Capsaicin-Sensitive Nerves Modulate Reactive Hyperemia in Rat Gut (43362)

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Abstract. **Reactive hyperemia (RH) is a local, vascular response that occurs following release from mechanical occlusion of an artery, with restoration of intra-arterial pressure. The mechanism of this postocclusion hyperemia in the gut has not been identified, although metabolic, myogenic, and neurogenic mediators of this response have been proposed. The present study was conducted to evaluate a possible modulatory role for sensory innervation of the intestinal vasculature in RH, using acute and chronic treatment with capsaicin applied in different ways. In anesthetized rats, the velocity of flowing blood in the gut was determined continuously with a pulsed Doppler velocimeter, and arterial pressure was determined with a transducer. The increase in calculated intestinal vascular conductance at the height of RH (C_h), the excess volume of blood accumulating during RH, and the duration of the hyperemia were also used to quantify RH after occluding the anterior mesenteric artery for 30, 60, and 120 sec. In the initial control group of rats, the maximal increases in the velocity of flowing blood during RH were 61 ± 4%, 90 ± 7%, and 129 ± 10% of control, conductances were increased to 192 ± 5%, 222 ± 12%, and 267 ± 15% of control, volumes were 3.5 ± 0.6 ml, 7.2 ± 0.4 ml, and 16.2 ± 1.8 ml, and durations of hyperemia were 78 ± 5 sec, 93 ± 6 sec, and 178 ± 7 sec, respectively, after each elapsed period of occlusion. Acute treatment with periarterial capsaicin significantly decreased peak conductances in RH by 15–35% for all occlusions tested and reduced both volume and duration values. Rats treated with capsaicin in neonatal life exhibited reduced C_h values, as did adult rats treated chronically with capsaicin. Both periarterial and intrajejunal treatment with capsaicin decreased the duration of RH. Hexamethonium increased both C_h and the duration of RH and tended to reverse reductions in these parameters caused by capsaicin. These results suggest that sensory innervation of the intestinal vasculature exerts a modulatory influence in the regulation of intestinal RH.** [P.S.E.B.M. 1992, Vol 199]

Reactive hyperemia (RH) is present in most vascular beds, including the intestine. It is a local vascular response, following release from arterial occlusion and restoration of arterial pressure, in which blood flow to the gut increases rapidly and overshoots the preocclusion value (1, 2). The underlying mechanism of intestinal RH has not received much recent investigative attention. Relaxation of intestinal resistance vessels, observed during RH, may involve humoral, myogenic, or neurogenic factors. The possible roles of myogenic and metabolic factors in the mediation of intestinal RH have been considered by other investigators (3–6).

Recent experimental evidence suggests that the intestinal hyperemia seen after release from arterial occlusion is modulated by altered activity of the sympathetic nerves (7). Thus, RH and the repayment of an oxygen debt (8) may be modulated by nervous mechanisms that promote reperfusion of the tissue after occlusion. Because of evidence for sympathetic and sensory interactions during periods of stress that alter cardiovascular parameters (9), we examined the possibility that such interactions might also occur during RH and that unmyelinated C fibers might participate in neurogenic modulation of RH. The purpose of this study was to evaluate the role of capsaicin-sensitive nerves of the gut in the modulation of intestinal RH.

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Our findings demonstrate a modulatory role for the sensory nervous system in intestinal RH.

Materials and Methods

Experiments were performed on 67 fasted male Sprague-Dawley rats (Sasco), weighing 270–320 g. Animals were anesthetized with 50 mg/kg ip sodium pentobarbital (Sigma). The animals were artificially ventilated (model 683; Harvard). The core temperature was maintained at 37°C by warming each animal with a heating pad, monitored by a rectal thermistor and regulator (model 74; Yellow Springs Instrument). During each experiment, systemic arterial blood pressure (BP) was monitored via a saline-filled catheter inserted into the right carotid artery and connected to a strain-gauge transducer (model P-50; Gould-Statham). The right jugular vein was cannulated for injection of drugs and supplemental anesthetic as needed. The heart rate was monitored electronically from the phasic blood flow estimations.

A midline laparotomy was performed to expose the main trunk of the anterior mesenteric artery for placement of a flow probe (1.0 mm i.d.) on the vessel to estimate the velocity of flowing blood (VBF). The probe was positioned 4–5 mm distal to the origin of the anterior mesenteric artery to avoid turbulence beneath the probe. VBF was measured with a directional pulsed Doppler velocimeter (model 545C-4; Bioengineering, University of Iowa). Signals were recorded as the pulsatile and mean flow velocities of a Doppler shift in kilohertz (10). Mechanical zero flow was established during each experiment with a stainless steel, vascular clamp for occlusion of the anterior mesenteric artery, placed distal to the flow probe so as not to compress the periarterial nerve trunks. Continuous recordings of mean BP and both phasic and mean VBF were made on a polygraph (model R611; Sensor Medics Dynograph). Routine monitoring of phasic Doppler signals was performed to ensure appropriate wave signal forms and to be certain that there was no aliasing or chopping of peak signals.

In eight separate groups of rats, 30, 60, and 120 sec of complete arterial occlusion were performed during control and experimental periods. In Table I, mean VBF and BP values are presented before occlusion (basal) and at the peak response of RH. Basal mesenteric arterial conductance and conductance at the time of peak VBF during RH were each calculated from the quotient of mean VBF divided by mean BP (mV/mm Hg) at each time. Conductance changes (C_h) were expressed as a percentage of basal conductance in Figures 1–6.[2]

[2] Peak velocity of blood flow is not a good index of vascular tone when changes in blood flow and pressure are occurring simultaneously (W. W. Lautt, Microvasc Res **37**:230–236, 1989). For a related discussion on measures of vascular tone and conductance, see Lautt and co-workers (Can J Physiol Pharmacol **66**:1174–1180, 1988).

