An investigation of the mechanisms responsible for a reduction in capillary filtration coefficient in the innervated cat jejunum on intravenous infusion of histamine

Previous investigations have shown that large doses of histamine infused intravenously (40 μg kg^{-1} min^{-1}) or smaller doses (0·1–10·0 μg kg^{-1} min^{-1}) infused intravenously after histaminase inhibition cause an increase in capillary filtration coefficient (CFC) in the sympathetically innervated cat jejunum. In contrast, small doses of histamine alone (0·01–10·0 μg kg^{-1} min^{-1}) cause a reduction in CFC in this tissue (Richardson, 1973, 1974).

This reduction in CFC on intravenous infusion of histamine is reversed to an increase by phentolamine in doses found adequate to block the effects of exogenous α-adrenoceptor stimulants (Richardson, 1974).

Changes in CFC are interpretable as (i) changes in functional exchange vessel area, due to constriction or dilatation of precapillary 'sphincters', and (ii) changes in vascular permeability (Folkow, Lundgren & Wallentin, 1963; Mellander & Johansson, 1968). In addition, in the sympathetically-innervated jejunum, indirect changes in CFC due to intravenous infusions of histamine may arise from: (iii) release of suprarenal medullary catecholamines, (iv) release of catecholamines from the sympathetic nerve endings in the tissue, (v) stimulation of sympathetic ganglia, (vi) reflex modulations in sympathetic vasoconstrictor tone, and (vii) variations in the tone of the intestinal smooth muscle resulting in varying compression of the vasculature. The relative importance of these mechanisms in causing a fall in CFC when histamine is infused intravenously is assessed in the present investigation.

The method used was a modification (Richardson, 1974) of the technique of Folkow & others (1963): cats were anaesthetized with chloralose (70 mg kg^{-1}, i.v.) after induction with halothane; phasic systemic arterial pressure was measured from a cannulated femoral artery with a Statham P23Gb transducer, and mean pressure and heart rate derived electronically. The animals breathed spontaneously throughout.

Loops of jejunum (mean 58 s.d. 12 g) were isolated apart from their connexions by the superior mesenteric artery and periarterial nerves. The superior mesenteric vein (SMV) was cannulated and blood flow measured with a cannulating flow probe and electromagnetic flowmeter (Cardio Vascular Instruments); the outlet from the SMV was open and the superior mesenteric venous pressure (SMVP) controlled by raising and lowering this outlet. The jejunum was placed in a plethysmograph and volume changes recorded continuously (Richardson, 1974). CFC was measured as the slow, continuous increase in volume resulting from the imposition of a 10 cm H_2O increase in SMVP for 1 min (Folkow & others, 1963).

Histamine acid phosphate (BDH) was infused intravenously for 15 min periods; a dose of 1·0 μg kg^{-1} min^{-1} was selected on the basis of previous findings (Richardson, 1974) to four groups of animals: Group A, in which the periarterial nerves and suprarenal glands were intact; Group B, in which the periarterial nerves were acutely divided; Group C, in which the suprarenal glands were acutely extirpated; and Group D in which CFC was not measured, but a small balloon inserted into the lumen of the jejunum, inflated to a pressure of 5 cm H_2O, and changes in intralumenal pressure monitored with a Statham P23V pressure transducer as an index of intestinal smooth muscle tone.

Variables are expressed as means $\pm$ s.e. means, and the significance of changes in variables assessed using Student's *t*-test, for paired data.

Control values, and values obtained during the intravenous infusion of histamine are shown in Table 1; in each experiment at least four, and usually five determinations of CFC were made before and during histamine infusions. Under control conditions,

the blood flow and the CFC were higher than in artificially-ventilated cats (Richardson, 1974) and closer to values reported by Folkow & others (1963) and Haglund & Lundgren (1972).

In the innervated preparations (Group A), intravenous histamine caused a significant ($P < 0.02$) reduction in CFC of $49.5 \pm 7.0\%$ with insignificant changes in other variables ($P > 0.3$).

Acute division of the periarterial sympathetic nerves (Group B) itself caused a consistent but not significant ($P > 0.05$) rise of $34.0 \pm 12.4\%$ in CFC from 0.060 ± 0.002 to 0.079 ± 0.003 ml min^{-1} mm Hg^{-1} per 100 g. Before denervation, one minute's bilateral common carotid arterial occlusion caused a reduction in jejunal volume of 0·1–0·8 ml per 100 g, whilst after denervation, this test produced a rise in volume of 0·1–0·4 ml per 100 g, the significant ($P < 0.05$) difference between these effects illustrating the efficacy of the denervation.

After denervation, histamine ($1.0\ \mu g\ kg^{-1}\ min^{-1}$, i.v.) caused a significant ($P < 0.02$) reduction in CFC, with insignificant changes in the other variables ($P > 0.1$; for blood flow $0.1 > P > 0.05$). The effects of histamine after denervation were not significantly different from the effects in the innervated preparations ($P > 0.2$).

