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TISSUE BLOOD FLOW AND DISTRIBUTION OF CARDIAC OUTPUT IN CATS: CHANGES CAUSED BY INTRAVENOUS INFUSIONS OF HISTAMINE AND HISTAMINE RECEPTOR AGONISTS

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1 The effects of infusions of histamine on blood pressure, cardiac output, heart rate, total peripheral resistance, stroke volume and tissue blood flow have been determined in anaesthetized cats using radio-active microspheres to measure cardiac output and tissue blood flow.

2 Histamine caused dose-dependent falls in blood pressure and total peripheral resistance over the dose-range 1×10^{-8} to 3.3×10^{-7} mol kg^{-1} min^{-1}. Histamine had no effect on cardiac output, heart rate or stroke volume.

3 Histamine caused vasodilatation in the heart and stomach, with increased blood flow through these organs, and in the small and large intestine where blood flow was maintained despite the falls in arterial blood pressure. Blood flow to the brain, kidneys, liver, adrenal glands, skeletal muscle, spleen and skin was reduced when arterial blood pressure fell. Vascular resistance increased in the skin and spleen, presumably due to reflex vasoconstriction when blood pressure fell.

4 The selective H_1-receptor agonist 2-(2-aminoethyl)pyridine lowered blood pressure and decreased total peripheral resistance but did not change cardiac output, heart rate or stroke volume. 2-(2-Aminoethyl)pyridine caused vasodilatation in the heart, small and large intestine and kidneys. Vascular resistance was increased in the spleen and skin.

5 The selective H_2-receptor agonist 4-methylhistamine also lowered blood pressure and decreased total peripheral resistance but did not change cardiac output, heart rate or stroke volume. 4-Methylhistamine caused vasodilatation in the heart, stomach, small and large intestines and skeletal muscle. Vascular resistance was increased in the skin.

Introduction

Dale and his colleagues (Dale & Laidlaw, 1910; 1919; Dale & Richards 1918) first described the potent depressor activity of histamine. The falls in blood pressure which followed histamine administration were associated with vasodilatation and presumably, a fall in total peripheral resistance. Subsequently, many studies have been made to investigate further the vasodilator properties of histamine, and vasodilatation has been studied after intra-arterial injection of histamine in many tissues including skeletal muscle (Haddy, 1960; Kjellmer & Odelram, 1965; Flynn & Owen, 1975), intestine (Lee, 1957, Flynn & Owen, 1975), kidney (Sinclair, Bell & Keyl, 1974) and the internal and external carotid beds (Tindall & Greenfield, 1973; Saxena, 1975).

In contrast, little is known about the effects of intravenous histamine on cardiac output and its distribution. Large doses of histamine, adequate to induce circulatory collapse, have been reported to decrease cardiac output (Blalock & Levy, 1937) whereas smaller doses may increase cardiac output (Delaunois, Kordecki, Polet & Ryzewski, 1959; Tucker, Weir, Reeves & Grover, 1975).

We have measured the effects of a range of doses of histamine, given by intravenous infusion, on blood pressure, cardiac output, total peripheral resistance and tissue blood flow. We have also taken the opportunity to compare the effects of histamine with those of a relatively selective histamine H_1-receptor agonist, 2-(2-aminoethyl)pyridine (Durant, Ganellin & Parsons, 1975) and a relatively selective histamine H_2-receptor agonist, 4-methylhistamine (Black, Duncan, Durant, Ganellin & Parsons, 1972). A preliminary account of part of this work has been presented to the British Pharmacological Society (Johnston & Owen, 1975).

Methods

Simultaneous measurements of cardiac output and blood flow to major organs can be achieved by use of radio-active microspheres. The principles and validation of the technique have been described in detail elsewhere (for example Rudolph & Heymann, 1967; Neutze, Wyler & Rudolph 1968; Wagner, Rhodes, Sasaki & Ryan, 1969; Warren & Ledingham, 1974; Johnston, 1975).

Cats of either sex (weight 1.2–4.0 kg) were anaesthetized by an intraperitoneal injection of chloralose, 60 mg/kg, and urethane, 700 mg/kg. The trachea was cannulated. Blood pressure was measured from the right brachial artery with a Statham P23A blood pressure transducer and monitored on a Devices M2 electronic recorder. Heart rate was measured from the blood pressure trace. A catheter was placed in the left ventricle of the heart via the right carotid artery to allow injection of microspheres into the heart. A second catheter was tied into the right femoral artery for withdrawal of blood at a known rate (5 ml/min) during the injection of microspheres.

