PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE 166, 263–270 (1981)

Microvascular Protein Efflux: Interaction of Histamine and H_1 Receptors[1] (41056)

T. KOZLOWSKI, R. M. RAYMOND, R. J. KORTHUIS, C. Y. WANG, G. J. GREGA, N. E. ROBINSON, AND J. B. SCOTT

Department of Physiology, Michigan State University East Lansing, Michigan 48824

Abstract. The effects of H_1 and H_2 receptor antagonists on histamine-induced increase in microvascular protein transport was examined in the dog forelimb and horse digit. Local intraarterial infusion of histamine (4 μg/min of the base) produces marked increases in lymph flow, lymph protein concentration, and the estimated permeability–surface area (*PS*) ratio in both the limb and digit (3). These increases were completely prevented in the horse digit by local administration of the H_1 antagonist, tripelennamine, and in the dog forelimb by the H_1 antagonist, diphenhydramine. In contrast, cimetidine or metiamide, H_2 antagonists, failed to greatly alter histamine-induced increases in lymph flow, lymph protein concentration, and PS ratios in the horse digit. Metiamide, except at an extremely high dose (1 mg/min), also failed to alter the histamine-induced increases in canine forelimb lymph flow, lymph protein concentration, and PS ratio. It is concluded that local infusion of histamine to the skin vasculature increases protein transport predominantly via interaction with an H_1 receptor.

Local intraarterial infusion of histamine into skin and skeletal muscle vascular beds produces marked edema (1–4). This edema is partly attributable to a rise in capillary hydrostatic pressure subsequent to a decrease in precapillary resistance (1, 5, 6), but, more importantly, the edema is due to an increase in microvascular protein transport with a resultant increase in interstitial protein concentration (1, 3, 7). The vascular as well as edemagenic properties of histamine have been classically attributed to actions of histamine on H_1 receptors. Little attention has been given the possibility that H_2 receptors are involved in the response. In the present study we attempted to delineate more precisely the histamine receptor(s) involved in the increased protein transport produced by local histamine administration by employing several H_1 and H_2 antagonists in the dog forelimb and horse digit.

Materials and Methods. *Canine forelimb.* Thirty-eight dogs weighing approximately 18–20 kg were anesthetized with sodium pentobarbital (30 mg/kg). Ventilation was maintained via a cuffed endotracheal tube connected to a Harvard respirator. Cutaneous incisions were made in the neck over the jugular furrow, in the right hindleg over the femoral artery, and in the right forelimb over the brachial artery, cephalic vein, and second dorsal metacarpal vein. The carotid artery, a side branch of the brachial artery, and the second metacarpal vein were isolated and cannulated for pressure measurements. All studies were done under constant flow conditions. Following administration of heparin (10,000 units intravenously) an extracorporeal circuit containing a blood pump was interposed between the femoral artery and the cannulated distal portion of the brachial artery. Two or three lymph vessels in the area of the cephalic vein were tied and one was cannulated with a length of PE 10 tubing. Lymph was collected during timed intervals in small graduated cylinders. Following collection the cylinders were sealed and frozen until protein determinations were performed. Drug infusions were made into the cannula of the brachial artery or into the jugular vein using a Harvard infusion pump.

In the first series of experiments, his-

[1] Presented in part at the October 1977 Fall meeting of the American Physiology Society. Supported in part by NIH Grant HL24363 and by a grant from Morris Animal Foundation. The authors are grateful for the technical assistance of Mr. Bill Stoffs and Don Anderson and Ms. Connie Kitazumi and Roberta Milar.

0037-9727/81/020263-08$01.00/0

tamine base (4 μg/min) was infused over a 60-min period. Vascular pressures were continuously measured during this period and six 10-min lymph samples were collected.

In the second series of experiments, either metiamide (250 μg/min or 1 mg/min) or diphenhydramine (100 μg/min or 1 mg/min) was infused locally into the brachial artery for 70 min. Histamine (4 μg base/min) was infused into the same artery beginning 10 min after institution of the blockers and continued for 60 min. Measurements of systemic arterial pressure, perfusion pressure, and small vein pressure were taken every 10 min. The total protein concentration in lymph and blood were measured spectrophotometrically (Beckman DB spectrophotometer) by the method of Waddell (8).

