40%. The heart rate rose by 0-15%. Phentolamine (0.5-2.0 mg/kg, i.v.) caused a rise in CFC and a slight fall in vascular resistance, and blocked the effects of phenylephrine on this tissue.

5 β-Adrenoceptor stimulation with isoprenaline (0.2 μg kg^{-1} min^{-1}, i.v.) caused a rise in CFC of 75-110%, a fall in blood pressure of 0-10%, a rise in blood flow of 10-60% and a rise in heart rate of up to 35%. Propranolol caused a transient rise in CFC when injected i.v. in a dose of 0.1 mg/kg, which was adequate to block the effects of isoprenaline.

6 Angiotensin (25-100 ng kg^{-1} min^{-1}, i.v.) caused falls in CFC of up to 100% and rises in vascular resistance. Aminophylline (0.2-0.4 mg kg^{-1} min^{-1}, i.v.) caused rises in CFC of up to 200% with falls in vascular resistance.

7 Histamine (0.01 to 1.0 μg kg^{-1} min^{-1}, i.v.) had little effect on vascular resistance, but 10 and 40 μg kg^{-1} min^{-1} caused falls in vascular resistance. Doses up to and including 10 μg kg^{-1} min^{-1} caused falls in CFC, but the higher doses, or smaller doses after histaminase inhibition caused rises in CFC. α-Adrenoceptor blockade reversed the fall in CFC caused by small doses of histamine, to a rise. Mepyramine completely blocked the effects of histamine on these preparations.

8 5-Hydroxytryptamine (33-100 μg kg^{-1} min^{-1}, i.v.) caused a rise in vascular resistance and a fall in CFC of up to 85%. These effects were blocked by methysergide (250 μg/kg, i.v.).

9 Rises in CFC indicate an increase in functional exchange vessel area in the tissue, and falls in CFC a decrease in the area available for vascular exchange. These changes are examined against the possibility of the drugs causing reflex adjustments in sympathetic tone, of systemic deactivation of intravenously administered drugs, and of drug effects on vascular permeability.

Introduction

The effects of noradrenaline and isoprenaline on the capillary filtration coefficient (CFC) of the jejunum of the anaesthetized cat have been studied by Folkow, Lundgren & Wallentin (1963), and other investigators using the same technique (Folkow, Lewis, Lundgren, Mellander & Wallentin, 1964a,b; Haglund & Lundgren, 1972). These workers measured drug effects on CFC where

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reflex adjustments in sympathetic tone had been eliminated by denervation and elimination of the adrenal medullary secretions, and effects of dilution of drugs by the systemic circulation and their possible deactivation in peripheral tissues were avoided by close-arterial infusions of the drugs.

The present investigation was undertaken to assess the likely effects of a range of drugs upon blood flow and exchange function in the jejunum of the cat in which the sympathetic innervation was left intact and the secretions from the suprarenal glands retained. Drugs were administered systemically by intravenous infusion or injection, and in this way the effect of low blood concentrations of drugs upon one vascular bed examined.

Functional aspects of the microcirculation have been reviewed by Mellander & Johansson (1968) and the terminology used here is based upon their classification. In the simplest tissues, regional vascular resistance is determined predominantly by tone in the precapillary resistance vessels, whilst the functional exchange vessel area is determined by the tone in the precapillary 'sphincters'. CFC is a measure of the exchange vessel area open to transvascular fluid movement (Pappenheimer & Soto-Rivera, 1948; Mellander, 1960; Folkow *et al.*, 1963) and evidence from other vascular beds suggests that this is controlled by the number of open precapillary 'sphincters' (Haley & Harris, 1949; Haley & Andem, 1950; Zweifach, 1954).

Angiotensin and aminophylline were selected to complement the study of the effects of phenylephrine and isoprenaline by examining the effects of vasoactive agents not acting on adrenoceptors. The effects of histamine and 5-hydroxytryptamine together with potentiators and antagonists of their effects complete this study; part of the results of a preliminary investigation of the effects of histamine have already been reported (Richardson, 1973a).

Methods

Anaesthesia was induced in healthy cats weighing between 2.2 and 5.7 kg by inhalation of halothane, and maintained with intravenous chloralose (Kuhlmann, Paris; 70 mg/kg), chloralose (50 mg/kg) with urethane (100 mg/kg), or pentobarbitone sodium (Nembutal, Abbott; 30 mg/kg). Whichever maintenance anaesthetic was used, there was no measurable difference in any control parameter.

The variables recorded were phasic systemic arterial pressure (in mmHg; 1 mmHg = 133Pa; mean pressure was derived as diastolic plus one-third of the pulse pressure), superior mesenteric venous pressure (mmHg), superior mesenteric venous flow (ml/min) and changes in the volume of a loop of jejunum (ml). All were recorded on a rectilinear hot-wire recorder (Devices, MX4). The heart rate was counted periodically from the arterial pressure record at high chart speed.

The trachea and left common carotid artery were cannulated and systemic arterial pressure measured with a strain gauge transducer (Bell & Howell 4-327-L221-1-B4M5) connected to the arterial cannula. The right external jugular vein was cannulated and connected to a 20 ml reservoir for the return of venous blood from the jejunal segment. An oral thermometer was inserted and the animal's temperature maintained at 37-38°C throughout.

The abdomen was opened in the midline and the greater omentum, spleen, large intestine, duodenum and pancreas extirpated. A loop of jejunum with a mean weight in 44 preparations of 62 g (s.d. = 17 g) was selected for experimentation, and the remainder of the small intestine extirpated. Artificial ventilation with 40% oxygen by volume in the inspired gas mixture was instituted and the blood rendered incoagulable with 250 or 300 u/kg of heparin (mucous heparin, Pularin, Evans Medical) followed by hourly supplements of 100 u/kg of the same solution.

The superior mesenteric vein (SMV) was cannulated with transparent vinyl tubing (3.05 mm i.d.; 4.13 mm o.d.) of about 40 cm in length; although the vein drains only a small proportion of its normal tissue, it is essential to minimize the possibility of obstructing the venous outflow, and so the largest cannulae possible were used. The pressure in the cannula about 5 cm from its insertion into the SMV was monitored with a second strain gauge transducer (Bell & Howell 4-327-L221-1-B4M5), and blood flow measured with a cannulated flowhead, in the venous cannula, which was connected to an electromagnetic flowmeter specially designed by a colleague, Mr J.D. Gasking, for the measurement of low venous flows.

Blood dripped from the outlet of the cannula in the SMV into a small reservoir from which it was pumped into the reservoir connected to the external jugular vein. The height of the outlet of the SMV cannula could be adjusted, and therefore the venous pressure was kept under direct and continuous control. Normally the venous pressure was kept at zero, with respect to the point of cannulation of the vein, and elevated by 10 cm H_2O for 1 min periods, to determine the CFC.

The segment of jejunum was inserted into a Perspex plethysmograph filled with a solution of

low molecular weight dextran in 0.9% w/v NaCl solution (Rheomacrodex, Pharmacia), maintained at 37-38°C with radiant lamps. Volume changes in the contents of the plethysmograph were monitored by means of an isometric transducer (Devices, model 2S-T-O2) connected rigidly to a Perspex 'float' which was placed in a syringe barrel containing dextran solution in continuity with that in the plethysmograph. Changes in the volume of the contents of the plethysmograph were reflected in small changes of under 0.5 cm in the height of the column of fluid in the syringe barrel, and hence in changes in the upthrust on the transducer. This recorder was linear over the ranges used.

Blood volume was maintained by priming the reservoirs and external vascular circuits with Rheomacrodex, which appears suitable for this purpose (Mainardi, Bhanganada, Mack & Lillehei, 1964; Atik, 1966; Eliasson & Samelius-Broberg, 1969), and which also retards blood coagulation (Walton, 1952).

Measurement of capillary filtration coefficient

The measurement of CFC in this tissue has been described and validated in full by Folkow *et al.*, (1963). In response to the elevation of venous pressure, the volume of the tissue increases in two stages; the first sharp increase in volume is due to the passive distension of the capacitance vessels, and the second, slower phase is due to fluid transuding into perivascular spaces in response to the imposition of an increment in venous pressure. This increase in volume due to fluid transudation is measured in ml of fluid transuded per minute, per mmHg rise in the venous pressure, per 100 g of tissue under study, i.e. ml min^{-1} $mmHg^{-1}$ 100 g^{-1}, and this is the capillary filtration coefficient.