Ten minutes after completion of the surgical procedures, when blood pressure and heart rate were stable, approximately 100,000 ^{46}Sc-labelled microspheres (25 μm diameter, 3M Company, Loughborough) were injected into the heart in order to measure resting cardiac output and tissue blood flows. Subsequently, intravenous infusions of 0.9% w/v NaCl solution (saline) (control experiments), histamine, 2-(2-aminoethyl)pyridine or 4-methylhistamine were given at a rate of 0.2 ml/minute. Thirty minutes later, and with the infusion still running, cardiac output and tissue blood flows were again measured with ^{85}Sr-labelled microspheres. The animal was then killed by an overdose of sodium pentobarbitone and the organs of interest dissected out, weighed and their radioactivity measured in a Nuclear Enterprises 8312 Detector. The total radioactivity was measured in all organs except skin and skeletal muscle. Samples of skin were taken from the hindquarters and skeletal muscle from the abdominal wall and the left leg. Control experiments were done in 8 cats; 6 cats per group were used for each dose of histamine and the histamine-like agonists.

In all experiments the radioactivity in the lungs was determined. The mean proportion of microspheres in the lungs was 4.68 ± 0.4% ($n = 30$). This would include nutritional flow to the tissue and any microspheres which did not trap in the first capillary bed downstream from the site of injection. The low proportion of microspheres trapped in the lung indicates little shunting of blood through non-capillary beds in the peripheral circulation. In one cat the proportion of microspheres found in the lung exceeded 30%. Data from this animal have not been included.

The homogeneity of distribution of microspheres is indicated by the close correlation between blood flows to the right and left kidneys ($r = 0.96$, $n = 30$).

Calculations

Cardiac output was calculated in ml/min from the number of microspheres in the blood withdrawn from the femoral artery at 5 ml/minute. Tissue blood flows were calculated from knowledge of cardiac output and the distribution of microspheres to tissues. Details of the calculations have been described by Johnston (1975).

Tissue blood flows were calculated in ml min^{-1} $100g^{-1}$ to provide values of flow per unit weight.

Tissue vascular resistance was calculated by dividing mean arterial blood pressure, mmHg, by tissue blood flow, ml min^{-1} $100g^{-1}$.

Values shown are mean ± s.e. mean. Significant changes in any parameter between control values and values measured during treatment periods were determined using a paired Student's t test. Comparisons across groups were made using an unpaired Student's t test.

Drugs

Histamine acid phosphate (BDH), 2-(2-aminoethyl)pyridine dihydrochloride and 4-methylhistamine dihydrochloride were prepared as solutions in saline.

Results

Tissue blood flow and distribution of cardiac output in cats

The mean values of tissue blood flows and the distribution of cardiac output to tissues are shown in Table 1. The blood flow to the liver exceeds the flow to any other single organ and accounts for about 20% of the total cardiac output. Blood flow per unit weight was greatest in the adrenal glands, kidneys and heart although the adrenal glands are so small that they take only 0.5% of cardiac output despite their high flow per unit weight.

Effect of intravenous infusions of saline

In eight control experiments the effects of a 30 min infusion of saline were determined. There were no changes in blood pressure or heart rate but a significant fall in cardiac output due to a fall in stroke volume. The fall in cardiac output with unchanged blood pressure led to a significant increase in calculated total peripheral resistance (Figure 1).

Blood flows to the brain, heart, kidneys and liver were well maintained with small falls in blood flow to

the stomach, skin and intestines. In the small intestine, blood flow fell from 44.9 ± 7.0 to 34.8 ± 4.3 ml min^{-1} $100g^{-1}$. This fall was statistically significant ($P < 0.05$). Blood flow values during saline infusion are shown in Table 2. There were no significant changes in calculated tissue vascular resistance.

Effect of intravenous infusions of histamine

Intravenous infusions of histamine caused dose-dependent falls in blood pressure and total peripheral resistance. The falls in blood pressure were statistically significant over the histamine dose range 3.3×10^{-7} to 3.3×10^{-8} mol kg^{-1} min^{-1}. The falls in total peripheral resistance were significant at 1 and 3.3×10^{-7} mol kg^{-1} min^{-1}. Stroke volume and hence cardiac output were reduced at all histamine infusion rates but the reductions were similar to those in the saline-treated group. Heart rate was unchanged by histamine infusions. These changes are shown in Figure 1.