Isolated equine digit. Thirteen ponies were anesthetized with thiamylal sodium (10 mg/kg body wt) given intravenously and anesthesia was maintained with sodium pentobarbital. All animals were ventilated with an air–oxygen mixture with ventilation adjusted to maintain Pa_{CO_2} between 35 and 45 mm Hg. The medial palmar artery, medial palmar vein, medial and lateral palmar nerves, and a lymphatic were isolated in the midmetacarpal region of the right forelimb. Remaining soft tissue was transected and an occlusive clamp was placed around the metacarpal bone. Heparin (500 units/kg body wt) was administered to prevent coagulation. A loop of polyethylene and latex tubing was interposed in the artery for infusion of drugs and measurement of arterial pressure. The vein was transected and a polyethylene cannula inserted into the distal portion so that venous outflow could be measured by timed collections in a graduated cylinder. Venous outflow was returned to the horse from a reservoir using a finger type blood pump. Small vein pressure was measured in the venous plexus at the junction of the hoof and the skin. The previously isolated lymphatic was cannulated with polyethylene tubing (PE 10) and lymph collected and handled as described for the dog forelimb. The digital preparation has been described in detail in previous manuscripts (3, 4, 6).

In all ponies two 10-min control lymph samples were collected during which time digital blood flow was measured several times. Average blood flows and pressures over each 10-min period are reported. Blocking agents were then infused intraarterially for 20 min and histamine (4 μg/min histamine base) with the blocking agent for an additional 30 min. Lymph samples were collected and blood flows measured throughout the infusions. Total protein concentration was determined in blood samples drawn at the end of each period. Tripelennamine (an H_1 antagonist), 250 μg/min, was given intraarterially to the digit of five ponies, metiamide (an H_2 antagonist), 250 μg/min, to five ponies, and cimetidine (an H_2 antagonist), 250 μg/min, to three ponies.

Treatment of data. In all experiments, a steady state was reached after 10 min of blocker infusion and after 30 min of blocker and histamine infusion. Data collected at these times were used to calculate the lymph to plasma protein concentration ratio R. An index of permeability-surface area product was then estimated by the formula (9, 10).

$$PS = \frac{LR}{1 - R}, \qquad [1]$$

where L is the total lymph flow. Assuming the effects of antagonist and histamine are proportional on all the vasculature, the single lymph flow l will be proportional to the total lymph flow, thus

$$L = Kl$$

Where the proportionality constant K may vary for different lymphatic networks. However, for the same network, the PS values of the two states may be compared by the ratio

$$\frac{(PS)_2}{(PS)_1} = \frac{L_2R_2}{1 - R_2} \Big/ \frac{L_1R_1}{1 - R_1} = \frac{l_2R_2}{1 - R_2} \Big/ \frac{l_1R_1}{1 - R_1}. \qquad [2]$$

All data from both species were analyzed by an analysis of variance randomized complete block design. Student–Newman–Keuls procedure evaluated differ-

ences between individual treatment effects. The level of significance was chosen as $P < 0.05$.

Results. Intraarterial infusion of histamine (4 μg/min) into the constantly perfused dog forelimb did not affect systemic blood pressure or skin small vein pressure but produced a significant fall in limb perfusion pressure (Table I). This is consistent with the concept that the drug alters resistance to flow mainly by dilating precapillary blood vessels. Following 10 min of histamine there were marked increases in lymph flow rate and lymph protein concentration. Both remained elevated throughout the subsequent 50 min of histamine infusion. Using the lymph flow and protein concentration data shown in Table I and the mean plasma protein concentration of 5.92 g% we calculated the ratio of estimated PS value of histamine to control to be 23. This indicates a large increase in permeability and/or surface area.

