Blood Flow Distribution with Adrenergic and Histaminergic Antagonists (42858)

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Abstract. **Superficial fibular nerve stimulation (SFNS) causes increased pre- and post-capillary resistances as well as increased capillary permeability in the dog hind paw. These responses indicate possible adrenergic and histaminergic interactions. The distribution of blood flow between capillaries and arteriovenous anastomoses (AVA) may depend on the relative effects of these neural inputs. Right hind paws of anesthetized heparinized dogs were vascularly and neurally isolated and perfused with controlled pressure. Blood flow distribution was calculated from the venous recovery of ^{85}Sr-labeled microspheres (15 μm). The mean transit times of ^{131}I-albumin and ^{85}Sr-labeled microspheres were calculated. The effects of adrenergic and histaminergic antagonists with and without SFNS were determined. Phentolamine blocked the entire response to SFNS. Prazosin attenuated increases in total and AVA resistance. Yohimbine prevented increased total resistance, attenuated the AVA resistance increase, and revealed a decrease in capillary circuit resistance. Pyrilamine attenuated total resistance increase while SFNS increased capillary and AVA resistances. Metiamide had no effect on blood flow distribution with SFNS. The increase in AVA resistance with SFNS apparently resulted from a combination of α_1 and α_2 receptor stimulation but not histaminergic effects.** [P.S.E.B.M. 1989, Vol 190]

The control of the microcirculation of the dog hind paw appears to involve more than one neural transmitter. Norepinephrine, acetylcholine, histamine, and possibly others may be included (1). Our recent studies on the dog hind paw circulation have indicated a possible interaction between adrenergic and histaminergic influences (2), particularly during superficial fibular nerve stimulation (SFNS).

The microcirculation of the dog hind paw consists of two major vascular circuits coupled in parallel. They are the nutritional or capillary circuit and the non-nutritional arteriovenous anastomoses (AVA) or shunts (3–6). The distribution of paw blood flow through these two circuits could depend upon the relative level of input, as well as the level of interactions, of the adrenergic and histaminergic neural inputs. It is well established that the distribution of blood flow between these circuits is in large part dependent upon reflexes (7) and local influences (8) that occur during body temperature regulation.

Therefore, the dog hind paw was vascularly and neurally isolated and perfused under conditions of controlled arterial pressure. The distribution of blood flow between the two circuits was measured with radioactive microspheres. The mean transit times of ^{131}I-albumin which passes through both circuits and of ^{85}Sr-labeled microspheres (15 μm in diameter) which passes through only the AVA circuit were compared. These measurements were made at control and during blockade with adrenergic and histaminergic antagonists with and without stimulation of the superficial fibular nerve.

Materials and Methods

Fifty-one mongrel dogs of both sexes average 18 ± 3 kg in weight were pretreated with 10 mg/kg morphine sulfate and anesthetized with 15–20 mg/kg pentobarbital. Forty-one dogs (Group A) were used to obtain the responses at control and during SFNS and for the studies involving receptor agonists and antagonists with SFNS as described below. Ten animals (Group B) were used to test the interactions between the agonist and antagonists compounds to be used with SFNS. The right hind paw was neurally and vascularly isolated at the ankle joint. The cranial tibial artery, lateral saphenous vein, tibial nerve, superficial fibular nerve, and deep fibular nerve were isolated. The nerves were doubly ligated and sectioned.

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The animals were administered 10 mg/kg heparin intravenously. The lateral saphenous vein outflow was passed through a scintillation detector. The cranial tibial artery was cannulated and perfused by means of PE tubing from the ipsilateral femoral artery. During cannulation procedures, blood flow to the hind paw was interrupted for less than 1 min. The tubing connecting the cranial tibial and femoral arteries has sidearms for measurement of perfusion pressures and for injection of indicators. The perfused blood was kept at 37°C. The temperature of the animal was maintained by means of a heating pad with continuous monitoring of rectal temperature (Yellow Springs).

Stimulations of the cut end of the superficial fibular nerve with minimal supramaximal intensity (30 ± 5 V, 0.3-msec pulse duration) were made at 11 Hz using hook electrodes pulled into oil-filled Tygon tubing. Elapsed time of each stimulus train averaged 7 ± 1 min. The ambient temperature was 24°C.

Sufficient postsurgical time was allowed for the animals to stabilize. It was unnecessary to immobilize the animals with a curare-like drug since stimulation of the nerves rarely elicited movement of the paws. In those instances where some movement did occur, the data were not different from paws that did not show movement.