The effects of histamine on regional blood flow varied substantially from tissue to tissue and are summarized in Table 2. The calculated changes in vascular resistance associated with these flow changes are summarized in Table 3. The proportion of microspheres in the lungs was not significantly changed by any infusion rate of histamine. This would indicate that the proportion of microspheres not trapped in capillary beds but able to shunt through larger vessels was not changed by histamine.

Histamine significantly increased coronary blood flow and decreased coronary vascular resistance at all histamine infusion rates. Coronary vasodilatation was the only significant response to histamine observed at the lowest infusion rate. The maximum increase in coronary blood flow during infusions of histamine was approximately 2-fold, the maximum fall in vascular resistance was 76%.

Histamine also increased blood flow to the stomach and decreased gastric vascular resistance. These responses to histamine showed poor dose-dependence, significant changes in both parameters occurring only at the two higher histamine dose-levels. The maximum increase in gastric blood flow, during histamine infusions at 1×10^{-7} mol kg^{-1} min^{-1}, was almost 4-fold, the maximum fall in vascular resistance was 86%.

Histamine significantly increased renal blood flow during infusions at 3.3×10^{-8} mol kg^{-1} min^{-1} and significantly decreased renal blood flow during infusions at 1 and 3.3×10^{-7} mol kg^{-1} min^{-1}. Renal vascular resistance was significantly reduced during infusions at 3.3×10^{-8} mol kg^{-1} min^{-1}.

Blood flow to the brain, liver and adrenal glands was not changed at the lower histamine infusion rates but significantly reduced at 1 and 3.3×10^{-7} mol kg^{-1} min^{-1}. Vascular resistance in these tissues was not significantly altered by histamine and the reduced blood flow at the higher infusion rates reflected the falls in mean arterial blood pressure at these higher histamine doses.

Blood flow to skeletal muscle tended to be reduced during infusion of histamine although none of the changes was statistically significant. Skeletal muscle vascular resistance was not significantly changed during infusion of histamine.

Skin blood flow was significantly reduced during infusion of histamine 3.3×10^{-8} to 3.3×10^{-7} kg^{-1} min^{-1}, the maximum reduction exceeding 80%. Skin vascular resistance was significantly increased during infusion at 1 and 3.3×10^{-7} mol kg^{-1} min^{-1}, the maximum increase exceeding 4-fold. Histamine also significantly reduced splenic blood flow (maximum decrease 90%) and increased splenic vascular resistance (maximum increase 7-fold) during infusion at 1 and 3.3×10^{-7} mol kg^{-1} min^{-1}.

Blood flow to the small and large intestine was essentially unchanged by histamine. Blood flow to the

Table 1 Tissue blood flow in anaesthetized cats ($n = 30$)

Tissue	*Blood flow (ml/min)*	*(ml min^{-1} 100 g^{-1})*	*% cardiac output*
Brain	17.9 ± 0.9	66.3 ± 3.1	5.4 ± 0.3
Heart	22.8 ± 1.1	306.1 ± 14.9	6.7 ± 0.3
Kidneys	40.0 ± 2.4	326.6 ± 14.9	14.4 ± 0.9
Stomach	4.9 ± 0.7	33.2 ± 4.5	1.4 ± 0.2
Gastric mucosa	3.2 ± 0.4	59.2 ± 10.3	0.9 ± 0.1
Small intestine	37.8 ± 3.4	50.8 ± 4.0	10.4 ± 0.6
Large intestine	12.4 ± 1.1	68.5 ± 5.8	3.5 ± 0.3
Liver**	69.8 ± 6.2	109.2 ± 9.9	20.2 ± 1.4
Adrenal glands	1.6 ± 0.1	477.4 ± 34.6	0.5 ± 0.03
Spleen	10.8 ± 1.5	206.9 ± 25.0	2.9 ± 0.3
Skeletal muscle	–	4.1 ± 0.3	–
Skin	–	5.3 ± 0.5	–

* Arterial blood flow only.