Drugs

The following drugs were used: aminoguanidine bicarbonate (Kodak-Eastman), aminophylline (Antigen), angiotensin amide (Hypertensin, Ciba), burimamide (SKF), compound 48/80 (Wellcome), histamine acid phosphate (BDH), 5-hydroxytryptamine creatinine sulphate (Sigma), isoprenaline sulphate (MacCarthay), mepyramine maleate (BDH), methysergide bimaleate (Deseril, Sandoz), noradrenaline acid tartrate (Levophed, Winthrop), phentolamine mesylate (Rogitine, Ciba), phenylephrine hydrochloride (Boots), practolol hydrochloride (Eraldin, I.C.I.) and propranolol hydrochloride (Inderal, I.C.I.).

Drugs were dissolved in, or diluted from the ampoules with, 0.9% w/v NaCl solution (saline) agonist drugs being infused over periods of 10 to 15 min at a rate of 0.125 ml/min from a slow-infusion pump, and other drugs being injected in volumes under 1 ml and washed in with 3 ml of saline. All drugs were administered intravenously except where stated otherwise in the results. If an agonist was administered before and after a drug which was expected to modify its action, a period of 10 to 15 min was allowed between injection of the second drug and the second infusion of the agonist. Doses are expressed in terms of the salts used.

Results

Control observations were obtained as the means of 7 to 10 observations in each experiment. The means of these values in 44 preparations ± the standard error of the means (s.e. mean) were: for systemic arterial mean pressure 118 ± 4 mmHg, for heart rate 188 ± 6 beats/min, for blood flow 23 ± 1 ml min^{-1} 100 g^{-1}, for regional vascular resistance 5.23 ± 0.29 PRU calculated as mmHg min 100 g ml^{-1}, and for capillary filtration coefficient 0.030 ± 0.003 ml min^{-1} $mmHg^{-1}$ 100 g^{-1}.

α-Adrenoceptor stimulation and blockade

Stimulation The effects of five intravenous infusions of phenylephrine in doses of 0.9 or 1.0 μg kg^{-1} min^{-1}, to different preparations are shown in Table 1. In every case, the onset of effects was rapid, peak effects being attained towards the ends of the infusion periods, and recovery was rapid, being complete within 10-12 min after the end of the infusion, though in 3 out of 7 cases the recovery of the blood flow was delayed up to 30 min, as in Figure 1.

On intravenous infusion of phenylephrine (0.9 or 1.0 μg kg^{-1} min^{-1}) there was a mean fall in CFC of 78% (range 55-85%), a mean fall in blood flow of 24% (range 10-40%), a mean rise in blood pressure of 7% (range 0-15%) and a mean rise in heart rate of 5% (range 0-15%). There was no evidence of any fall in heart rate, which would be the expected baroreceptor reflex response to an elevated arterial pressure.

In one further experiment an intravenous infusion of noradrenaline (0.75 μg kg^{-1} min^{-1}) caused a 75% fall in CFC, a 15% fall in blood flow and a 30% rise in mean arterial pressure.

Blockade Phentolamine was injected acutely in ten preparations, and the effects are shown in Table 2 and illustrated in Figure 1. The effects were short-lived in five out of ten preparations, and maintained for more than 20 min in the other

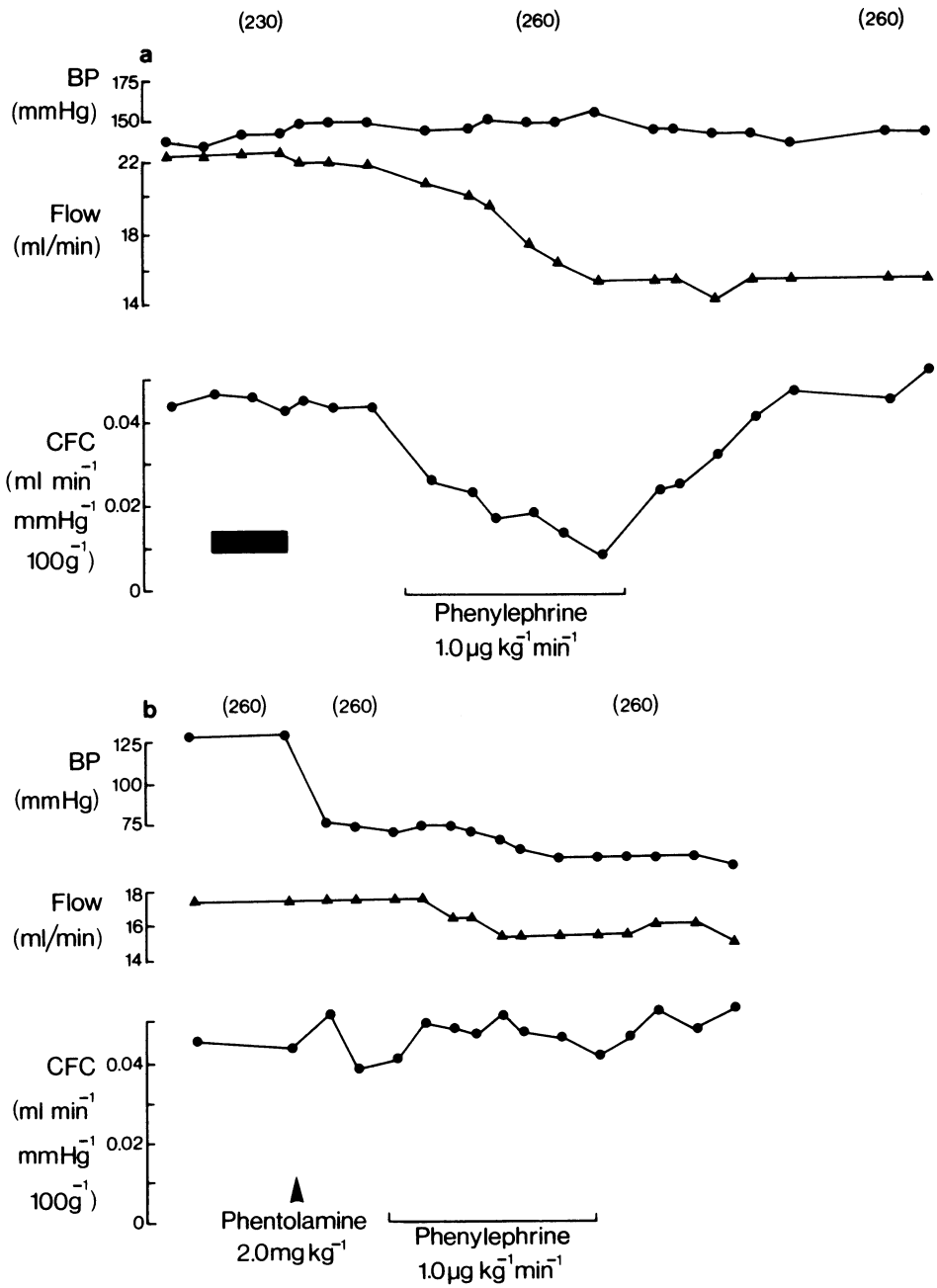

Fig. 1 (a) The effects of phenylephrine on the vasculature of the cat jejunum; (b) effects of phentolamine, and of phenylephrine after phentolamine on the cat jejunum. Experiment 4, cat, female, 3.7 kg. Anaesthetized with halothane and pentobarbitone (40 mg/kg, i.v.).

The black horizontal bar represents 10 min, and in both panels, the variables are from above downwards: mean systemic arterial pressure, blood flow and capillary filtration coefficient. Weight of loop of jejunum post mortem = 66 g. The figures in parentheses represent the heart rate in beats/minute.

five. On intravenous injection of 1.0 mg/kg, to four preparations, there was a mean rise in CFC of 111% (range 60-135%), a mean fall in blood flow of 10% (from a rise of 20% to a fall of 20%), a mean fall in blood pressure of 39% (range 30-40%) and a mean rise in heart rate of 9% (range 5-10%). The injection of 2.0 mg/kg produced a mean rise in CFC of 66% (range 5-110%), a mean rise in blood flow of 1% (from a fall of 20% to a rise of 20%), a mean fall in blood pressure of 37% (range 20-45%) and a mean rise in heart rate of 6% (ranged from a fall of 15% to a rise of 25%) in a total of five preparations.