Parameter measurements were made in Group A during the control period, during SFNS, during antagonist infusion, and during antagonist infusion and SFNS. In Group B determinations of agonist-induced changes in blood flow were made alone and in the presence of antagonists. Systemic arterial pressure, paw perfusion pressure, and venous outflow pressure were monitored using Statham P23Db transducers. Arterial inflow (Q_T) was monitored with a Carolina Medical electromagnetic flow meter. The data were recorded on an Electronics for Medicine DR-8 recorder. Venous outflow (Q_T) was measured by a timed collection of the effluent in a graduated cylinder (a separate collection was made for each injected isotope, see below). Blood containing isotope was not returned to the dog and therefore a continuous infusion of homologous, heparinized donor blood (approximately 700 ml) was made at approximately the same rate as venous outflow.

The paw was severed and weighed at the end of each experiment. The average paw weight was 248 g. ^{131}I-Albumin (0.3–0.5 μCi ^{131}I) and ^{85}Sr-labeled microspheres (15 ± 0.3 μm) were sequentially injected as a bolus into a sidearm of the arterial cannula. The time concentration curves of the indicators in the venous effluent were monitored by means of a previously described hole-through scintillation detector and rate meter (9). Each injection was made in less than 1 sec and although this transiently changed pressure and flow, the recording showed no persistent change in vascular resistance. Completion of the dilution curve was ascertained by return of the recording to background levels. Indicator recovery was subsequently measured by determining the radioactivity of a mixed sample of the venous effluent collected during the period of the dilution curve. There was no distortion of the curves due to recirculation since the indicator was not returned to the animals. The mean transit time ($\bar{t}$) in seconds was calculated according to the method of Hamilton *et al.* (10).

The ^{131}I-albumin injected in 0.25 ml of blood was a plasma label and would be expected to flow through all patent microvessels. Therefore, $\bar{t}$ of the venous time-concentration curve would be determined by the flow patterns and velocities in both the AVA and capillary circuits. Recovery of the ^{131}I-albumin should be essentially complete unless capillary permeability increased.

It has been shown (8, 11, 12) that 15 μm in diameter microspheres pass through open AVA but not through capillary circuits. The ^{85}Sr-labeled microspheres venous time-concentration curve $\bar{t}$ will reflect flow patterns and velocities only in the AVA circuit. A bolus injection of 0.25 ml of blood containing 1.5 × 10^5 ^{85}Sr-labeled microspheres (3M) (15 ± 0.3 (SD) μm in diameter) was made into the arterial inflow tubing, and the venous outflow was collected as usual. The radioactivity (^{85}Sr) recovered (cpm/ml times volume of blood) divided by the amount of radioactivity injected (cpm) provides an index of AV shunt flow. The greater the percentage recovered, the greater the flow through open AV shunt vessels. Microspheres not recovered are lodged in the microvessels of the parallel capillary circuits. AV shunt flow (Q_S) was calculated as follows (8):

$$Q_s = Q_T \times \frac{\text{cpm } ^{85}\text{Sr-labeled microspheres recovered}}{\text{cpm } ^{85}\text{Sr-labeled microspheres injected}}$$

where Q_T is the total hind paw blood flow.

Capillary circuit flow (Q_c) can then be calculated as

$$Q_c = Q_T - Q_s$$

It should be noted that the indicators were injected sequentially but in random sequence. There were no consistent effects due to order of injections.

The effects of the following compounds on the response to superficial fibular nerve stimulation were studied in Group A. The infusion volumes for the drugs were 0.3 ml/min: (i) Phentolamine mesylate (three dogs), an antagonist of both α_1 and α_2 receptors, was administered 1 mg/paw intraarterially (i.a.) as a bolus injection followed by a continuous i.a. infusion at 0.5 mg/min. (ii) Prazosin (five dogs), an α_1 antagonist, was infused i.a. at 1 mg/min. (iii) Yohimbine (four dogs), an α_2 antagonist, was infused i.a. at 0.5 mg/min to 1 mg/min. (iv) Pyrilamine maleate (seven dogs), an H_1 receptor antagonist, was infused. (v) Metiamide (three dogs), an H_2 receptor antagonist, was administered. (vi) The combination of pyrilamine maleate and metiamide was infused (five dogs). The H_1 and H_2 receptor antagonists were each administered at 8 mg/kg i.v. in a bolus injection followed 15 min later by an i.a. infusion of 2 mg/min for the duration of the experiment. For comparative purposes, norepinephrine (0.5 μg/min) was infused for 5 min without SFNS (3 dogs) and SFNS alone was studied in 11 dogs.

In Group B dogs, standard bolus (0.25 ml) injections of the following agonists were tested against the antagonists listed above: norepinephrine (0.8 μg), angiotensin II (2.6 μg), phenylephrine (0.05 μg), clonidine (0.07 μg), histamine (75 μg), and sodium nitroprusside (0.7 μg).

All data are reported with standard errors of the means (X ± SEM). Appropriately related points were compared using analysis of variance and the Newman-Keuls range test. Statistical significance was accepted with a probability of less than 0.05. Statistics performed on groups with *n* less than 5 may be questionable. However, in all such groups in this study the results were highly consistent. Also, the number of dogs available for study was extremely limited, thus influencing our groupings.