The effects of H_1 and H_2 blockade on the response of the canine forelimb to histamine are presented in Table II. Neither the blockers alone nor the blockers in combination with histamine altered aortic pressure or skin small vein pressure. However, during metiamide (250 μg/min) or diphenhydramine (100 μg/min) histamine decreased perfusion pressure. This response was not seen during the higher dose of either blocker. Neither antagonist, at any dose employed, produced regular changes in limb perfusion pressure.

It is also evident from Table II that the blockers per se had no effect on lymph flow or lymph protein concentration. Moreover histamine did not affect lymph flow or lymph protein concentration during either the high or low dose of diphenhydramine. The PS ratio of histamine plus diphenhydramine to control was 0.99 for the low dose and 1.30 for the high dose of the blocker. Similarly, during the high dose of metiamide (1 mg/min) histamine failed to increase lymph flow or lymph protein concentration. The PS ratio was 0.803. In contrast, during metiamide (250 μg/min) histamine produced large increases in lymph flow and lymph protein concentration. The corresponding PS ratio was 54.

The response of the horse digit to histamine in the presence H_1 or H_2 blockers is seen in Table III. Digital blood flow was not significantly affected by any of the blockers alone or by histamine in the presence of the blockers. However, during tripelannamine and histamine, digital blood flow decreased in three and increased in two preparations while during the combination of histamine and metiamide blood flow increased in four and decreased in one. During the histamine–cimetidine infusion blood flow increased in all three digits studied. Intraarterial infusion of histamine alone (4 μg/min) to the equine digit produces an increase in blood flow (4).

During tripelennamine alone or during tripelennamine plus histamine there were no significant changes in lymph flow or lymph protein concentration. The PS ratio for blocker plus histamine to control was 1.4. In contrast, during infusion of either metiamide or cimetidine, a local intraarterial infusion of histamine caused marked increases in lymph flow and lymph protein concentration. The PS ratio during metiamide and histamine was 43 and during cimetidine and histamine it was 9.1. The magnitude of the increases in lymph flow and protein concentrations are similar to those produced by histamine alone in this preparation (3, 4).

Discussion. In the present study, the increases in lymph flow, lymph protein concentration and estimated PS value produced by histamine were almost completely prevented by local administration of the H_1 antagonists tripelennamine (250 μg/min) in the horse or diphenhydramine (100 μg/min or 1 mg/min) in the dog. In contrast, in the horse local administration of the H_2 antagonists, cimetidine (250 μg/min), or metiamide (250 μg/min) failed to prevent large increases in lymph flow, lymph protein concentration, and PS ratio during histamine. The estimated PS ratio increased by 43 times during histamine and metiamide and 9 times during histamine and cimetidine. It should be kept in mind that when the PS ratio is high the actual increase in PS value may be much less than that estimated by Eq [1], since the formula ignores bulk flow effects which might be consider-

TABLE I. EFFECT OF INTRAARTERIAL INFUSION OF HISTAMINE (4 μg/min BASE) ON HEMODYNAMICS, LYMPH PROTEIN CONCENTRATION, AND LYMPH FLOW IN CANINE FORELIMBS PERFUSED AT CONSTANT INFLOW[a]

	Time (min)							
	Control		Histamine					
	−10	0	10	20	30	40	50	60
Systemic pressure (mm Hg) (N = 8)	135 ± 6.3	135 ± 6.6	132 ± 9.1	130 ± 11.1	128 ± 11.0	126 ± 11.5	126 ± 11.5	126 ± 12.2
Perfusion pressure (mm Hg) (N = 8)	133 ± 6.6	135 ± 7.3	95.9 ± 2.7*	90.9 ± 7.2*	90.0 ± 8.0*	89.4 ± 7.9*	90.7 ± 7.4*	90.7 ± 8.0*
Small vein pressure (mm Hg) (N = 7)	9.1 ± 0.8	9.3 ± 0.9	11.7 ± 1.5	11.6 ± 1.4	11.6 ± 1.3	10.6 ± 1.8	8.2 ± 1.8	10.5 ± 1.4
Lymph flow (ml/10 min) (N = 8)	0.01 ± 0.001	0.01 ± 0.001	0.03 ± 0.01	0.08 ± 0.04*	0.08 ± 0.04*	0.10 ± 0.04*	0.11 ± 0.06*	0.10 ± 0.05*
Lymph protein (g%)[b] (N = 8)	2.9 ± 0.36	2.9 ± 0.34	3.0 ± 0.33	3.8 ± 0.39*	3.9 ± 0.48*	4.0 ± 0.42*	4.0 ± 0.43*	4.1 ± 0.45*

* $P < 0.05$ compared to time zero control.
[a] Forelimb flow averaged 93 ml/min.
[b] Plasma protein concentration = 5.92 ± 0.68 g%.