In three experiments, phenylephrine was infused intravenously in a dose of 1.0 $\mu g\ kg^{-1}\ min^{-1}$ after the intravenous injection

Table 1 The effects of α-adrenoceptor stimulation by phenylephrine on the intestinal vasculature of the cat

Experiment	*Phenylephrine ($\mu g\ kg^{-1}\ min^{-1}$)*	*Weight of jejunal loop (g)*	*Change in CFC*	*Change in blood flow*	*Change in BP*	*Change in heart rate*
			(means of control values – peak of drug effects)			
1	0.9	65	−55% (0.018-0.008)	−20% (15-12)	+5% (115-120)	no effect (210-210)
2	1.0	62	−75% (0.092-0.022)	−10% (13-12)	+10% (110-120)	no effect (240-240)
3	1.0	86	−80% (0.099-0.019)	−40% (27-19)	no effect (65-65)	+5% (200-210)
4	1.0	66	−85% (0.049-0.008)	−30% (25-18)	+5% (150-155)	+15% (230-260)
5	1.0	66	−75% (0.022-0.005)	−20% (11-9)	+15% (110-125)	+5% (230-240)

Table 2 The effects of α-adrenoceptor blockade by phenylephrine on the intestinal vasculature of the cat

Experiment	*Phentolamine ($mg\ kg^{-1}$)*	*Weight of jejunal loop (g)*	*Change in CFC*	*Change in blood flow*	*Change in BP*	*Change in heart rate*
			(means of control values – peak of drug effects)			
6	0.5	73	+25% (0.024-0.030)	no effect (14-14)	−40% (90-65)	+15% (240-270)
7	1.0	68	+135% (0.021-0.049)	+20% (14-17)	−40% (100-60)	+10% (230-250)
8	1.0	66	+120% (0.022-0.048)	−10% (9-8)	−30% (115-80)	+10% (240-260)
9	1.0	60	+60% (0.010-0.016)	−20% (14-11)	−45% (140-80)	+5% (210-220)
10	1.1	55	+130% (0.015-0.034)	+20% (14-17)	−40% (120-70)	+10% (180-200)
11	2.0	66	+15% (0.049-0.056)	no effect (17-17)	−35% (130-85)	no effect (260-260)
12	2.0	67	+5% (0.023-0.024)	+20% (10-12)	−20% (130-105)	+10% (180-200)
13	2.0	49	+105% (0.014-0.029)	−10% (6-5½)	−45% (55-30)	−15% (210-180)
14	2.0	52	+75% (0.024-0.042)	−20% (10-8)	−40% (140-100)	+10% (210-230)
15	2.0	24	+110% (0.012-0.025)	+15% (7-8)	−45% (110-60)	+25% (160-200)

of phentolamine (1.0 or 2.0 mg/kg) and these phenylephrine infusions were without effect on all variables measured.

β-Adrenoceptor stimulation and blockade

Stimulation Isoprenaline was infused in doses from 0.1 to 1.0 $\mu g\ kg^{-1}\ min^{-1}$ on ten occasions to nine preparations (Table 3). In every case, the onset of effects was rapid, peak effects were attained within the first 5 min of the infusion and thereafter there was a slight recession from the peak effects. Recovery was rapid, and complete within 5 min of the end of the infusions (Figure 2).

On four occasions, isoprenaline was infused intravenously in a dose of 0.1 $\mu g\ kg^{-1}\ min^{-1}$, without effect on blood flow or mean systemic arterial pressure, but producing a mean rise in CFC of 38% (range 26-60%) and a mean rise in heart rate of 8% (range 0-15%). On three occasions, 0.2 $\mu g\ kg^{-1}\ min^{-1}$, intravenously, produced a mean rise in CFC of 95% (range 75-110%), a mean rise in blood flow of 28% (range 10-60%), a mean fall in blood pressure of 7% (range 0-10%) and a mean rise in heart rate of 12% (range 0-35%).

Blockade Propranolol was injected intravenously to seven preparations in a dose of 0.1 mg/kg producing a mean rise in CFC of 85% (range 60-100%), an effect which typically persisted for 10 min or less after the injection (Figure 2). The heart rate fell by 20-30% and, in contrast to the effect on CFC, the effect of propranolol on heart rate persisted for the remainder of the experiment. There was no consistent effect on blood flow or pressure.

In four experiments, isoprenaline was infused intravenously at a rate of 0.1 or 0.2 $\mu g\ kg^{-1}\ min^{-1}$ after propranolol (0.1 mg/kg). There was no effect on CFC or heart rate, though there was a tendency for the blood flow and pressure to rise by 10-20% during the infusion of isoprenaline after propranolol. The reason for this is obscure, but might involve α-adrenoceptor stimulation. In a single experiment, 2.0 mg/kg of practolol was ineffective in blocking the vascular effects of isoprenaline, though it did block the rise in heart rate seen with isoprenaline in the absence of practolol.

Angiotensin

Angiotensin was infused intravenously to four preparations in doses from 25 to 160 ng kg^{-1}

Table 3 The effects of β-adrenoceptor stimulation by isoprenaline on the intestinal vasculature of the cat

Experiment	*Isoprenaline* ($\mu g\ kg^{-1}\ min^{-1}$)	*Weight of jejunal loop (g)*	*Change in CFC*	*Change in blood flow*	*Change in BP*	*Change in heart rate*
			(means of control values – peak of drug effects)			
16	0.1	50	+30% (0.021-0.027)	no effect (12-12)	no effect (95-95)	no effect (270-270)
17	0.1	76	+25% (0.034-0.042)	no effect (19-19)	no effect (85-85)	+15% (190-220)
18	0.1	58	+60% (0.063-0.101)	no effect (10-10)	no effect (120-120)	+15% (160-180)
19	0.1	35	+35% (0.035-0.048)	no effect (9-9)	no effect (110-110)	no effect (195-195)
19	0.2	35	+100% (0.036-0.071)	+60% (8-13)	no effect (105-105)	no effect (180-180)
20	0.2	95	+75% (0.026-0.045)	+15% (14-17)	−10% (130-120)	+35% (180-240)
21	0.2	65	+110% (0.030-0.063)	+10% (12-13)	−10% (125-115)	no effect (220-220)
1	0.37	65	+95% (0.015-0.029)	+5% (15-16)	no effect (115-115)	no effect (170-170)
2	0.5	62	+190% (0.018-0.052)	+5% (13-14)	no effect (110-110)	+15% (240-270)
22	1.0	40	+50% (0.046-0.070)	+60% (8-13)	no effect (85-85)	+10% (200-220)