Results

Hemodynamics. Table I presents the hemodynamic data and Table II and Figure 1 present the blood flow distribution data between nutritional (capillary, Q_c) and non-nutritional (arteriovenous anastomosis, Q_s) circuits in the dog hind paw during control, infusion of antagonist drugs, and during SFNS. The blood flow resistance increased significantly to 195% of the control value with SFNS. The control flow distribution as determined from the ^{85}Sr-labeled microsphere recovery was 64% Q_s and 36% Q_c. SFNS did not significantly change Q_c while significantly decreasing Q_s to 30% of the control value.

When norepinephrine was infused into the dog paw, the blood flow resistance increased significantly to approximately 156% of control. The significant decrease ($P < 0.05$) in Q_s was to 56% of control with no change in Q_c.

Administration of the α-adrenergic receptor antagonists phentolamine, prazosin, and yohimbine did not significantly change blood flow resistance of the whole paw. Blood flow distribution was not significantly changed by phentolamine. Prazosin significantly ($P < 0.05$) decreased Q_c to 55% of control with an increase to 121% in Q_s. Yohimbine significantly ($P < 0.05$) decreased Q_s to 66% of control and significantly increased Q_c to 146% of control. The presence of phentolamine blocked the affect of SFNS on blood flow resistance and distribution. However, SFNS in the presence of prazosin altered blood flow distribution so that Q_s was significantly ($P < 0.05$) decreased to 60% of control and Q_c was increased to 117% of control. SFNS

Table I. Hemodynamic Effects of SFNS, Norepinephrine, and Receptor Blockade during SFNS (Group A)

	N	Pm^a (mm Hg)	P_V (mm Hg)	Q_T (ml/min)	R (mm Hg)/ml/min
Control	11	109 ± 2	3 ± 0.8	26.1 ± 0.7	4.1 ± 0.5
SFNS	11	110 ± 5	2 ± 0.4	13.5 ± 1.5[b]	8.0 ± 1.7[b]
Control	3	106 ± 2	3 ± 0.7	22.2 ± 4.0	4.6 ± 1.1
Norepinephrine	3	107 ± 2	2 ± 0.3	14.5 ± 1.7[b]	7.2 ± 1.2[b]
Control	3	116 ± 2	1 ± 0.7	27.5 ± 1.0	4.2 ± 0.4
Phentolamine	3	117 ± 4	1 ± 0.6	25.8 ± 1.2	4.1 ± 0.2
Phentolamine + SFNS	3	113 ± 1	1 ± 0.5	26.9 ± 1.2	4.2 ± 0.7
Control	5	116 ± 6	3 ± 0.5	26.1 ± 1.8	4.3 ± 0.4
Prazosin	5	117 ± 9	3 ± 0.6	24.3 ± 2.5	4.7 ± 0.5
Prazosin + SFNS	5	119 ± 9	3 ± 0.8	21.9 ± 2.2[b]	5.3 ± 0.4[b]
Control	4	110 ± 7	2 ± 0.7	26.0 ± 1.2	4.2 ± 0.3
Yohimbine	4	119 ± 8	1 ± 1.0	24.6 ± 1.3	4.8 ± 0.5
Yohimbine + SFNS	4	116 ± 8	2 ± 1.2	25.4 ± 1.9	4.9 ± 0.5
Control	7	110 ± 5	3 ± 0.5	27.5 ± 2.7	3.9 ± 0.4
Pyrilamine maleate	7	107 ± 3	3 ± 0.8	25.7 ± 1.9	4.0 ± 0.6
Pyrilamine + SFNS	7	110 ± 4	3 ± 0.8	16.8 ± 1.1[b]	6.4 ± 0.7[b]
Control	3	106 ± 2	3 ± 0.7	21.2 ± 4.0	4.8 ± 1.0
Metiamide	3	106 ± 3	3 ± 0.7	20.9 ± 3.9	4.9 ± 1.4
Metiamide + SFNS	3	104 ± 3	1 ± 0.4	7.8 ± 1.0[b]	13.2 ± 1.5[b]
Control	5	104 ± 12	3 ± 0.7	23.2 ± 1.3	4.4 ± 0.5
Pyrilamine + metiamide	5	105 ± 2	3 ± 0.8	21.9 ± 1.5	4.7 ± 0.6
Pyrilamine + metiamide + SFNS	5	111 ± 2	3 ± 0.5	13.8 ± 2.9[b]	7.8 ± 2.3[b]

[a] Pm, mean arterial pressure; P_V, venous outflow pressure; Q_T, total blood flow; R, resistance.

[b] Significantly different from control ($P < 0.05$).