TABLE II. EFFECT OF H_1 (DIPHENHYDRAMINE) AND H_2 (METIAMIDE) ANTAGONISTS ON VASCULAR PRESSURES, LYMPH FLOW AND PROTEIN CONCENTRATION DURING HISTAMINE INFUSION (4 μg/min) IN THE DOG FORELIMB PERFUSED AT CONSTANT FLOW[a]

	Time (min)					
	Control		Blocker	Blocker + histamine		
	−10	0	10	20	40	70
Systemic pressure (mm Hg)						
Metiamide[a] (n = 6)	129.7 ± 5.4	134.7 ± 8.4	135.0 ± 8.2	137.5 ± 13.3	132.8 ± 10.2	134.2 ± 8.6
Metiamide[b] (n = 6)	133.3 ± 8.1	133.3 ± 8.1	135.8 ± 8.6	133.0 ± 8.1	130.0 ± 6.8	130.5 ± 8.4
Diphenhydramine[c] (n = 6)	131.5 ± 4.8	134.5 ± 6.7	139.8 ± 8.5	135.8 ± 6.1	138.2 ± 6.9	141.3 ± 7.7
Diphenhydramine[d] (n = 6)	131.7 ± 7.5	131.0 ± 6.7	131.2 ± 6.6	130.7 ± 7.4	130.7 ± 5.8	127.0 ± 6.3
Perfusion pressure (mm Hg)						
Metiamide[a] (n = 6)	120.0 ± 5.0	117.5 ± 9.5	125.3 ± 8.7	82.5* ± 6.3	85.8* ± 6.9	94.2* ± 7.4
Metiamide[b] (n = 6)	125.2 ± 7.6	133.5 ± 11.1	132.0 ± 12.2	123.8 ± 33.3	119.8 ± 11.0	127.7 ± 12.0
Diphenhydramine[c] (n = 6)	124.2 ± 6.1	139.7 ± 8.3	141.7 ± 6.9	91.0* ± 3.8	97.5* ± 4.2	108.5* ± 7.6
Diphenhydramine[d] (n = 6)	135.2 ± 3.8	107.5 ± 4.8	105.0 ± 4.8	100.8 ± 5.4	102.3 ± 5.8	106.7 ± 4.9
Small vein pressure (mm Hg)						
Metiamide[a] (n = 6)	9.8 ± 0.9	10.0 ± 0.9	9.8 ± 0.9	10.3 ± 1.1	11.0 ± 0.9	10.0 ± 1.3
Metiamide[b] (n = 6)	11.5 ± 1.4	11.8 ± 1.5	12.3 ± 1.3	12.2 ± 1.1	11.5 ± 1.2	12.0 ± 0.7
Diphenhydramine[c] (n = 6)	12.0 ± 1.1	12.2 ± 1.0	12.0 ± 1.1	13.8 ± 1.9	13.8 ± 1.4	14.0 ± 1.7
Diphenhydramine[d] (n = 6)	11.3 ± 1.0	12.0 ± 1.1	12.5 ± 1.1	12.3 ± 0.9	12.6 ± 1.1	12.3 ± 0.8
Lymph flow (ml/10 min)						
Metiamide[a] (n = 6)	0.02 ± 0.01	0.02 ± 0.01	0.02 ± 0.01	0.20* ± 0.03	0.33* ± 0.09	0.25 ± 0.06
Metiamide[b] (n = 6)	0.02 ± 0.01	0.02 ± 0.01	0.02 ± 0.01	0.02 ± 0.01	0.02 ± 0.01	0.02 ± 0.01
Diphenhydramine[c] (n = 6)	0.02 ± 0.01	0.02 ± 0.01	0.02 ± 0.01	0.02 ± 0.01	0.02 ± 0.01	0.02 ± 0.01
Diphenhydramine[d] (n = 6)	0.02 ± 0.01	0.02 ± 0.01	0.02 ± 0.01	0.02 ± 0.01	0.02 ± 0.01	0.02 ± 0.01
Lymph protein (g%)						
Metiamide[a] (n = 6)	1.40 ± 0.13	1.35 ± 0.11	1.27 ± 0.11	2.77* ± 0.40	3.28* ± 0.24	3.37* ± 0.37
Metiamide[b] (n = 6)	1.47 ± 0.08	1.48 ± 0.09	1.50 ± 0.07	1.45 ± 0.07	1.53 ± 0.08	1.70 ± 0.11
Diphenhydramine[c] (n = 6)	1.65 ± 0.16	1.82 ± 0.14	1.70 ± 0.18	1.67 ± 0.20	1.72 ± 0.18	1.78 ± 0.17
Diphenhydramine[d] (n = 6)	1.47 ± 0.11	1.48 ± 0.12	1.57 ± 0.15	1.50 ± 0.13	1.53 ± 0.13	1.68 ± 0.15