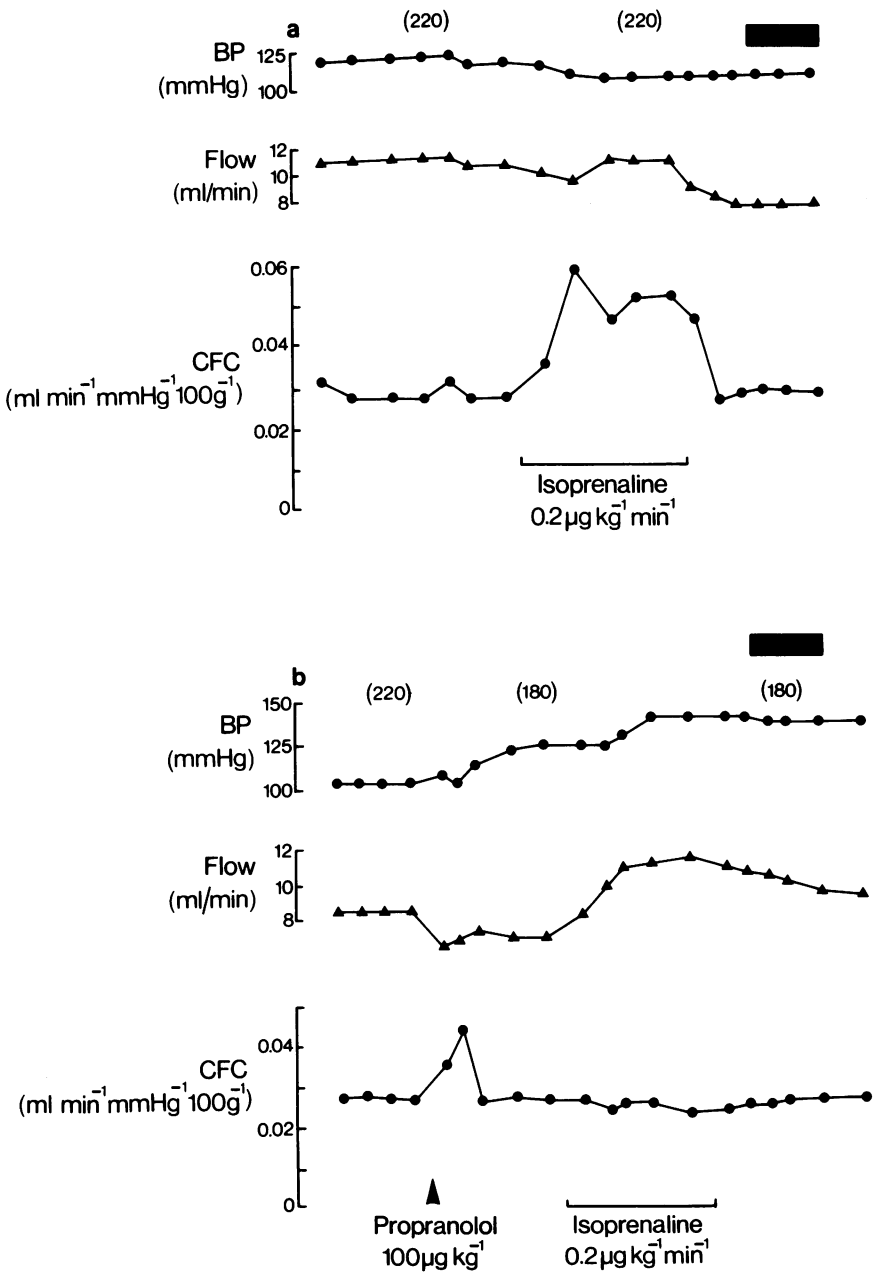

Fig. 2 (a) The effects of isoprenaline on the vasculature of the cat jejunum; (b) effects of propranolol and of isoprenaline after propranolol on the cat jejunum. Experiment 21; cat, male, 3.2 kg. Anaesthetized with halothane and chloralose (70 mg/kg, i.v.). The figures in parentheses show the heart rate in beats/minute.

The black horizontal bars represent 10 min, and in both panels, the variables are from above downwards: mean systemic arterial pressure, blood flow and capillary filtration coefficient. Weight of loop of jejunum post mortem = 65 g.

min^{-1} (Table 4). The onset of effects was rapid, peak effects being attained towards the end of the infusion periods; recovery was also rapid, being complete within 10-15 min from the end of the infusion. In two preparations, 25 ng kg^{-1} min^{-1} produced a mean fall in CFC of 50%, a mean fall in blood flow of 15%, a mean rise in systemic arterial pressure of 8% and no effect on heart rate.

Because angiotensin releases suprarenal catecholamines *in vitro* and *in vivo* (Peach, Cline & Watts, 1966; Staszewska-Barczak & Vane, 1967; Robinson, 1967), three infusions of angiotensin were performed after phentolamine (2.0 mg/kg), a dose found to be adequate to block the effects of exogenous phenylephrine. There is no evidence (Table 4) that α-adrenoceptor blockade modifies the responses of the preparation to angiotensin.

Aminophylline

Aminophylline was infused intravenously on six occasions to five preparations (Table 5); in each case the onset of effects was rapid, peak effects being attained towards the end of the infusion

Table 4 The effects of angiotensin on the intestinal vasculature of the cat

Experiment	*Angiotensin (μg kg^{-1} min^{-1})*	*Weight of jejunal loop (g)*	*Change in CFC*	*Change in blood flow*	*Change in BP*	*Change in heart rate*
			(means of control values – peak of drug effects)			
(a) Angiotensin alone						
23	0.025	63	−40% (0.029-0.018)	−20% (14-11)	+15% (110-125)	no effect (270-270)
14	0.025	52	−60% (0.025-0.010)	−10% (10-9)	no effect (125-125)	no effect (190-190)
15	0.10	40	−100% (0.032-0.000)	+10% (10-11)	+25% (120-150)	no effect (170-170)
19	0.16	35	−100% (0.052-0.000)	no effect (9-9)	+65% (70-115)	−10% (130-120)
(b) Angiotensin after phentolamine (2.0 mg kg^{-1})						
14	0.025	52	−65% (0.030-0.011)	−10% (9-8)	no effect (90-90)	no effect (200-200)
15	0.01	55	−50% (0.034-0.017)	+10% (10-11)	+20% (70-85)	no effect (240-240)
14	0.10	52	−75% (0.043-0.011)	no effect (10-10)	−15% (40-35)	−10% (220-200)

Table 5 The effects of aminophylline on the intestinal vasculature of the cat

Experiment	*Aminophylline (mg kg^{-1} min^{-1})*	*Weight of jejunal loop (g)*	*Change in CFC*	*Change in blood flow*	*Change in BP*	*Change in heart rate*
			(means of control values – peak of drug effects)			
15	0.20	40	+80% (0.009-0.016)	+30% (7-9)	−15% (60-50)	+10% (170-180)
23	0.20	50	+25% (0.021-0.026)	no effect (13-13)	−5% (130-125)	no effect (180-180)
24	0.25	96	+300% (0.014-0.042)	+90% (11-21)	−15% (80-70)	+5% (180-190)
25	0.25	40	+100% (0.010-0.020)	−10% (11-10)	−10% (165-150)	+5% (170-180)
26	0.25	84	+85% (0.012-0.022)	−10% (12-12)	−15% (150-125)	no effect (230-230)
27	0.40	50	+170% (0.017-0.046)	+15% (12-14)	−5% (130-125)	+20% (190-230)

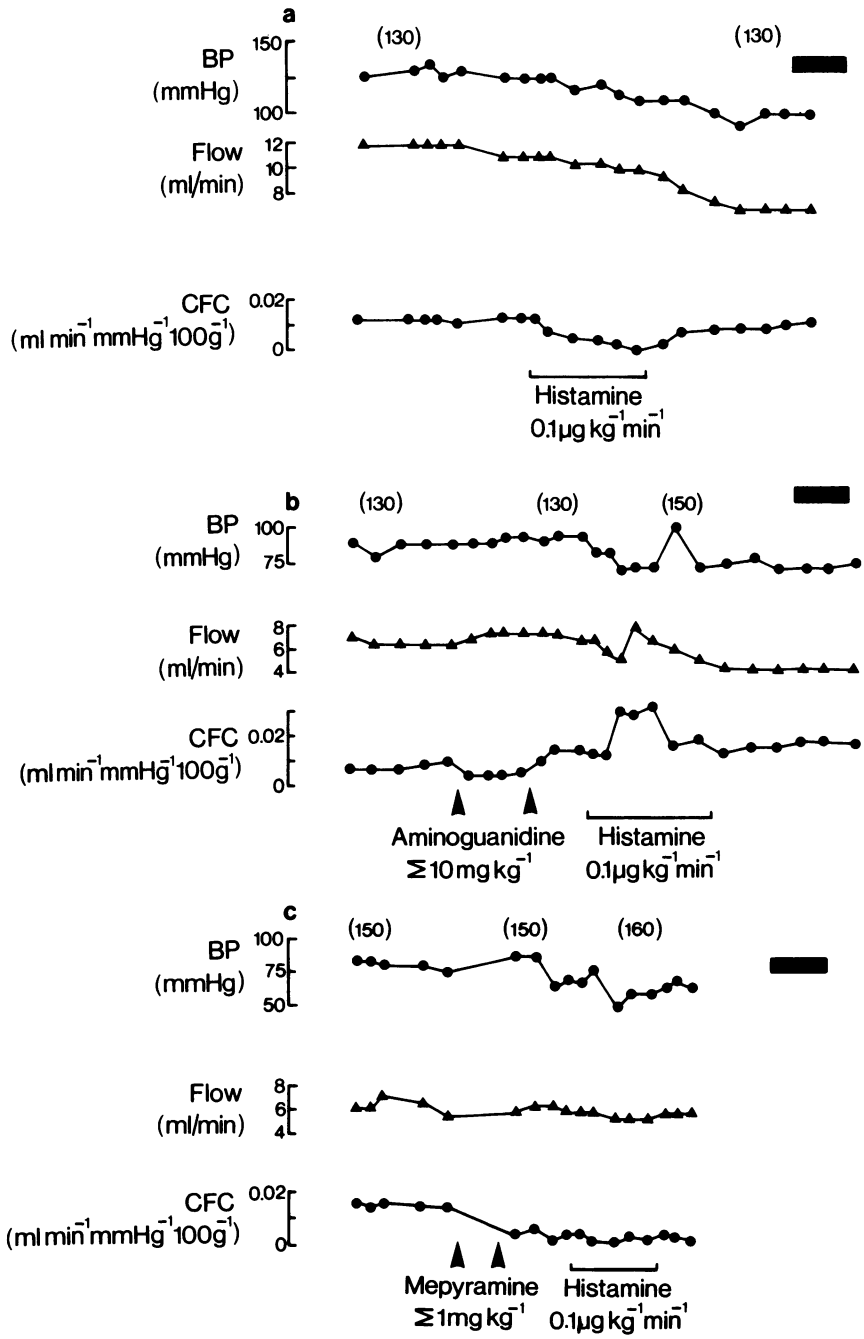

Fig. 3 (a) The effects of histamine on the vasculature of the cat jejunum; (b) effects of aminoguanidine and of histamine after aminoguanidine on the vasculature of the cat jejunum; (c) effects of mepyramine and of histamine after mepyramine on the vasculature of the cat jejunum.