Table II. Microsphere Recovery, Blood Flow Distribution, and Mean Transit Time Data with SFNS and Receptor Blockade (Group A)

	% Recovery ^{85}Sr-labeled microspheres	Q_s (ml/min)	Q_c (ml/min)	$\bar{t}$[a] ^{131}I-Albumin (sec)	$\bar{t}$ ^{85}Sr-labeled microspheres (sec)
Control	64 ± 3	16.7 ± 1.1	9.4 ± 0.8	28.7 ± 2.6	17.0 ± 0.8
SFNS	38 ± 4[b]	5.1 ± 0.9	8.4 ± 1.4	65.3 ± 7.2[b]	45.9 ± 3.5[b]
Control	77 ± 6	17.1 ± 1.6	5.1 ± 1.0	29.4 ± 2.8	21.5 ± 3.6
Norepinephrine	67 ± 12	9.7 ± 1.2	4.8 ± 0.8	46.3 ± 8.9[b]	30.3 ± 6.6[b]
Control	65 ± 7	18.1 ± 2.7	9.4 ± 1.9	35.6 ± 0.8	26.2 ± 2.2
Phentolamine	67 ± 10	17.4 ± 3.5	8.3 ± 2.2	32.4 ± 4.3[c]	31.8 ± 2.0
Phentolamine + SFNS	62 ± 10	16.9 ± 3.5	9.4 ± 3.4	32.5 ± 3.3	28.2 ± 3.4
Control	60 ± 4	15.1 ± 1.5	11.0 ± 1.5	27.8 ± 4.1[c]	29.0 ± 6.0
Prazosin	75 ± 3[b]	18.2 ± 2.1[b]	6.1 ± 1.8[b]	42.8 ± 7.0[b]	25.9 ± 5.0
Prazosin + SFNS	41 ± 7[b]	9.0 ± 2.3[b]	12.9 ± 2.2	46.4 ± 6.0[b]	25.3 ± 2.0
Control	64 ± 10	16.6 ± 2.1	9.4 ± 1.5	28.3 ± 0.7	24.5 ± 1.8
Yohimbine	41 ± 7[b]	10.9 ± 1.5[b]	13.7 ± 2.1[b]	38.4 ± 5.8[b]	29.2 ± 1.9
Yohimbine + SFNS	37 ± 9[b]	8.8 ± 1.3[b]	16.5 ± 1.8[b]	39.3 ± 1.0[b]	24.6 ± 2.6
Control	64 ± 7	18.5 ± 3.4	9.0 ± 1.6	36.1 ± 4.8	34.2 ± 3.8
Pyrilamine maleate	49 ± 5[b]	12.6 ± 1.7[b]	13.1 ± 1.7[b]	36.0 ± 2.7	31.2 ± 1.9
Pyrilamine + SFNS	45 ± 6[b]	7.6 ± 1.0[b]	9.2 ± 1.1	80.6 ± 8.1[b]	47.1 ± 7.2[b]
Control	74 ± 6	15.7 ± 1.5	5.5 ± 0.9	30.4 ± 2.3	22.5 ± 3.5
Metiamide	72 ± 5	15.0 ± 1.8	5.9 ± 0.8	26.1 ± 1.1	19.2 ± 5.1
Metiamide + SFNS	47 ± 6[b]	3.6 ± 0.6[b]	4.2 ± 0.6[b]	44.1 ± 7.8[b]	35.0 ± 7.7[b]
Control	65 ± 6	15.1 ± 2.1	8.1 ± 1.6	35.2 ± 4.6	33.3 ± 3.7
Pyrilamine + metiamide	56 ± 6	12.2 ± 1.4	9.7 ± 1.4	37.7 ± 6.2	27.8 ± 3.8
Pyrilamine + metiamide + SFNS	48 ± 4[b]	6.8 ± 2.0[b]	7.0 ± 1.2	67.4 ± 12.0[b]	52.2 ± 8.9[b]

[a] Significantly greater than $\bar{t}_{Sr}$.
[b] Significantly different from control ($P < 0.05$).
[c] Not significantly greater than $\bar{t}_{Sr}$.

in the presence of yohimbine further decreased Q_s to 53% of control and further increased Q_c to 175% of control in contrast to the drug alone values.

Administration of the histaminergic antagonists pyrilamine and metiamide individually and together did not significantly change blood flow resistance. Blood flow distribution was not altered by metiamide. However, pyrilamine significantly decreased Q_s to 66% of control and significantly increased Q_c to 145% of control ($P < 0.05$). Pyrilamine plus metiamide marginally increased Q_c. SFNS during infusion of pyrilamine further decreased Q_s to 41% of control ($P < 0.05$) and returned Q_c to the control level ($P < 0.05$). The decrease in Q_s was also significantly less than with pyrilamine alone ($P < 0.05$). SFNS with metiamide significantly decreased Q_s to 23% of control and decreased Q_c to 76% of control ($P < 0.05$). SFNS during the infusion of pyrilamine plus metiamide significantly decreased Q_s to 45% of control ($P < 0.05$) and marginally decreased Q_c to 85% of control.