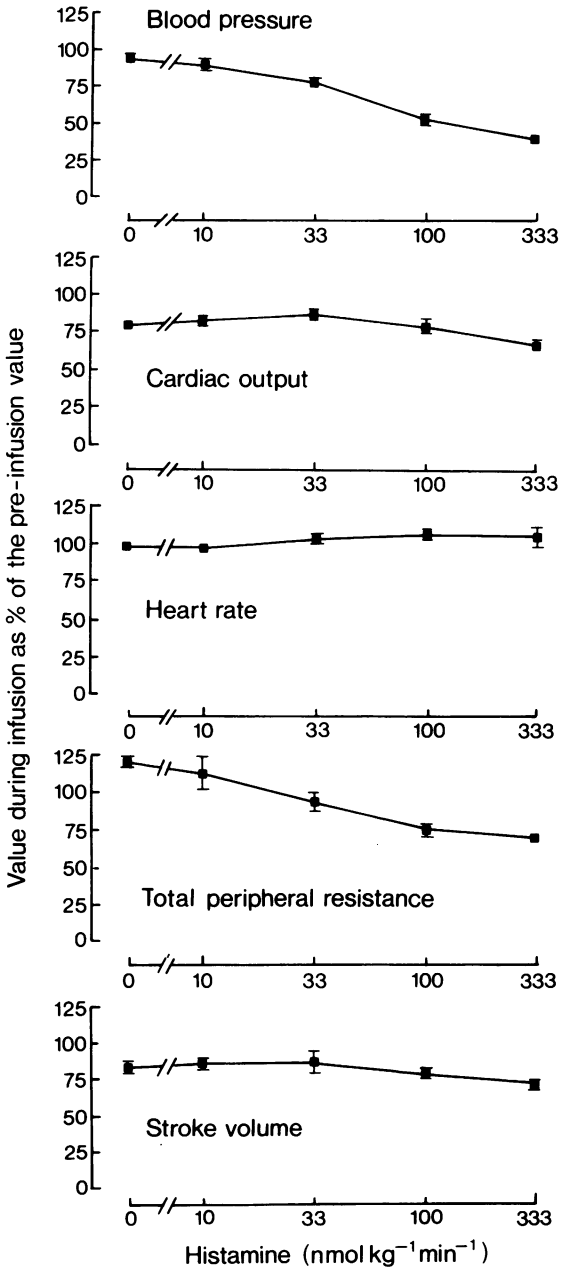

Figure 1 Anaesthetized cats. Comparison of the effects of histamine with the effects of saline (shown as 'O') on blood pressure, cardiac output, heart rate, total peripheral resistance and stroke volume. Values during infusions are expressed as a % of the pre-infusion control value. Vertical lines show s.e. mean. Histamine caused dose-dependent decreases in blood pressure and total peripheral resistance but did not change heart rate. Cardiac output and stroke volume fell in all groups including the group infused with saline.

intestine tended to fall during infusions of saline and similar falls occurred during the infusion of histamine 1 and 3.3×10^{-8} mol kg^{-1} min^{-1} whereas at the higher histamine infusion rates blood flow to the intestine was unchanged. Histamine significantly reduced intestinal vascular resistance during infusion at 1 and 3.3×10^{-7} mol kg^{-1} min^{-1}.

The changes in tissue blood flow were sufficient to cause a redistribution of cardiac output. Blood flow to the heart increased from $7.9 \pm 0.7\%$ in saline-treated cats to $23.1 \pm 1.1\%$ during infusion of histamine, 1×10^{-7} mol kg^{-1} min^{-1}. There was also a significant increase in distribution of cardiac output to the stomach; the proportions of cardiac output distributed to the brain, kidneys, liver, spleen and adrenal glands were reduced. These changes are shown in Table 2.

Effect of intravenous infusions of 2-(2-aminoethyl)pyridine

2-(2-Aminoethyl)pyridine, 1×10^{-6} mol kg^{-1} min^{-1} caused a significant fall in blood pressure and total peripheral resistance. Mean blood pressure fell from 142.0 ± 2.2 mmHg before the infusion to 104.0 ± 4.0 mmHg during the infusion; mean total peripheral resistance fell from 0.31 ± 0.02 units before the infusion to 0.25 ± 0.02 units during the infusion. 2-(2-Aminoethyl)pyridine did not change cardiac output, heart rate or stroke volume significantly. These changes and the changes in tissue blood flow due to 2-(aminoethyl)pyridine are shown in Table 4. 2-(2-Aminoethyl)pyridine did not significantly increase blood flow in any tissue but significantly decreased flow to the brain, liver, spleen and skin. These tissue blood flows were associated with significant decreases in vascular resistance in the heart (41%) kidneys (43%) large intestine (47%) and small intestine (57%). 2-(2-Aminoethyl)pyridine significantly increased resistance in the spleen (29%) and skin (124%). There was no change in resistance in the brain, stomach adrenal glands, skeletal muscle or liver.