The black horizontal bars represent 10 min, and in all panels, the variables are from above downwards: mean systemic arterial pressure, blood flow and capillary filtration coefficient. Weight of loop of jejunum post mortem = 84 g.

Experiment 29, cat, male, 4.6 kg. Halothane and chloralose (70 mg/kg) anaesthesia. Figures in parentheses represent the heart rate in beats/minute.

periods, and recovery was also rapid, being complete within 10 min of the end of the infusions. In three experiments, 0.25 mg kg^{-1} min^{-1} was infused producing a mean increase in CFC of 195% (range 85-300%), a mean rise in blood flow of 23% (ranging from falls of 10% to a rise of 90%), a mean fall in systemic arterial pressure of 13% (range 10-15%) and a mean rise in heart rate of 3% (range 0-5%). The smaller dose of 0.2 mg kg^{-1} min^{-1}, used on two occasions produced effects similar to but less pronounced than those of the higher dose.

Histamine, and the analysis of its actions

Histamine was infused intravenously on one occasion to each of ten preparations and intra-arterially via a catheter placed in the descending aorta 2 cm proximal to the origin of the superior mesenteric artery in one further experiment, in doses of 0.1, 1.0, 10.0 and 40.0 μg kg^{-1} min^{-1} (Table 6, part (a)). The effects were not qualitatively the same with respect to changes in CFC over the whole of this dose range, and attempts were made to analyse reasons for the differences found.

Histamine alone The intravenous infusion of histamine 0.1 μg kg^{-1} min^{-1} on five occasions produced a mean fall in CFC of 67% (range 50-100%), a mean rise in blood flow of 2% (ranged from falls of 10% to rises of 15%), a fall in blood pressure of a mean of 4% (ranging from a rise of 10% to a fall of 20%) and a mean rise in heart rate

Table 6 The effects of histamine on the intestinal vasculature of the cat

Experiment	*Histamine ($\mu g\ kg^{-1}\ min^{-1}$)*	*Weight of jejunal loop (g)*	*Change in CFC*	*Change in blood flow*	*Change in BP*	*Change in heart rate*
			(means of control values – peak of drug effects)			
(a) In the absence of pretreatment						
28	0.1	87	−55% (0.045-0.020)	−10% (17-15)	−10% (120-110)	+5% (165-175)
6	0.1	73	−50% (0.040-0.020)	no effect (14-14)	−5% (100-95)	+10% (250-270)
29	0.1	84	−100% (0.012-0.000)	−10% (13-12)	−20% (140-115)	no effect (130-130)
15	0.1	55	−60% (0.014-0.006)	+15% (14-16)	+10% (120-130)	no effect (180-180)
30	0.1	54	−70% (0.020-0.006)	+15% (13-15)	+5% (75-80)	−5% (240-230)
31	1.0	66	−65% (0.035-0.012)	no effect (18-18)	−10% (115-105)	no effect (200-200)
32	1.0	44	−75% (0.044-0.012)	no effect (17-17)	−15% (105-90)	no effect (130-130)
33	10.0	53	−100% (0.032-0.000)	+15% (16-18)	−15% (140-120)	+10% (170-190)
34	10.0 (i.a.)	90	−90% (0.027-0.003)	−10% (20-18)	−25% (80-60)	+5% (210-220)
35	40.0	80	+215% (0.036-0.114)	+25% (16-20)	−30% (90-65)	+10% (165-180)
36	40.0	46	+110% (0.013-0.027)	−10% (11-12)	−30% (110-75)	+5% (170-180)
(b) After hexamethonium (5 mg kg^{-1}, i.v.)						
37	0.01	54	−15% (0.028-0.024)	no effect (16-16)	no effect (125-125)	+5% (255-270)
37	0.1	54	−40% (0.030-0.018)	no effect (16-16)	−10% (125-110)	no effect (270-270)
37	1.0	54	−100% (0.028-0.000)	−10% (16-15)	−15% (120-105)	no effect (270-270)

of 2% (from a fall of 5% to a rise of 10%). The doses of 1.0 and 10.0 $\mu g\ kg^{-1}\ min^{-1}$ were infused on two occasions each, producing mean falls in CFC of 70 and 90% respectively, mean rises in blood flow of 0 and 3%, mean falls in blood pressure of 13 and 20% and mean rises in heart rate of 0 and 8%. The falls in CFC with doses up to and including 10.0 $\mu g\ kg^{-1}\ min^{-1}$ were progressive throughout the infusion, peak effects being attained towards the end of the infusions (Figure 3).

In contrast, the intravenous infusion of 40 $\mu g\ kg^{-1}\ min^{-1}$ of histamine to two preparations caused a mean increase in CFC of 163%. There was a variable effect on flow with a mean rise of 8%, a mean fall in blood pressure of 30% and a mean rise in heart rate of 8%. In both cases, peak effects were attained during the first half of the infusion period; on cessation of the infusion, although blood flow, pressure and heart rate returned to pretreatment values, the CFC fell to a value lower than that obtained before the infusion, and remained reduced for up to 20 minutes.

At each dose, histamine caused a fall in vascular resistance; at doses up to and including 10 $\mu g\ kg^{-1}\ min^{-1}$ the CFC was reduced, but at 40 $\mu g\ kg^{-1}\ min^{-1}$, the CFC increased. In order to examine the possibility that part of these effects might be due to reflex adjustments of sympathetic tone, since a fall in arterial pressure would be expected to cause a reflex fall in CFC (Oberg, 1964), histamine was infused in doses of 0.01, 0.1, 1.0 and 10.0 $\mu g\ kg^{-1}\ min^{-1}$ after hexamethonium bromide (5 mg/kg, i.v.). The effects are listed in

Table 6 *continued*

Experiment	*Histamine ($\mu g\ kg^{-1}\ min^{-1}$)*	*Weight of jejunal loop (g)*	*Change in CFC*	*Change in blood flow*	*Change in BP*	*Change in heart rate*
			(means of control values – peak of drug effects)			
33	10.0	53	−100% (0.051-0.000)	+40% (10-14)	−15% (80-70)	+10% (130-130)
34	10.0	90	−100% (0.044-0.000)	+10% (19-21)	no effect (60-60)	no effect (150-150)
(c) After aminoguanidine (10 mg kg^{-1}, i.v.)						
29	0.1	84	+90% (0.017-0.032)	+10% (9-10)	−20% (115-90)	+15% (130-150)
38	0.1	62	−30% (0.038-0.027)	−25% (16-12)	no effect (90-90)	no effect (180-180)
38	1.0	62	+115% (0.035-0.076)	−10% (18-16)	−15% (80-70)	+10% (180-200)
30	1.0	54	+70% (0.015-0.025)	+15% (13-15)	no effect (70-70)	+5% (210-220)
26	1.0	84	+100% (0.012-0.024)	+15% (12-14)	−5% (140-130)	no effect (180-180)
39	1.0	34	+95% (0.018-0.035)	+10% (12-13)	no effect (130-130)	+10% (130-140)
7	10.0	68	−45% (0.014-0.008)	+35% (15-20)	−20% (95-75)	+15% (200-230)
(d) After phentolamine (2 mg kg^{-1}, i.v.)						
15	0.1	55	+25% (0.034-0.043)	+10% (17-19)	−35% (90-60)	+5% (200-210)
31	1.0	66	+55% (0.050-0.078)	+20% (20-24)	−15% (75-65)	no effect (230-230)
39	1.0	34	+70% (0.018-0.030)	no effect (6-6)	no effect (60-60)	+5% (200-210)
7	10.0	68	+70% (0.034-0.057)	+20% (17-20)	−35% (60-40)	−10% (230-230)

Table 6, part (b), and do not differ markedly from those in the absence of ganglion blockade.