Indicator Recoveries. The recovery in the venous outflow of ^{131}I-albumin was consistent and averaged 93 ± 1% for all of the experimental procedures. The recovery of ^{85}Sr-labeled microspheres is reported in Table II. The variability of recovery after two consecutive injections of ^{85}Sr-labeled microspheres was 3.4 ± 1.4% (10 dogs). SFNS significantly decreased the recovery of microspheres ($P < 0.05$). Phentolamine and metiamide did not change the recovery of microspheres from control values. Norepinephrine, yohimbine, pyrilamine, and pyrilamine plus metiamide each significantly reduced the recovery of microspheres ($P < 0.05$). Prazosin significantly increased the recovery of microspheres ($P < 0.05$). SFNS with phentolamine did not change the recovery of microspheres. SFNS with prazosin, SFNS with metiamide, and SFNS with pyrilamine and metiamide reduced microsphere recovery significantly below the control and antagonist only levels. SFNS with yohimbine and SFNS with pyrilamine each had microsphere recoveries similar to that with the compounds alone.

Mean Transit Times. The mean transit times ($\bar{t}$) as measured from the venous outflow time-concentration curves of the plasma label ^{131}I-albumin ($\bar{t}_A$) and ^{85}Sr-labeled microspheres ($\bar{t}_{Sr}$) (15 μm) are presented in Table II during control, infusion of antagonist drugs, and SFNS. With two exceptions noted in Table II and Figure 2, $\bar{t}_A$ was significantly ($P < 0.05$) greater than for $\bar{t}_{Sr}$. The labeled albumin would be expected to flow through all patent capillaries and AVA in the microcir-

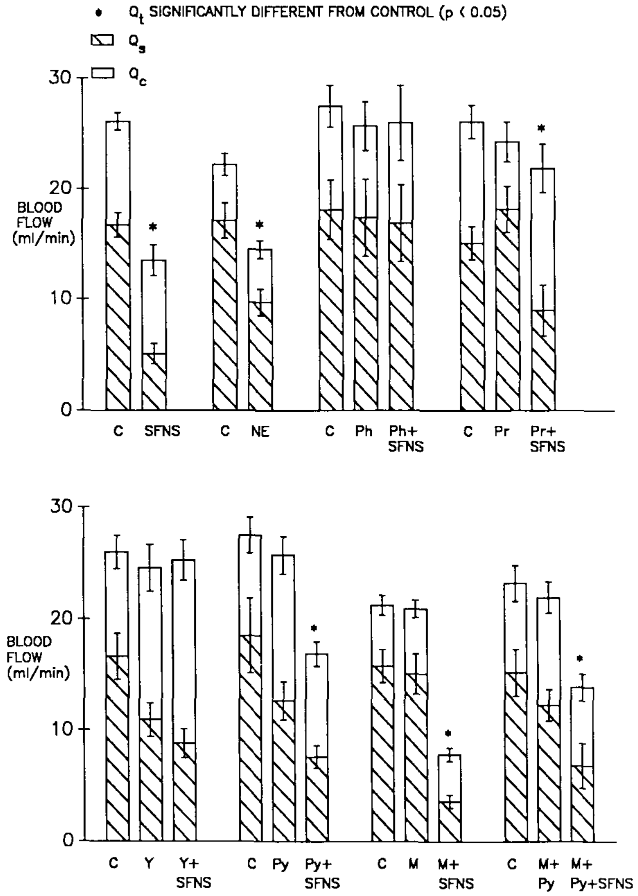

Figure 1. Total (Q_T), AVA (Q_s), and nutritional (Q_c) blood flow in the dog hind paw during SFNS with adrenergic and histaminergic antagonists. Brackets indicate ± SEM of Q_S and Q_c. See Table I for Q_T values. NE, norepinephrine; Ph, phentolamine; Pr, prazosin; Y, yohimbine; Py, pyrilamine; M, metiamide.

culation whereas the labeled microspheres reaching the venous outflow would be those having passed through the microvascular circuits containing patent AVA.

SFNS significantly ($P < 0.05$) increased $\bar{t}_A$ and $\bar{t}_{Sr}$ to 228% and 270% of control, respectively. In contrast, norepinephrine significantly increased $\bar{t}_A$ to 157% and $\bar{t}_{Sr}$ to 141% of control.

The α-adrenergic receptor antagonist phentolamine did not change $\bar{t}_A$ and $\bar{t}_{Sr}$ from the control values. However, prazosin and yohimbine significantly increased $\bar{t}_A$ to 153% and 136% of the control values without changing $\bar{t}_{SR}$. SFNS in the presence of these compounds did not significantly alter these values from the drug-induced levels.