Effect of intravenous infusions of 4-methylhistamine

4-Methylhistamine, 1×10^{-6} mol kg^{-1} min^{-1} lowered arterial blood pressure from a mean value of 110.6 ± 12.9 mmHg before the infusion to 46.4 ± 4.1 mmHg during infusion. The fall in blood pressure was due to a large significant fall in total peripheral resistance from 0.28 ± 0.03 units before the infusion to 0.13 ± 0.01 units during infusions. Heart rate, cardiac output and stroke volume were not significantly changed by 4-methylhistamine. These changes and the changes in tissue blood flow due to 4-methylhistamine are shown in Table 4.

Despite the very large fall in blood pressure during infusion of 4-methylhistamine, significant increases in blood flow occurred in the heart, stomach, and large intestine, blood flow to the small intestine was

Table 2 The effect of histamine on blood flow and proportion of cardiac output to tissues (blood flow ml min^{-1} 100 g^{-1}, cardiac output % of total)

	Histamine infusion rate mol kg^{-1} min^{-1}				
Tissue	0	1×10^{-8}	3.3×10^{-8}	1×10^{-7}	3.3×10^{-7}
Brain	63.1 ± 6.0	72.2 ± 5.7	66.5 ± 10.2	40.6 ± 4.6*	31.6 ± 0.8*
	(7.6 ± 0.8)	(7.6 ± 1.0)	(4.7 ± 0.9)*	(5.1 ± 0.9)*	(3.0 ± 0.3)*
Heart	281.3 ± 32.2	361.5 ± 43.0*	593.6 ± 61.5*	657.4 ± 53.1*	610.3 ± 109.2*
	(7.9 ± 0.7)	(10.5 ± 1.3)	(12.7 ± 1.5)*	(23.1 ± 1.1)*	(17.3 ± 2.4)*
Kidneys	374.1 ± 28.3	359 ± 42.8	409.1 ± 37.6*	239.1 ± 23.3*	220.1 ± 56.7*
	(21.9 ± 1.5)	(18.1 ± 1.5)	(18.3 ± 3.1)	(14.0 ± 2.1)*	(11.4 ± 2.6)*
Stomach	17.3 ± 2.2	22.9 ± 3.2	40.1 ± 6.4	94.4 ± 18.5*	64.5 ± 13.8*
	(1.2 ± 0.2)	(1.3 ± 0.1)	(1.6 ± 0.2)	(5.5 ± 1.4)*	(4.2 ± 0.6)*
Small intestine	34.8 ± 4.3*	35.3 ± 3.0	44.5 ± r.9	37.1 ± 10.5	56.3 ± 16.2
	(9.7 ± 1.0)	(9.0 ± 0.6)	(9.2 ± 0.8)	(11.2 ± 3.0)	(15.6 ± 4.2)
Large intestine	50.6 ± 8.9	57.6 ± 5.6	69.1 ± 10.7	54.0 ± 11.6	116.8 ± 20.9
	(3.1 ± 0.5)	(3.8 ± 0.4)	(3.5 ± 0.5)	(4.1 ± 0.9)	(8.3 ± 2.3)*
Liver	97.1 ± 8.2	109.8 ± 14.4	125.6 ± 25.7	54.3 ± 4.4*	42.2 ± 8.8*
	(23.8 ± 2.8)	(25.6 ± 5.0)	(23.2 ± 3.2)	(14.5 ± 2.0)*	(12.3 ± 2.0)*
Spleen	198.4 ± 71.4	130.4 ± 53.5	277.9 ± 94.5	32.9 ± 8.1*	12.1 ± 4.3*
	(3.2 ± 0.9)	(2.0 ± 0.8)	(4.2 ± 1.2)	(0.6 ± 0.2)*	(0.3 ± 0.1)*
Adrenal glands	469.4 ± 81.8	444.0 ± 62.7	546.8 ± 109.3	382 ± 54.3*	109.3 ± 52.2*
	(0.7 ± 0.1)	(0.6 ± 0.1)	(0.5 ± 0.1)	(0.5 ± 0.1)	(0.3 ± 0.1)
Skeletal muscle	4.4 ± 0.8	3.9 ± 0.8	3.7 ± 1.0	2.8 ± 0.3	2.0 ± 0.4
Skin	3.5 ± 0.6	4.8 ± 0.3	3.1 ± 0.7*	1.4 ± 0.2*	0.8 ± 0.2*

The values in parentheses are the percentage cardiac output distributed to each tissue.
All values shown are those measured during the infusions of saline (shown as 0) or histamine. Statistical analysis of significant changes within each group was made by a paired *t* test on values before and during the infusion.
* Significantly different from the pre-infusion values, $P < 0.05$.