Aminoguanidine The histaminase inhibitor aminoguanidine (Ghosh & Schild, 1958) was injected intravenously in a dose of 10 mg/kg to seven preparations. It caused a rise in blood pressure of under 5%, a rise in blood flow of 5-10% and variable effects of under 10 min duration on the CFC. Histamine was infused in doses of 0.1, 1.0 and 10.0 $\mu g\ kg^{-1}\ min^{-1}$ on seven occasions to six preparations pretreated with aminoguanidine (10 mg/kg, i.v.). The dose of 1.0 $\mu g\ kg^{-1}\ min^{-1}$ produced a mean rise in CFC of 95% in four experiments (range 70-115%) whereas this dose in the absence of aminoguanidine produced a mean fall in CFC of 70%. As well as a rise in CFC, this dose of histamine after aminoguanidine caused a mean rise in blood flow of 8%, a mean fall in systemic arterial pressure of 4%, and a mean rise in heart rate of 6%. When histamine caused a rise in CFC after aminoguanidine, the peak effect was attained in the first half of the infusion period, thereafter there being a marked recession of the effect such that in 3 preparations the CFC returned to preinfusion values during the continued infusion of histamine (Fig. 3), and in three other preparations the CFC declined, and after the end of the infusion reached a value lower than that found before the start of the infusion. In two out of seven preparations, infusions of histamine after aminoguanidine caused reductions in CFC, though these were smaller than found when the same doses of histamine were infused in the absence of aminoguanidine (Table 6, parts (a) and (c)).

Mepyramine The histamine H_1-receptor blocking drug mepyramine (Black, Duncan, Durant, Ganellin & Parsons, 1972) was injected intravenously in doses of 1.0 or 2.0 mg/kg, to six preparations. There was either a slight rise in systemic arterial pressure of under 5% or no effect, a fall in blood flow of 0-30% (mean 17%) and a mean fall in CFC of 48% (range 25-85%) except in one case where no variable was affected. Histamine was infused in doses of 0.1 to 10.0 $\mu g\ kg^{-1}\ min^{-1}$ after mepyramine in 6 preparations and was without effect (Figure 3). The blockade of the effects of histamine occurred whether the initial effect had been to cause a fall in CFC, or after aminoguanidine, a rise in CFC (3 experiments each).

Burimamide The H_2-receptor blocking drug, burimamide (Black *et al.*, 1972) was injected intravenously in a dose of 5.0 mg/kg to two preparations. This caused a slight increase in blood flow (under 10%) with no effect on blood pressure. In one case the CFC rose by 50% and in the other fell by 60%, but these effects were not maintained for more than 5 minutes. This dose of burimamide did not affect the subsequent response to histamine 1.0 $\mu g\ kg^{-1}\ min^{-1}$ whether the initial effect of histamine had been to cause a rise in CFC after aminoguanidine, or a fall in CFC (1 experiment each).

Adrenoceptor blockade As differential histamine receptor blockade did not differentiate between the actions of histamine in causing both a rise and a fall in CFC, the possibility that one or both of these effects might be due to released catecholamines was considered (Staszewska-Barczak & Vane, 1965; Everett & Mann, 1967; Govindaraj & Kerr, 1968; Nagao, Sato, Nakajima & Kiyomoto, 1971).

Histamine in doses which alone caused reductions in CFC (i.e. 0.1, 1.0 and 10.0 $\mu g\ kg^{-1}\ min^{-1}$), caused rises in CFC after α-adrenoceptor blockade with phentolamine (Table 6d). Histamine, 1.0 $\mu g\ kg^{-1}\ min^{-1}$, in the absence of pretreatment caused a mean fall in CFC of 70%, but after α-adrenoceptor blockade, this dose caused a mean rise in CFC of 63%. After phentolamine, this dose of histamine caused a rise of up to 20% or no effect on blood flow, a fall of up to 35% in mean arterial pressure and variable but slight effects on heart rate.

In two further experiments, histamine was infused in a dose of 1.0 $\mu g\ kg^{-1}\ min^{-1}$ after aminoguanidine, to cause rises in CFC, and these infusions repeated after β-adrenoceptor blockade with 0.1 mg/kg intravenous propranolol. The administration of propranolol did not modify the effects of the subsequent dose of histamine. In the four experiments where histamine was infused after phentolamine, the effects were progressive, peak effects being attained towards the end of the infusions, and in no case was there any sign of a 'post-infusion reaction' of the CFC. In these experiments, the CFC returned to its pre-infusion values within 15 min of the end of the infusion.

Compound 48/80 To compare the effects of released endogenous histamine with those of exogenous histamine, compound 48/80 was infused over 10 min, or injected in divided doses over the same period in doses of 0.1 or 1.0 mg/kg, intravenously. A typical response is shown in Fig. 4.; the CFC initially rose in each of three experiments, in two by 300-350% and in the third by over 1000%, these effects being concomitant with rises in blood flow of 10-25% and no effect on systemic arterial pressure. These initial effects lasted for only about 2 min from the first

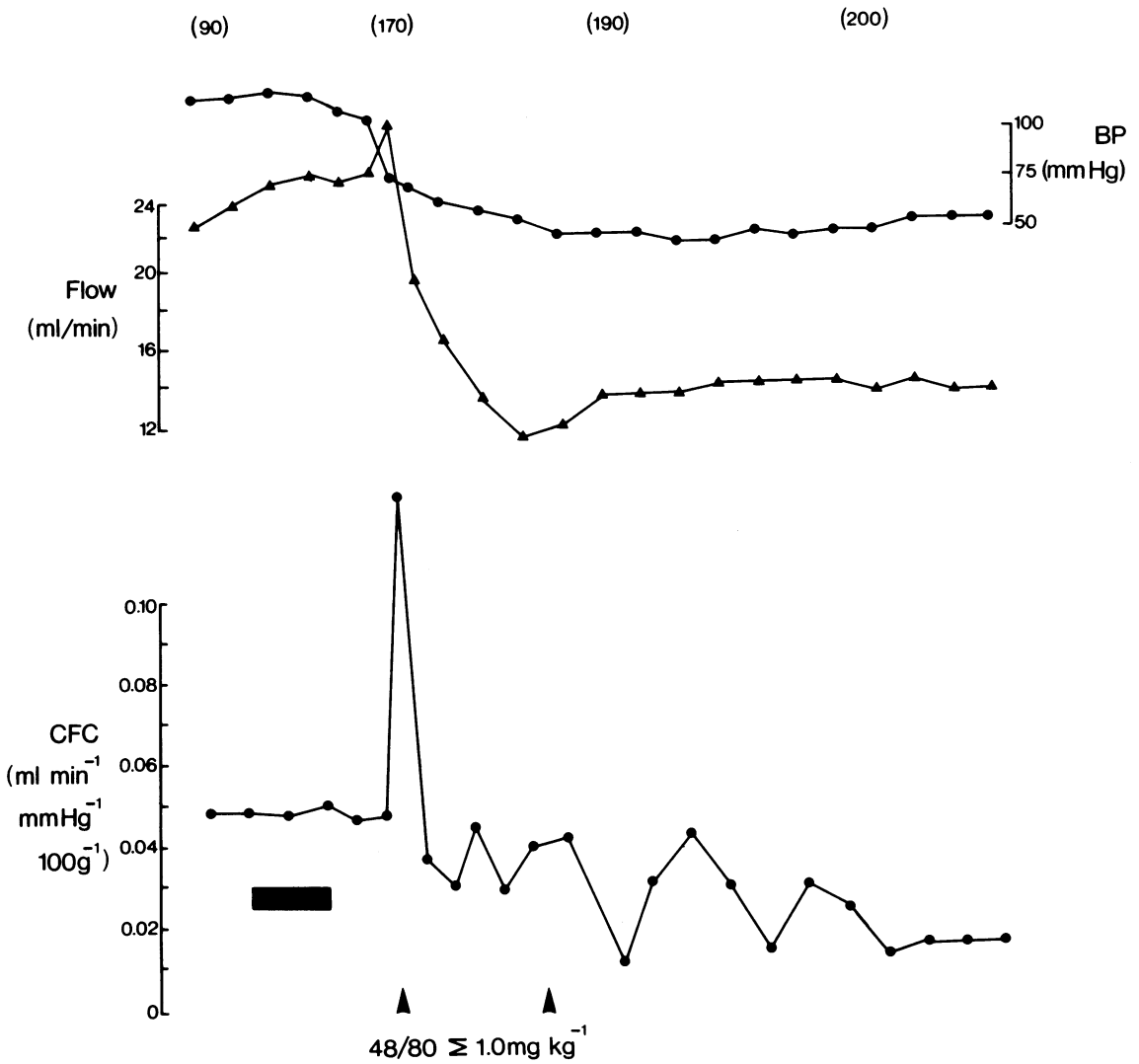

Fig. 4 The effects of Compound 48/80 on the vasculature of the cat jejunum. A total dose of 1 mg/kg was injected in five equal doses between the two arrows. Experiment; cat, female, 3.7 kg. Anaesthetized with halothane and chloralose (70 mg/kg, i.v.).