The histamine receptor antagonists pyrilamine and metiamide administered individually and in combination did not significantly change $\bar{t}_A$ and $\bar{t}_{Sr}$ from the control values. However, SFNS with pyrilamine resulted in significant ($P < 0.05$) increases to $\bar{t}_A$ to 223% of control and $\bar{t}_{Sr}$ to only 138% of control. The increase in $\bar{t}_A$ was significantly greater than for $\bar{t}_{Sr}$ ($P < 0.05$). SFNS with metiamide resulted in similar significant increased in $\bar{t}_A$ and $\bar{t}_{Sr}$ to 145% and 156% of control. SFNS with the combination of pyrilamine and metiamide resulted in significant increases ($P < 0.05$) in $\bar{t}_A$ and $\bar{t}_{Sr}$ to 191% and 157% of control. Again, the $\bar{t}_A$ increase was significantly greater than the $\bar{t}_{Sr}$ increase ($P < 0.05$).

Agonist-Antagonist Interactions. The data in Table III show relationships between the agonists and antagonists tested. Angiotensin responses were not significantly modified by any of the antagonists. The norepinephrine constrictor response was partially blocked ($P < 0.05$) by pyrilamine, pyrilamine plus metiamide, and prazosin and completely blocked by yohimbine. The response to phenylephrine was blocked by pyrilamine, pyrilamine plus metiamide, prazosin, and yohimbine. Clonidine responses were reduced ($P < 0.05$) by pyrilamine and pyrilamine plus metiamide and blocked by yohimbine. The vasodilatory responses to sodium nitroprusside were not affected by any of the antagonists. The response to histamine was reduced by pyrilamine, nearly blocked by metiamide, and essentially blocked by the combination of pyrilamine and metiamide ($P < 0.05$).

Discussion

The distribution of blood flow between the parallel-coupled segments of the dog hind paw, the nutritional

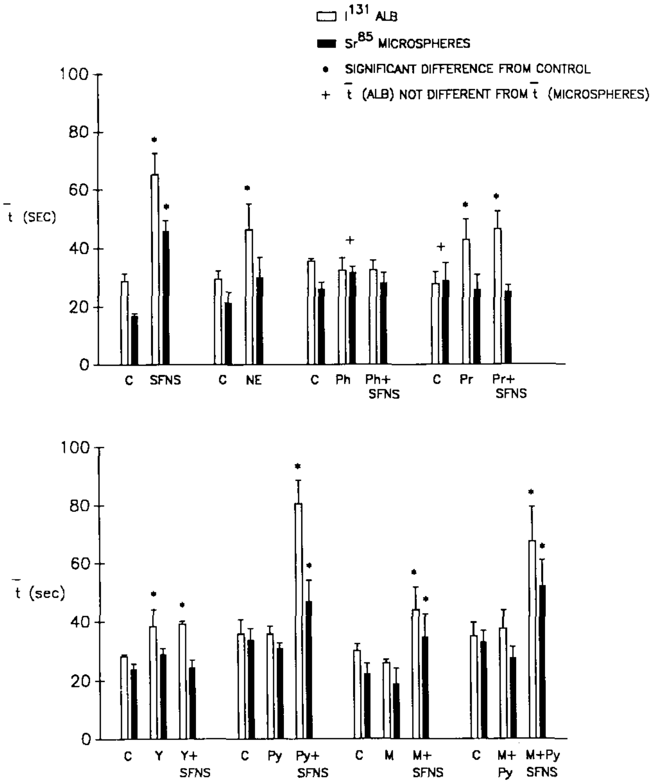

Figure 2. Mean transit time ($\bar{t}$) of ^{131}I-albumin and ^{85}Sr-labeled microspheres through the dog hind paw during SFNS with adrenergic and histaminergic antagonists. Brackets indicate ± SEM. $\bar{t}$ ALB was significantly greater ($P < 0.05$) than $\bar{t}$ microspheres in all cases except where noted by + and in Table II. Abbreviations same as in Figure 1.

Table III. Blood Flow in the Presence of Agonist as a Percentage of Baseline Flow with and without Antagonists Present (Group B)

	Baseline (F)^a	Pyrilamine (F)	Metiamide (F)	Pyrilamine + Metiamide (F)	Prazosin (F)	Yohimbine (F)
Angiotensin	36 ± 9	48 ± 11	34 ± 3	38 ± 4	38 ± 9	48 ± 14
Norepinephrine	42 ± 5	88 ± 6^b	32 ± 5	74 ± 12^b	88 ± 12^b	100 ± 0^b
Phenylephrine	43 ± 7	99 ± 1^b	28 ± 3	100 ± 0^b	95 ± 5^b	94 ± 6^b
Clonidine	34 ± 5	74 ± 11^b	37 ± 6	82 ± 4^b	45 ± 7	95 ± 5^b
Nitroprusside	117 ± 2	127 ± 4	114 ± 3	117 ± 5	129 ± 6	139 ± 15
Histamine	124 ± 5	111 ± 3^b	106 ± 3^b	101 ± 3^b	112 ± 6	131 ± 20

[a] F = % baseline blood flow.
[b] Significantly different from control ($P < 0.05$).

or capillary circuit, and the non-nutritional or arteriovenous anastomosis circuit could be the result of several control systems (19). Two neural controls that have been implicated are the α-adrenergic system and the histaminergic system (13). Since there is evidence for considerable interaction between the agonists and the receptors involved, it was considered necessary to evaluate the effects of the two systems using a combination of adrenergic and histaminergic antagonists. This was done during stimulation of the superficial fibular nerve that influences both the nutritional and AVA circuits in the dog hind paw and appears to contain fibers involved with both the adrenergic and histaminergic systems (2).