Table 3 Effect of histamine on tissue vascular resistance (mmHg ml^{-1} min^{-1} 100 g^{-1})

	Histamine infusion rate mol kg^{-1} min^{-1}				
Tissue	0	1×10^{-8}	3.3×10^{-8}	1×10^{-7}	3.3×10^{-7}
Brain	1.86 ± 0.14	1.68 ± 0.4	1.92 ± 0.36	1.77 ± 0.25	2.01 ± 0.10
Heart	0.40 ± 0.05	0.35 ± 0.04*	0.19 ± 0.02*	0.11 ± 0.01*	0.12 ± 0.02*
Kidneys	0.30 ± 0.04	0.41 ± 0.06	0.28 ± 0.03*	0.29 ± 0.03	0.39 ± 0.15
Stomach	7.33 ± 1.08	5.67 ± 0.76	3.12 ± 0.50	0.83 ± 0.15*	0.98 ± 0.23*
Small intestine	3.69 ± 056	3.53 ± 0.45	2.63 ± 0.30	2.22 ± 0.33	1.45 ± 0.41*
Large intestine	2.77 ± 0.56	2.20 ± 0.34	1.83 ± 0.36	1.52 ± 0.28*	0.59 ± 0.10*
Liver	1.23 ± 0.15	1.17 ± 0.15	1.02 ± 0.14	1.40 ± 0.15	1.52 ± 0.33
Spleen	1.80 ± 0.94	1.39 ± 0.26	0.65 ± 0.20	3.08 ± 0.91*	8.09 ± 2.9*
Adrenal glands	0.33 ± 0.09	0.30 ± 0.04	0.33 ± 0.14	0.19 ± 0.03	0.40 ± 0.09
Skeletal muscle	34.2 ± 7.31	37.0 ± 5.0	49.9 ± 12.52	25.3 ± 2.26	34.9 ± 4.34
Skin	49.1 ± 17.61	27.6 ± 3.77	60.4 ± 23.11	57.0 ± 11.0	138.55 ± 74.7*

All values shown are those measured during the infusions of saline (shown as 0) or histamine. Statistical analysis of significant changes within each group was made by a paired *t* test on values before and during the infusion.
* Significantly different from the pre-infusion values $P < 0.05$.

unchanged and flow to all other tissues was reduced, particularly to the liver, spleen and skin. 4-Methylhistamine caused significant decreases in resistance in the heart (by 74%), the stomach (89%), the small intestine (73%), the large intestine (77%) and skeletal muscle (49%). Resistance was not significantly changed in the brain, kidneys, liver, adrenal glands and skin but was significantly increased in the spleen (860%).

Discussion

The depressor and vasodilator properties of histamine were first described in 1910 by Dale & Laidlaw. Although peripheral vasodilatation would inevitably contribute to the depressor responses to intravenous histamine, little is known about the possible contribution of changes in cardiac output.

Prior to our study it was reported that large doses of histamine decreased cardiac output during periods of histamine-induced circulatory collapse in dogs (Blalock & Levy, 1937). Smaller doses of histamine may cause modest and only transient increases in cardiac output (Delaunois *et al.*, 1959; Tucker *et al.*, 1975). In our experiments there was no evidence that histamine infusions, covering a dose range from 1×10^{-8} to 3.3×10^{-7} mol kg^{-1} min^{-1} had any significant effect on cardiac output. The doses used ranged from one almost without effect on blood pressure to the maximum infusion rate the cats could survive. In each case cardiac output fell slightly during the infusion but a fall of similar magnitude also occurred during infusions of saline. The sustained plateau fall in blood pressure caused by continuous intravenous infusions of histamine therefore appears to be independent of changes in cardiac output, and is due to a fall in total peripheral resistance. The measurement of cardiac output in these experiments was made after 30 min of infusion. At this time blood pressure was constant and any transient changes in cardiac output during the period before the blood pressure became constant would not have been observed.