* $P < 0.05$ compared to time zero control.
[a] 250 μg/min, i.a.; plasma protein = 5.85 ± 0.95 g%.
[b] 1 mg/min, i.a.; plasma protein = 5.46 ± 0.61 g%.
[c] 100 μg/min, i.a.; plasma protein = 5.46 ± 0.52 g%.
[d] 1 mg/min, i.a.; plasma protein = 4.94 ± 0.48 g%.
[e] Forelimb flow averaged 120 ml/min.

TABLE III. EFFECT OF H_1 (TRIPELENNAMINE) AND H_2 (METIAMIDE AND CIMETIDINE) ANTAGONISTS ON EQUINE DIGITAL BLOOD FLOW, VASCULAR-PRESSURES, LYMPH FLOW, AND PROTEIN CONCENTRATION DURING HISTAMINE-INFUSION

	Time (min)						
	Control		Blocker		Blocker + histamine		
	−10	0	10	20	30	40	50
Digital blood flow (ml/min)							
Tripelennamine[a] (n = 5)	74.8 ± 14.4	85.2 ± 22.2	69.0 ± 18.3	70.8 ± 22.7	76.8 ± 22.8	81.6 ± 23.1	80.8 ± 21.1
Metiamide[a] (n = 5)	79.2 ± 19.4	75.6 ± 14.0	70.4 ± 17.3	74.4 ± 16.2	99.2 ± 10.1	95.2 ± 10.7	94.4 ± 15.7
Cimetidine[a] (n = 3)	130.0 ± 12.1	129.3 ± 16.4	128.0 ± 17.4	126.0 ± 15.5	144.3 ± 12.2	142.7 ± 20.1	136.7 ± 15.3
Systemic pressure (mm Hg)							
Tripelennamine (n = 5)	122.8 ± 7.1	121.0 ± 12.8	110.6 ± 7.0	122.6 ± 3.4	122.6 ± 2.1	126.4 ± 4.1	126.2 ± 6.1
Metiamide (n = 5)	103.2 ± 4.6	98.0 ± 3.7	88.0 ± 6.2	96.4 ± 3.7	96.8 ± 4.6	98.4 ± 5.5	101.6 ± 5.0
Cimetidine (n = 3)	103.7 ± 16.4	125.3 ± 12.7	118.7 ± 5.5	116.7 ± 5.5	130.7 ± 4.7	133.3 ± 4.7	135.3 ± 2.9
Small vein pressure (mm Hg)							
Tripelennamine (n = 5)	42.0 ± 9.5	36.6 ± 8.1	23.8 ± 6.5	26.6 ± 6.7	26.2 ± 5.2	29.2 ± 6.7	29.2 ± 5.0
Metiamide (n = 5)	43.4 ± 9.8	42.2 ± 10.8	41.4 ± 9.0	46.4 ± 11.9	45.8 ± 10.8	47.6 ± 9.1	51.8 ± 8.6
Cimetidine (n = 3)	55.3 ± 7.7	55.0 ± 6.7	52.0 ± 5.9	53.0 ± 4.6	67.7* ± 3.5	68.3* ± 3.3	67.7* ± 3.8
Lymph flow (ml/10 min)							
Tripelennamine (n = 5)	0.06 ± 0.01	0.06 ± 0.02	0.03 ± 0.01	0.02 ± 0.01	0.03 ± 0.01	0.06 ± 0.02	0.05 ± 0.01
Metiamide (n = 5)	0.06 ± 0.04	0.04 ± 0.02	0.03 ± 0.01	0.04 ± 0.02	0.35* ± 0.14	0.50* ± 0.17	0.44* ± 0.11
Cimetidine (n = 3)	0.09 ± 0.06	0.10 ± 0.07	0.06 ± 0.03	0.06 ± 0.01	0.38* ± 0.11	0.46* ± 0.12	0.45* ± 0.06
Lymph protein (g%)							
Tripelennamine (n = 5)	2.26 ± 0.28	2.28 ± 0.27	2.10 ± 0.35	2.46 ± 0.47	2.40 ± 0.53	2.33 ± 0.36	2.71 ± 0.19
Metiamide (n = 5)	2.62 ± 0.33	2.70 ± 0.35	2.42 ± 0.34	2.87 ± 0.29	3.44 ± 0.21	4.03* ± 0.29	4.45* ± 0.08
Cimetidine (n = 3)	2.15 ± 0.36	2.40 ± 0.25	2.56 ± 0.55	2.81 ± 0.09	3.20 ± 0.17	3.36* ± 0.21	3.63* ± 0.07
Plasma protein (g%)							
Tripelennamine (n = 5)	6.01 ± 0.64		5.96 ± 0.36			5.7 ± 0.20	
Metiamide (n = 5)	6.61 ± 0.23		6.25 ± 0.28			6.22 ± 0.43	
Cimetidine (n = 3)	6.58 ± 0.80		6.78 ± 0.87			6.70 ± 0.53	

[a] 250 μg/min, i.a.