The black horizontal bar represents 10 min, and the records are from above downwards: mean systemic arterial pressure, blood flow and capillary filtration coefficient. The weight of the loop of jejunum post mortem was 72 g and the figures in parentheses represent the heart rate in beats/minute.

injection, or start of an infusion, and were succeeded by a protracted phase where the CFC was reduced by 40-50%, the blood flow fell by 50-60% and the systemic arterial pressure also fell, by 45-80%. The preparations did not recover from these effects.

5-Hydroxytryptamine

5-Hydroxytryptamine (5-HT) was infused intravenously to five preparations in doses from 5.0 to 50.0 $\mu g\ kg^{-1}\ min^{-1}$ (Table 7). The effect of three intravenous infusions of 50 $\mu g\ kg^{-1}\ min^{-1}$ was to produce a mean fall in CFC of 58% (range 40-70%), a mean rise in blood flow of 15% (from a fall of 10% to a rise of 55%), a fall in systemic arterial pressure of 13% (range 0-35%) and a mean increase in heart rate of 15% (range 0-35%). Effects were rapid in onset, peak effects attained towards the end of the infusions, and recovery was

Table 7 The effects of 5-hydroxytryptamine (5-HT) on the intestinal vasculature of the cat

Experiment	*5-HT* ($\mu g\ kg^{-1}\ min^{-1}$)	*Weight of jejunal loop (g)*	*Change in CFC*	*Change in blood flow*	*Change in BP*	*Change in heart rate*
			(means of control values – peak of drug effects)			
(a) No pretreatment						
40	5.0	60	−30% (0.025-0.017)	no effect (13-13)	no effect (120-120)	no effect (170-170)
2	33	66	−50% (0.014-0.007)	−15% (16-14)	no effect (115-115)	+10% (250-270)
41	50	54	−60% (0.026-0.010)	+55% (14-22)	−35% (150-100)	+35% (180-240)
23	50	63	−45% (0.027-0.015)	no effect (13-13)	−5% (95-90)	+10% (220-240)
14	50	52	−70% (0.022-0.007)	−10% (10-9)	no effect (120-120)	no effect (190-190)
(b) After hexamethonium (5 mg kg^{-1}, i.v.)						
42	5.0	60	−75% (0.025-0.006)	−20% (10-8)	no effect (80-80)	+15% (150-170)
43	50	54	−40% (0.019-0.011)	+10% (9-10)	+10% (70-75)	+55% (130-200)
44	100	65	−65% (0.030-0.010)	−15% (14-12)	+30% (65-85)	+40% (130-180)

complete within 10 min of the end of the infusions.

Rises in heart rate generally occurred when blood pressure fell, and because of the possibility of a baroreceptor reflex being involved, three infusions of 5-HT were performed after hexamethonium (5.0 mg/kg intravenously) (Table 7b). These results do not demonstrate a modification of the effects of 5-HT on this preparation by prior ganglion blockade, and the heart rate rose in each case where 5-HT was infused after hexamethonium.

Methysergide itself caused a transient fall in CFC of 15-30% with concomitant rises in blood pressure of a similar degree. There was no effect on blood flow, and no effect of methysergide persisted for more than 5 min in any of four preparations to which it was injected ($250\ \mu g\ kg^{-1}$, i.v.). Methysergide in this dose blocked the effects of subsequent doses of 5-HT (33 or $50\ \mu g\ kg^{-1}\ min^{-1}$ i.v.), but the effects of these doses of 5-HT survived α-adrenoceptor blockade with phentolamine (2.0 mg/kg) intravenously, without attenuation of their effects.

Discussion

The results of this investigation show that the vascular exchange function in the jejunum of the anaesthetized cat is highly sensitive to the systemic administration of low doses of a range of drugs. Despite dilution of the drugs in the circulation and their possible deactivation in passing through the lungs (Vane, 1969), and despite possible reflex adjustments of sympathetic vasoconstrictor tone, vascular effects of all of the drugs selected for investigation were demonstrable in these preparations.

Capillary filtration coefficient has been shown to be a measurement which is independent of blood flow, perfusion pressure or vascular resistance in these preparations (Richardson, 1974), and the present investigation demonstrates that systemic administration of drugs in low doses may affect the CFC, a measure of the area of exchange vessel open for vascular exchange, without significantly affecting either blood pressure or blood flow through the tissue.

The only study of the effects of baroreceptor and chemoreceptor reflexes on CFC in the small intestine was that of Oberg (1964) in which it was shown that rises in carotid sinus pressure tended to produce rises in CFC, and that falls in carotid sinus pressure produced falls in CFC. The reflex effects of vasopressor drugs in these preparations would therefore be to tend to increase the CFC, and drugs with a hypotensive effect would cause reflex falls in CFC. In the present experiments, 40% oxygen by volume was administered in the

inspired mixture to avoid possible chemoreceptor stimulation.

In general, drugs with a pressor action were found to produce falls in CFC in the present experiments, indicating constriction of precapillary 'sphincters' leading to a reduction in the functional exchange vessel area; conversely, drugs which caused a fall in blood pressure tended to cause rises in CFC. These effects are opposite in direction to the expected reflex effects resulting from baroreceptor reflexes, but whenever changes in heart rate indicated possible involvement of baroreceptor reflexes in these experiments, the drug infusions were repeated after ganglion blockade to assess the likely effect of reflex modulations of sympathetic tone on the effects of the drugs on the CFC.

Folkow *et al.* (1963), found control CFC values in their denervated preparation of the order of 0.17 ml min^{-1} $mmHg^{-1}$ 100 g^{-1} (20 experiments). Haglund & Lundgren (1972) found control CFCs of 0.052 ± 0.004 (mean ± s.e. mean) ml min^{-1} $mmHg^{-1}$ 100 g^{-1}, in 23 experiments. In the 44 experiments of the present series, the mean CFC was 0.030 ± 0.003 ml min^{-1} $mmHg^{-1}$ 100 g^{-1}, under control conditions. The involvement of a small amount (2-5 g) of lymphoid tissue at the base of the mesentery with a CFC of 0.02-0.04 ml min^{-1} $mmHg^{-1}$ 100 g^{-1} (Folkow *et al.*, 1963) is unlikely to affect these control values significantly.

The fact that the CFC was lower in the innervated preparations of the present series, compared with the denervated preparations of earlier work suggests that the preparations were under some degree of sympathetic vasoconstrictor tone. The fact that drugs which reduce or abolish sympathetic tone, such as hexamethonium, phentolamine, trimetaphan and guanethidine all caused rises in CFC and reductions in vascular resistance in preparations of the type used in the present experiments (Richardson, 1973b) supports this possibility.

The effects of systemically administered α- and β-adrenoceptor stimulants are similar to the effects of similar drugs administered close-arterially to denervated preparations (Folkow *et al.*, 1963) and are in accordance with the classification of vascular adrenoceptors by Ahlquist (1948). Uptake and removal of phenylephrine or isoprenaline seems unlikely to be significant in passage through the lungs, and the effect of phenylephrine on heart rate, an increase, is opposite to the expected effect which would result from a baroreceptor reflex arising from increased arterial pressure. The effects on CFC of both drugs were opposite to the effects which would result from changes in systemic arterial pressure (Oberg, 1964), and the lowest dose of isoprenaline caused substantial changes in CFC without affecting blood flow or arterial pressure. These experiments show that phenylephrine causes a rise in vascular resistance and a reduction in CFC, indicating constriction of precapillary resistance vessels and precapillary 'sphincters'; isoprenaline has the opposite effects, dilating both precapillary resistance vessels and precapillary 'sphincters'.