Since there are interactions between control systems (1), a series of experiments was conducted to show relationships between the agonists and antagonists tested. Independent agonists were tested to ensure reactivity of the vascular system. The vasoconstrictor angiotensin and the vasodilator sodium nitroprusside responses were not modified by any of the antagonist compounds. The responses to norepinephrine were partially blocked by pyrilamine and prazosin and completely blocked by yohimbine. Phenylephrine an α_1 agonist was blocked by pyrilamine prazosin and yohimbine. The α_2 receptor responses to clonidine were partially blocked by pyrilamine and nearly totally blocked by yohimbine. These responses indicated that the H_1 receptor antagonist also blocks responses to α-adrenergic agonists. Neither pyrilamine or metiamide totally blocked the response to histamine. However, the combination of the H_1 and H_2 receptor antagonists did block the vasodilator actions of histamine. The adrenergic blockers prazosin and yohimbine did not significantly affect the histamine response.

The lack of specific selectivity of the antagonists used in this study make interpretation of the results difficult. Yohimbine, the α_2 receptor antagonist, also blocks the actions of α_1 agonists and pyrilamine, the H_1 antagonist, blocks α-adrenergic agonists. However, we have found varying the dosage does not improve the situation since the antagonists then do not effectively block the appropriate activity, e.g., pyrilamine does not block the effects of histamine. Therefore, the interpretations of the data are made with these difficulties taken into consideration.

It has been reported previously that SFNS increases blood flow resistance by constricting arterioles, AVA, small arteries, and small veins (14–18). In addition, the data in this report show that SFNS causes a significant decrease in Q_s with no change in Q_c. This supports the hypothesis that SFNS has its major resistance effect on the AVA circuit. Previous experiments using the permeability surface area product and the capillary filtration coefficient measurements to assess flow distribution have been inconclusive and have even suggested, in the presence of other data to the contrary, that capillary flow was reduced (6). The microsphere recovery data are more consistent and reliable being free of the many criticisms such as flow dependency of the permeability surface product and accurate determination of the fraction of the venous pressure increment transmitted back to the capillaries when determining the capillary filtration coefficient.

Even though flow redistribution was unequal, $\bar{t}_A$ and $\bar{t}_{Sr}$ were both increased by comparable amounts with SFNS. The microspheres reaching the venous outflow have to pass through vessels greater than 15 μm in diameter which presumably would be the AVA circuit (8, 11, 12). Therefore, increased resistance with constant perfusion pressure in this circuit could be expected to reduce volume flow and therefore reduce the velocity of flow and increase $\bar{t}_{Sr}$ if the cross-sectional area decreased proportionately less than resistance increased. Since albumin circulates through both of the parallel-coupled circuits, $\bar{t}_A$ would also be expected to increase due to the reduced flow velocity through the AVA circuit and thereby prolonging the downslope of the time-concentration curve. Also since SFNS affects the arterioles, redistribution of flow to longer capillary circuits would contribute to the elevated $\bar{t}_A$. It is noteworthy that with SFNS the recovery of microspheres was significantly reduced whereas during norepinephrine infusion there was no significant change. This would indicate SFNS selectively increased AVA resistance whereas norepinephrine may have increased nutritional circuit resistance. However, Q_c was not changed.

The α_1-blocking agent prazosin did not significantly change the total blood flow resistance but did decrease Q_c and increased Q_s. As would be expected, $\bar{t}_A$ was increased due to the elevated resistance and possible redistribution of flow in the capillary circuit without changing $\bar{t}_{Sr}$. Prazosin apparently blocked α-receptors in the AVA circuit, resulting in a large decrease in resistance and flow redistribution toward the AVA. This might suggest that the AVA circuit has a preponderance of α_1 receptors that were blocked by this drug. However, SFNS in the presence of prazosin resulted in redistribution of flow similar to that without any antagonist, i.e., a significant reduction in Q_s and returned Q_c to the control level. This suggests prazosin blocked the effects of the adrenergic agonists on α_1 receptors in the AVA circuits of the hind paw preparation. However, since the increase in AVA circuit resistance with SFNS was not blocked it would appear that the postjunctional α_2 receptors were not affected by the adrenergic antagonist. Since the reduction in Q_s was moderately attenuated, this would suggest some α_1 receptor control of AVA. The $\bar{t}_A$ was elevated by prazosin and not further changed by SFNS. This could result from lower flow velocity in the capillary circuit along with possible redistribution of flow to longer circuits in the capillary circuit. This could be the result of unmasking of undefined vasodilator neural effects with SFNS since Q_c increased.