Although the depressor response to histamine was due to peripheral vasodilatation it was clear that dilatation was not uniform in all tissues. Vasodilatation occurred in the heart at all infusion rates, the kidneys at 3.3×10^{-8} mol kg^{-1} min^{-1}, the large intestine and stomach at 1 and 3.3×10^{-7} mol kg^{-1} min^{-1} and in the small intestine at 3.3×10^{-7} mol kg^{-1} min^{-1}. The dilatation was sufficient to permit increased blood flow to the heart and stomach and to maintain intestinal blood flow despite the lowered mean arterial blood pressure. Blood flow to the kidney was also increased during infusion at 3.3×10^{-7} mol kg^{-1} min^{-1}.

No vasodilatation occurred in the brain, liver,

Table 4 Effect of infusions of 2-(2-aminoethyl)pyridine (1×10^{-6} mol kg^{-1} min^{-1}) and 4-methyl histamine 1×10^{-6} mol kg^{-1} min^{-1}) on blood pressure, heart rate, cardiac output, stroke volume, total peripheral resistance and tissue blood flow

	2-(2-Aminoethyl)pyridine		*4-Methyl histamine*	
	Pre-infusion	*During infusion*	*Pre-infusion*	*During infusion*
Blood pressure (mmHg)	142.0 ± 2.2	104.0 ± 4.0*	110.6 ± 12.9	46.4 ± 4.1*
Heart rate (beats/min)	247.0 ± 10.5	255.0 ± 24.3	228.0 ± 14.9	238.0 ± 20.0
Cardiac output (ml/min)	472.6 ± 37.5	436.7 ± 33.6	400.8 ± 50.9	345.8 ± 14.4*
Stroke volume (ml)	1.77 ± 0.24	1.65 ± 0.35	1.77 ± 0.23	1.49 ± 0.13*
Total peripheral resistance (mmHg ml^{-1} min^{-1})	0.31 ± 0.02	0.25 ± 0.02*	0.28 ± 0.03	0.13 ± 0.01*
Tissue blood flow (ml min^{-1} 100 g^{-1})				
Brain	58.5 ± 4.4	43.5 ± 5.9*	69.1 ± 9.4	27.4 ± 4.9*
Heart	420.7 ± 53.9	517.4 ± 86.2	266.0 ± 46.0	404.4 ± 46.0*
Kidneys	346.5 ± 31.9	452.9 ± 32.4	357.1 ± 37.0	168.2 ± 24.0*
Stomach	36.3 ± 5.1	25.1 ± 1.5	38.1 ± 16.1	94.2 ± 8.4*
Small intestine	55.4 ± 9.1	58.3 ± 7.9	49.4 ± 11.4	67.6 ± 10.2
Large intestine	90.7 ± 20.4	112.9 ± 18.4	81.5 ± 14.3	138.4 ± 7.2*
Liver	137.8 ± 43.8	97.2 ± 25.8*	67.5 ± 6.9	19.9 ± 4.4*
Spleen	324.3 ± 48.1	78.1 ± 21.1*	217.4 ± 31.7	26.1 ± 9.4*
Adrenal glands	678.6 ± 231.8	630.7 ± 145.6	525.1 ± 130.7	215.6 ± 85.2*
Skeletal muscle	3.8 ± 0.6	3.7 ± 0.7	3.8 ± 0.9	2.6 ± 0.5
Skin	4.4 ± 0.9	1.5 ± 0.3*	5.8 ± 1.9	1.6 ± 0.2*

* Significantly different from the pre-infusion values $P < 0.05$.

adrenal glands or skeletal muscle at any dose level and vasoconstriction occurred in the spleen and skin at the two higher histamine infusion rates.

Histamine-induced vasodilatation in the heart has been described previously, usually in *in vitro* preparations (see review by Rocha e Silva, 1966), although Parratt (1969) also reported that intravenous injections of histamine increased coronary blood flow in anaesthetized monkeys. In our experiments coronary vasodilatation was dose-dependent and could be detected during all infusions of histamine. Coronary vasodilatation was the only significant histamine-induced change detected at the lowest histamine infusion rate. Histamine infusions lowered blood pressure with no change in cardiac output, and so decreased cardiac work. It seems likely that the coronary vasodilatation caused by histamine was due to a direct effect on the coronary circulation rather than a metabolic response to increased cardiac work.