Phentolamine causes a rise in CFC and a fall in vascular resistance, but as well as blocking peripheral α-adrenoceptors, may stimulate central hypotensive centres (Hilliard, Bagwell & Daniell, 1972) and has positive inotropic and chronotropic actions (Gould, Zahir & Shariff, 1971) due either to β-adrenoceptor stimulation (Gould *et al.*, 1971) or to a baroreceptor reflex initiated by the fall in systemic arterial pressure (Zener & Harrison, 1973). Such a baroreceptor reflex would cause a fall in CFC (Oberg, 1964), and so the effect seen in these experiments of a rise in CFC with phentolamine seems likely to be due in part at least to a reduction in sympathetic vasoconstrictor tone.

Propranolol caused a rise in CFC indicating an increase in the functional exchange vessel area due to dilatation of precapillary 'sphincters', without effect on other variables. Since propranolol lacks partial agonist activity (Barrett & Carter, 1970), the most likely explanation of this effect on CFC is a temporary reduction in sympathetic tone resulting from a transient membrane stabilizing effect (Fitzgerald, 1972).

Angiotensin caused a constriction of precapillary resistance vessels and precapillary 'sphincters'; the effect on CFC was apparent after the infusion of 25 ng kg^{-1} min^{-1}, i.v., and since the preparation used was pure angiotensin-II, no activation of the drug on passing through the lungs was possible (Vane, 1969).

Since the effects on CFC were opposite to the expected reflex effects resulting from a rise in systemic arterial pressure (Oberg, 1964), and the effects survived α-adrenoceptor blockade, it seems that the effects seen on intravenous infusion of angiotensin were direct effects of the drug on the jejunal vasculature, and not indirect effects arising from changes in sympathetic vasoconstrictor tone or to released endogenous catecholamines. This is in accordance with the conclusions of Staszewska-Barczak & Vane (1967) and Supek, Uroic, Gjuris & Marijam (1962) that catecholamine-releasing effects of angiotensin do not contribute significantly to the vascular effects of low doses of the drug.

Aminophylline caused a dilatation of precapillary resistance vessels and precapillary 'sphincters' manifest as a fall in vascular resistance and a rise in

CFC. Falls in blood pressure on infusion of aminophylline were accompanied by rises in heart rate, and whilst the mechanism of this effect was not examined, it is possible that reflex enhancement of sympathetic vasoconstrictor tone resulting from the fall in systemic arterial pressure might have reduced the effect of aminophylline on CFC. Similar effects were seen with sodium nitroprusside, another peripheral vasodilator, but one which lacks central nervous system stimulant actions (Richardson, 1973b).

The effects of histamine have not previously been studied on CFC in the intestine. The effects of reductions in vascular resistance were in accordance with previous reports of the effects of histamine on gastric and intestinal vascular beds (Texter, Chou, Merrill, Laureta & Frouch, 1964) and with the possible involvement of histamine in active reflex vasodilatation in other vascular beds (Schayer, 1962; Beck, 1965). Histamine, in the absence of pretreatment, caused a constriction of the precapillary 'sphincters' at low doses (i.e. a fall in CFC) and a dilatation of the precapillary 'sphincters' at higher doses (i.e. a rise in CFC).

A fall in systemic arterial pressure would be expected to result in a reflex fall in CFC (Oberg, 1964), but the falls in CFC observed on infusion of low doses of histamine survived ganglion blockade, as did the rises in heart rate. The increases in heart rate seem likely to be due to stimulation of cardiac H_2-receptors (Black *et al.*, 1972), but in preliminary experiments burimamide did not alter the effects of histamine on CFC in the jejunum.

Histamine increases vascular permeability (Rowley, 1964; Spector & Willoughby, 1968; Clementi & Palade, 1969) and drugs which cause an increase in vascular permeability would be expected to enhance the exudation of fluid from the vasculature resulting from an increased venous pressure, and so to increase the CFC. A possible explanation of the two effects of histamine on CFC is therefore that the direct effect on vascular histamine receptors is to cause a fall in CFC, and that the rise in CFC seen with higher doses (or with small doses after histaminase inhibition) is due to an increase in vascular permeability.

An alternative interpretation is that the direct effect on vascular histamine receptors results in an increased CFC and that the reduction in CFC seen with small doses of histamine results from α-adrenoceptor stimulation by catecholamines released either from the suprarenal medulla (Staszewska-Barczak & Vane, 1965) or from the intestine (Everett & Mann, 1967) by the action of histamine.

The fact that doses of histamine which alone cause falls in CFC, cause rises in CFC after phentolamine strongly suggests that the fall in CFC is due to α-adrenoceptor stimulation. The establishment of this explanation depends on the lack of antihistamine activity of phentolamine: Fleckenstein (1952) demonstrated that phentolamine transiently antagonizes the effects of histamine on the rabbit ear vessels, in contrast to a very prolonged adrenoceptor blocking action. Whilst histamine hypersensitivity in asthmatics is reduced by both phentolamine and phenoxybenzamine (Govindaraj & Kerr, 1968), this effect is thought to be due to α-adrenoceptor blockade in the lungs of asthmatics, and not to blockade of bronchial histamine receptors (Kerr, Govindaraj & Patel, 1971).

Since phentolamine lacks significant antihistamine activity, and since histamine is capable of releasing endogenous catecholamines, the most probable explanation of the effects of histamine on jejunal CFC is that the reduction in vascular exchange function caused by low doses of histamine is the result of α-adrenoceptor stimulation by released endogenous catecholamines, and that the dilatation of precapillary 'sphincters' manifest by a rise in CFC with higher doses is the direct effect of stimulation of histamine H_1-receptors.

This explanation also accords with the observation that in the absence of α-adrenoceptor blockade, rises in CFC produced by histamine (either in large doses, or after histaminase inhibition) do not last for the full duration of the histamine infusion, and after the infusion, the CFC may be reduced to values below the pre-infusion control values.

These observations are incompatible with the explanation that the direct effect is to cause a fall in CFC due to histamine receptor stimulation in the jejunal vasculature, and that the rise is due to increased vascular permeability.

The effects of compound 48/80 accord with the suggested mechanisms of action of histamine in that the brief initial phase where CFC is elevated may well be due to the systemic release of histamine, whilst the subsequent phase from which the preparations did not recover may be related to anaphylactic shock effects.

Both histamine and 5-HT have been implicated in the production of increased vascular permeability (Rowley, 1964), and although this is a common action, the effects of the two drugs on CFC are dissimilar. Although this plethysmographic preparation cannot be used to differentiate between drug effects on precapillary 'sphincters' and on vascular permeability, the effects of the autacoids may be taken as evidence that changes in vascular permeability were not a major influence on the recorded changes in CFC. Furthermore, in

experiments in which histamine and 5-HT were used, there were no continuous increases in the volume of the contents of the plethysmographs, or signs of oedema of the paws, as would be expected if there was a generalized increase in vascular permeability.

Since the effects of 5-HT, of constriction of precapillary 'sphincters' with an overall dilatation of precapillary resistance vessels, were blocked by methysergide, they are characterized as being due to stimulation of 'D' receptors (Gaddum & Picarelli, 1957). The changes in vascular resistance were variable, and although a mean fall was evident, individual experiments leave room for doubt; 5-HT is extensively deactivated in the lungs (Vane, 1969) and this probably accounts for the rather high doses of the drug needed to produce effects on the intestinal vasculature after systemic administration.

In 1934, Anrep, Cerqua & Saaman demonstrated an inverse relationship between intestinal smooth muscle tone and intestinal blood flow, and Sidky & Bean (1956) showed that rhythmic contractions of the intestinal smooth muscle could exert a 'pumping' effect on the blood flow. The possibility therefore arises that effects of drugs on intestinal smooth muscle might affect vascular dimensions; Scott & Dabney (1964) found that in general, higher doses of drugs were needed to elicit changes in intestinal smooth muscle tone than were needed to alter vascular resistance, and in the present investigation, doses were chosen to produce measurable changes in variables measured, but not increased beyond these levels without clear indication. Furthermore, phenylephrine relaxes intestinal smooth muscle, but produced a constrictor effect on precapillary resistance and 'sphincter' vessels, and histamine contracts intestinal smooth muscle, but causes a fall in vascular resistance and a dilatation of the precapillary 'sphincters' manifest as a rise in CFC. This suggests that it is improbable that alterations in intestinal smooth muscle tone significantly affected the measurements of vascular parameters made in the present investigation.

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