The adrenergic α_2-blocking agent yohimbine, in contrast to prazosin, caused decreased Q_s and increased Q_c. Thus, vessel wall receptors in arterioles (20) of the capillary circuit apparently were blocked, reducing resistance through this circuit and thus redistributing the flow toward the capillaries. The elevated AVA resistance may be the result of a direct affect of yohimbine on the vessels of this circuit. $\bar{t}_A$ and $\bar{t}_{Sr}$ both increased due to the elevated flow through the longer and more complex capillary bed and the increased resistance in the AVA. As with prazosin, SFNS in the presence of yohimbine significantly reduced Q_s and increased Q_c, again possibly due to vasodilator influences with SFNS. However, in this case the total flow resistance was minimally changed. Thus, the resistance increase in the AVA was essentially balanced by a resistance decrease in the nutritional circuit. This is supported by the increase in $\bar{t}_A$ due to the larger fraction of flow through the circuitous capillary beds.

Although pyrilamine did not significantly change total resistance, the balance between nutritional and non-nutritional circuit resistances were altered so that Q_s was decreased and Q_c was increased. Pyrilamine, although an H_1 receptor antagonist, has properties similar to the adrenergic blockers. Like yohimbine, Q_s was decreased and Q_c was significantly increased by the drug. There was little change in $\bar{t}_A$ or $\bar{t}_{Sr}$. This was unlike either prazosin or yohimbine, both of which increased these values. Therefore, the H_1 receptor antagonist appears to not increase the complexity of the nutritional circuit, allowing the increased blood flow to pass rapidly through the vasculature. SFNS during blockade with pyrilamine increased total resistance, decreased Q_s even further, but significantly decreased Q_c to the control level. Therefore, the increased total resistance was the result of increases in both AVA resistance and in nutritional flow resistance. As would be expected with increased resistance, $\bar{t}_A$ and $\bar{t}_{Sr}$ were increased. The much greater increase in $\bar{t}_A$ than $\bar{t}_{Sr}$ would suggest that the increase in capillary circuit resistance not only reduced the blood flow rate but also resulted in longer more circuitous routes.

Metiamide, an H_2 receptor antagonist, did not alter the total resistance or the resistances in the two parallel-coupled circuits. Therefore, as expected $\bar{t}_A$ and $\bar{t}_{Sr}$ were unchanged. However, SFNS greatly increased total flow resistance, resulting in a large decrease in Q_s with a small decreased in Q_c with significant increases in $\bar{t}_A$ and $\bar{t}_{Sr}$. Since this response to SFNS was very similar to the response to SFNS with no antagonist drug present, it would appear that H_2 receptors were not involved in this response.

The combination of the H_1 and H_2 receptor antagonists did not alter total resistance, did not significantly change Q_s and Q_c, and consequently did not change $\bar{t}_A$ and $\bar{t}_{Sr}$. It would appear that metiamide modified the response to pyrilamine alone, indicating interaction between the drugs and the H_1 and H_2 receptors. The major responses to SFNS in the presence of the H_1 and H_2 receptor antagonists were a significant increase in total resistance with a significant decrease in Q_s and a minimal decrease in Q_c. $\bar{t}_A$ and $\bar{t}_{Sr}$ were also significantly increased. The response to SFNS in the presence of pyrilamine and metiamide did not differ from the response to SFNS without antagonists.

It is evident that the distribution of blood flow between the AVA and capillary circuits in the dog hind paw during SFNS was not modified by the histaminergic receptors. Since the antiadrenergic and antihistaminergic actions of pyrilamine may compete, this could result in no change in the responses to SFNS. However, the adrenergic receptors were clearly involved in the response since phentolamine, an α_1 and α_2 antagonist, blocked the entire response to SFNS. Prazosin attenuated the increase in total resistance as well as the increase in AVA resistance. Yohimbine prevented increased total resistance, attenuated the increase in AVA resistance, and unmasked a decrease in capillary circuit resistance. It would appear that the increase in AVA resistance with SFNS was due to a combination of α_1 and α_2 receptor stimulation. Yohimbine apparently blocked α_2 receptors in the nutritional circuit, resulting in reduced resistance with SFNS that may have been due to cholinergic, substance P, or other vasodilator controls. Since H_1 and H_2 blockers either mimicked the adrenergic blockers or had no effect on blood flow distribution, histaminergic effects apparently were not important in this regard. This is true even though histamine is released with SFNS which results in increased capillary permeability to albumin (2).

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