* $P < 0.05$ compared to time zero control.

able at high lymph flow rates. Nevertheless Eq. [2] serves as a qualitative indicator for changes in the permeability-area product since Eq. [2] incorporates changes in both lymph flow and lymph to plasma concentration ratios. Although neither drug at the low dose could be considered an effective antagonist, it would appear that cimetidine is slightly more effective than metiamide in blocking the permeability effects produced by histamine. In this regard, it has previously been reported that cimetidine may have H_1 antagonistic properties (11) and this may account for the difference. In the dog forelimb, the H_2 blocker metiamide (250 μg/min) also failed to block the histamine induced increases in lymph flow, lymph protein concentration, and PS. However, infusion of the agent at 1 mg/min eliminated all increases. The finding that the histamine-induced increase in microvascular protein transport can be blocked by a high but not a moderate dose of metiamide suggests that this drug also possesses some H_1 antagonistic properties or that an extremely high dose of a H_2 antagonist can partially block the effect of histamine to increase permeability.

Bhargava *et al.* (12) have recently reported that the histamine-induced increase in capillary permeability of peritoneal blood vessels of mice could be blocked with an H_1 receptor antagonist, mepyramine, but not with burimamide, an H_2 receptor antagonist. Further, a combination of mepyramine and burimamide did not offer any greater protection than mepyramine alone. These authors concluded that histamine increases capillary permeability through interaction with an H_1 receptor. In contrast, Dabney *et al.* (13) and Dobbins *et al.* (14) reported that cimetidine or mepyramine, respectively, blocks the increase in lymph flow and protein transport produced by low doses of histamine in the dog forelimb. These investigators interpreted their preliminary data to mean that both H_1 and H_2 receptors are involved in the permeability alterations induced by histamine. In light of the present study and the study of Bhargava *et al.* (12), an alternative explanation is that the H_1 antagonistic properties of cimetidine were responsible for blockade of the permeability effects produced by the low histamine dosage. Also it has recently been reported that a wide variety of unrelated agents will interfere with the action of histamine to increase protein efflux through an action independent of receptor blockade (15).