Histamine-induced increases in gastric blood flow, usually during periods of histamine-induced acid secretion, are well documented (e.g. Harper, Reed & Smy, 1968; Jacobsen & Chang, 1969). The doses of histamine used in this study are known to stimulate acid secretion in cats (Harper *et al.*, 1968; Parsons, personal communication) and it is reasonable to assume that acid secretion was increased during the larger infusions used in these experiments. The histamine-induced vasodilatation might, therefore, have been due to a direct effect on the gastric vasculature or metabolic response to the increased gastric work during acid secretion.

In the kidneys, histamine appeared to cause some vasodilatation when blood pressure was only slightly reduced. The dilatation was less at higher infusion rates, and renal blood flow decreased. The kidneys play a major role in the reflex control of systemic blood pressure and many vasodilator compounds cause an increased secretion of renin from the kidney (e.g. Pettinger, Campbell & Keeton, 1973). Renin release may well occur during the sustained hypotensive response to histamine. The renal vascular response to histamine might reflect a complex balance between histamine-induced vasodilatation and renin/angiotensin-induced vasoconstriction.

Histamine dilates intestinal resistance vessels after intra-arterial administration (Lee, 1957; Flynn & Owen, 1975). In these experiments vasodilatation could be detected during intravenous infusions of histamine. The dilatation was less marked than in the heart or stomach but adequate to maintain flow during histamine-induced hypotension. Similar results were recently reported by Krarup (1975) using flow probes to measure intestinal blood flow.

Histamine had no effect on vascular resistance in the brain, liver, adrenal glands and skeletal muscle, and blood flow fell as blood pressure fell. Although there were no significant changes in hepatic vascular resistance, there was a tendency for resistance to increase during the larger infusions of histamine. Krarup (1975) recently reported significant increases in hepatic vascular resistance during intravenous infusions of histamine.

Histamine increased vascular resistance in the spleen and skin. These increases occurred during infusions of histamine which lowered mean arterial blood pressure. Sympathetic stimulation is particularly effective in causing vasoconstriction in these organs. The increase in vascular resistance in the spleen and skin is probably part of the homeostatic reflex mechanisms initiated by the fall in mean blood pressure.

Both 2-(2-aminoethyl)pyridine, a histamine H_1-receptor agonist (Durant *et al.*, 1975) and 4-methylhistamine, a histamine H_2-receptor agonist (Black *et al.*, 1972) lowered blood pressure and decreased total peripheral resistance. Both compounds tended to reduce cardiac output but the change was similar to the change during saline infusions. The depressor response seems therefore to be due entirely to peripheral vasodilatation. 2-(2-Aminoethyl)pyridine did not significantly increase blood flow to any tissue although vascular resistance was decreased in the heart, kidneys and small and large intestines but increased in the spleen and skin. 4-Methylhistamine reduced vascular resistance in the heart, stomach and small and large intestines, and increased resistance in the spleen and skin. The coronary and intestinal vasodilatation during histamine infusions was qualitatively mimicked by both histamine receptor agonists whereas vasodilatation in the stomach was mimicked only by 4-methylhistamine.

These results suggest that both histamine H_1- and H_2-receptors are present in the coronary and intestinal vasculature and both can mediate vasodilatation. In contrast, vasodilatation in the stomach, whether a direct vascular effect or a metabolic response to acid secretion, appears to be an H_2-receptor phenomenon.

Vasoconstriction in the spleen and skin was caused by both agonists and is probably part of the reflex response to the hypotension caused by each agonist.

2-(2-Aminoethyl)pyridine caused renal vasodilatation whereas 4-methylhistamine did not. The renal vascular response to histamine was complex and was probably due to a balance between the direct vasodilator effects of histamine and indirect reflex effects associated with the hypotension. Meaningful comparison of the two agonists would therefore require similar falls in blood pressure. The apparent different effects of the agonists on renal vasculature may not reflect different direct effects on the vascular bed.

In conclusion, it has been shown that the sustained fall in blood pressure during infusion of histamine is due to peripheral vasodilatation. This occurs predominantly in the heart, stomach and intestine; there

is no vasodilatation in the brain, liver, adrenal glands or skeletal muscle. The selective histamine receptor agonists, 2-(2-aminoethyl)pyridine and 4-methylhistamine also lower blood pressure by causing peripheral vasodilatation.

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