In adrenalectomized preparations (Group C), the jejunal volume rose progressively, an effect not seen in other preparations. Results were discarded after the volume had risen by 10 ml per 100 g, and two preparations were discarded completely because of large volume increases during the control period. In four preparations (Table 1, C), histamine caused a significant ($P < 0.05$) reduction in CFC of $43.8 \pm 9.1\%$ and in jejunal vascular resistance of $12.0 \pm 1.5\%$. The effect of histamine on adrenalectomized preparations was not significantly different from the effects in control animals of Group A ($P > 0.1$).

To examine the effects of histamine on jejunal intralumenal pressure, $1.0\ \mu g\ kg^{-1}\ min^{-1}$ was infused intravenously on 9 occasions to 4 preparations, resulting in an insignificant ($P > 0.5$) rise in intralumenal pressure from 5.4 ± 0.2 to 6.9 ± 2.5 cm H_2O. The effect of histamine on other variables was neither significant ($P > 0.3$) nor significantly different from the effects in preparations where CFC was measured ($P > 0.5$). The responsiveness of the preparations was shown by the fact that in each case, pentagastrin (Peptavlon, ICI) $0.1\ \mu g\ kg^{-1}\ min^{-1}$ intravenously caused increases in intralumenal pressure.

Table 1. *The effects of histamine on cat jejunal vasculature*

Group	Systemic arterial mean pressure (mmHg)		Heart rate (beats min^{-1})		Blood flow (ml min^{-1} 100 g^{-1})		Jejunal vascular resistance (mmHg ml^{-1} min 100 g)		Capillary filtration coefficient (ml min^{-1} $mmHg^{-1}$ 100 g^{-1})	
	Cont.	Hist.	Cont.	Hist.	Cont.	Hist.	Cont.	Hist.	Cont.	Hist.
Group A: innervated (n = 4)	139·3 ±13·8	134·3 ±11·7	179·8 ±25·6	184·5 ±28·7	42·3 ±4·7	41·3 ±4·2	3·35 ±0·14	3·30 ±0·22	0·059 ±0·006	0·030** ±0·003
Group B: denervated (n = 4)	125·0 ±22·8	117·5 ±21·5	182·0 ±29·9	191·5 ±24·7	33·8 ±4·4	40·3 ±3·4	3·78 ±0·74	2·94 ±0·52	0·078 ±0·008	0·041** ±0·010
Group C: adrenalectomized (n = 4)	118·5 ±11·1	108·5 ±12·8	191·0 ±20·1	199·2 ±17·2	37·3 ±2·4	39·0 ±4·2	3·24 ±0·41	2·85* ±0·35	0·053 ±0·006	0·030* ±0·006
Group D: intralumenal P. (n = 4)	145·0 ±5·7	137·6 ±3·0	209·8 ±11·5	223·3 ±9·0	49·8 ±1·3	52·8 ±3·2	2·93 ±0·17	2·70 ±0·21	Not measured	

Each value is the mean ± s.e. mean immediately before (Cont.) and during (Hist.) the infusion of $1.0\ \mu g\ kg^{-1}\ min^{-1}$ i.v. of histamine for 15 min.

* = significantly different from control ($P < 0.05$). ** = significantly different from control ($P < 0.02$). Other changes are not statistically significant ($P > 0.05$).

These results demonstrate that 1·0 μg kg^{-1} min^{-1} of histamine intravenously causes similar reductions in CFC in the sympathetically-innervated jejunum as in the acutely denervated preparation, and similar effects whether the suprarenal glands are intact or acutely extirpated. This indicates that the reduction in CFC due to histamine is not the result of stimulation of the coeliac ganglia or of the release of suprarenal medullary catecholamines, and, together with the fact that changes in systemic arterial pressure were small and insignificant, shows that reflex increases in sympathetic vasoconstrictor tone are unlikely to be a major contribution to the reduction in CFC caused by this dose of histamine.

Further, because histamine at this dose level did not significantly alter jejunal intralumenal pressure, it is improbable that the fall in CFC was the result of vascular compression due to increased intestinal smooth muscle tone.

The increases in volume of the adrenalectomized preparations were probably the result of release of corticosteroids during manipulation of the glands; whilst this may complicate the interpretation of results from these preparations, in one case where no such volume increment was seen, histamine exerted effects indistinguishable from the effects in the remaining preparations.

Previous investigations (Richardson 1973, 1974 & unpublished observations) have shown that the fall in CFC when histamine is infused intravenously is reversed to a rise by phentolamine, suggesting an involvement of α-adrenoceptors; preliminary experiments suggested that the effects of histamine on this preparation were not modified by burimamide, but all effects of histamine on this preparation have been shown to be abolished by mepyramine (Richardson, 1974).

An interaction of histamine with α-adrenoceptors seems a less probable interpretation of these actions than an action of histamine in releasing noradrenaline from intestinal sympathetic nerve endings (Everett & Mann, 1967). Such an action would cause a reduction in CFC by α-adrenoceptor stimulation (Folkow & others, 1963; Richardson, 1974) and this would be abolished by phentolamine. The CFC technique does not permit the separation of effects on precapillary 'sphincters' from effects on vascular permeability *in vivo*. The rise in CFC seen on infusion of histamine after phentolamine or aminoguanidine or with large doses of histamine might therefore be due either to dilatation of precapillary 'sphincters', or to an increased vascular permeability.

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