Results of the present study support previous investigations which suggest that the vasodilator effects produced by local administration of histamine in dog (16, 17) and sheep (18) result from activation of both H_1 and H_2 receptors. While small doses of H_1 and H_2 antagonists failed to block histamine-induced vasodilation in the dog, high doses of both metiamide and diphenhydramine prevented the histamine-induced fall in perfusion pressure in this constant flow preparation. In the horse, the changes in blood flow resulting from infusion of histamine with the antagonists are statistically inconclusive. However, examination of individual animal data suggests tripelennamine more consistently blocked the vasodilator action of histamine than did metiamide or cimetidine. Thus, as suggested by others, the H_1 receptor may be most prominent in the vasodilator response. In this regard, the blockade of vasodilation by a high dose of metiamide in the dog may be due to significant H_1 antagonistic properties of this agent.

It is interesting to note that the dosage of H_1 blocker (100 μg/min) which prevented the histamine-induced increase in protein transport in the dog, failed to prevent vasodilation suggesting that the H_1 receptors mediating protein transfer are more sensitive that the H_1 receptors mediating vasodilation.

1. Haddy, F. J., Scott, J. B., and Grega, G. J., Int. Rev. Physiol. Cardiovasc. Physiol. II 9, 63 (1976).
2. Rippe, B., and Grega, G. J., Acta Physiol. Scand. 103, 252 (1978).
3. Robinson, N. E., Jones, G. A., Scott, J. B., and Dabney, J. M., Proc. Soc. Exp. Biol. Med. 149, 805 (1975).
4. Robinson, N. E., Scott, J. B., Dabney, J. M., and Jones, G. A., Amer. J. Vet. Res. 37, 1171 (1976).
5. Grega, G. J., Kline, R. L., Dobbins, D. E., and Haddy, F. J., Amer. J. Physiol. 223, 1165 (1972).
6. Robinson, N. E., Dabney, J. M., Weidner, W. J.,

Jones, G. A., and Scott, J. B., Amer. J. Vet. Res. **36**, 1249 (1975).
7. Haddy, F. J., Scott, J. B., and Grega, G. J., Amer. J. Physiol. **223**, 1172 (1972).
8. Waddell, W. J., J. Lab. Clin. Med. **48**, 311 (1956).
9. Renkin, E. M., Physiologist **7**, 13 (1964).
10. Renkin, E. M., and Garlick, D. G., *in* Capillary Permeability (E. Crone and N. A. Lassen, eds.), p. 552. Academic Press, New York (1970).
11. Drazen, J. M., Venugopalan, C. S., and Soter, N. A., Physiologist **20**, 23 (1977).
12. Bhargava, K. P., Nath, R., and Palit, G., Brit. J. Pharmacol. **59**, 349 (1977).
13. Dabney, J. M., Swindall, B. T., Johnson, J. R., Haddy, F. J., and Dobbins, D. E., Physiologist **20**, 20 (1978).
14. Dobbins, D. E., Swindall, B. T., Credd, C. A., Haddy, F. J., and Dabney, J. M., Physiologist **21**, 20 (1978).
15. Grega, G. J., Maciejko, J. J., Raymond, R. M., and Sak, D. P., Circ. Res. **46**, 265 (1980).
16. Giles, R. W., Heise, C., and Wilcken, D. E. L., Circ. Res. **40**, 541 (1977).
17. Powell, J. R., and Brody, M. J., J. Pharmacol. Exp. Therap. **196**, 1 (1976).
18. Woods, Jr., J. R., Brinkman, III, C. R., Ryner, J., Martinek, H., and Assali, N. S., Proc. Soc. Exp. Biol. Med. **151**, 811 (1976).

Received April 25, 1980. P.S.E.B.M. 1981, Vol. 166.