Portal venous pressure was not measured in these experiments and was not included in the calculation of conductance, because we have previously found that portal pressure changes in these types of experiments by 3 mm Hg or less (11). However, in a separate control study (Group X), we reexamined this matter and found that the magnitude of change in portal pressure did not significantly affect the calculation of C_h in RH studies.

The volume of excess blood accumulating during RH (termed "volume") was determined from the recording of VBF as the area under the RH curve, whose base is a horizontal line connecting the basal VBF to the end of the hyperemia. A measurement system (Jandel Scientific Sigma Scan) was used to convert units of area into milliliters of blood. The duration of RH was measured in seconds after release from occlusion, from the point in time when VBF exceeded the basal value until VBF had returned to the basal value.

After the surgical preparation was completed, hemodynamic parameters were allowed to stabilize for 30 min. One of 10 experimental protocols was then initiated. In each protocol, a group of at least five rats was studied. In Group I rats, RH responses following 30-, 60-, and 120-sec arterial occlusions were observed before and after administration of capsaicin (Fluka), which was applied locally to periarterial nerves to evoke functional depletion of neuropeptides (11–14). Silastic coated sponge cuffs were used to apply 0.5 mg of a 1% (w/v) solution of capsaicin to the nerves. The vehicle for capsaicin consisted of 10% ethanol, 10% Tween 80, and 80% physiological saline. The perineural cuff was placed around the trunk of the anterior mesenteric artery, and 0.05 ml of the capsaicin solution was injected inside the cuff. One half hour after periarterial placement of capsaicin, when mean BP and VBF values were stable, RH responses were recorded again, following each period of arterial occlusion.

In Group II rats, the three sequential durations of arterial occlusions were performed before and within 15 min after a slow intravenous injection of hexamethonium (Sigma) in a dose of 10.0 mg/kg. Possible acute interactions of sympathetic nerves and sensory nerves on RH were explored in this group by comparing control responses to those following ganglionic blockade and to those following ganglionic blockade combined with periarterial capsaicin (9, 14–16).

In Group III rats, RH responses were examined for all three occlusion periods, under control conditions, following application of periarterial capsaicin (11–13), and then following both periarterial capsaicin and hexamethonium. The two drugs were administered as described previously.

In Group IV rats, arterial occlusions were performed 30 min after a solution of capsaicin was applied intrajejunally via a silicone rubber cannula inserted into the proximal part of the jejunum through a small

incision located 2 cm from the pylorus. A 2-ml volume of the previously described capsaicin solution was injected into the jejunal lumen (11, 13). To determine the extent of delivery of the drug, 2 ml of Evans blue dye (Eastman) containing 4 mg of capsaicin was injected into the intestinal lumen. In this group, the RH response following a 60-sec occlusion period was also examined after both intrajejunal capsaicin infusion and subsequent administration of hexamethonium.

In Group V rats, RH responses were observed during the three periods of arterial occlusions in littermates from Group VI rats, both before (control) and after periarterial capsaicin. The drug was applied as described above.

In Group VI rats, the RH response was studied in animals that had been pretreated with capsaicin in neonatal life (12, 17, 18). In these animals 50 mg/kg of capsaicin was injected subcutaneously on the second and on the third days of life to evoke the chronic action of capsaicin on sensory nerves (11, 13, 16, 19–21). Control rats from the same litters (Group V, control) were sham treated with the same volume of the vehicle for capsaicin. When sham-treated and capsaicin-treated rats had attained weights of 270–300 g, they were used for experiments. The same-treated rats served as controls for neonatally capsaicin-treated animals.

In Group VII, adult rats were pretreated with the vehicle used for Group VIII rats (adult capsaicin treatments). Hence, Group VII rats served as controls for Group VIII rats.

In Group VIII, adult rats were chronically pretreated with capsaicin (170 mg total dose divided into daily subcutaneous injections for 7 days, followed by 2 days without injections, before the experiment was initiated; 19, 20). Then, after anesthetization and surgical preparation, RH responses were compared, before and after hexamethonium, with responses observed in animals from Group VII.[3]

In Groups IX and X, two separate series of rats were studied in order to provide control data concerning possibly confounding variables. In Group IX (six rats), temporal effects on RH responses were evaluated by performing 60 sec of occlusion and release manipulations at zero time, 40 ± 2 min later, and 104 ± 23 min later. A comparison was made of RH parameters between these repeated occlusions over time.

In Group X (five rats), C_h values were calculated from control experiments in which RH was elicited after 30-, 60-, and 120-sec occlusions. In addition to measuring VBF and BP, portal venous pressure was also measured. C_h values were computed in two ways: (i) from basal and peak conductance calculations in which mean portal pressure values were subtracted from mean BP values; and (ii) from basal and peak conductance calculations in which portal pressure values were not subtracted from BP values. A statistical comparison was made of the difference between C_h computations.

Statistics

All data are presented as means ± SE. The significance of changes in measured values from control was determined using the two-tailed Student's *t* test for either grouped or paired data, with a confidence limit of less than 5%. Analysis of variance procedures were used to examine the multivariate factors of time of occlusion and treatments on the RH responses (C_h, volume, and duration of RH).

Results

In the first four experimental groups, the mean basal mesenteric VBF was 2.4 ± 0.2 V, under control conditions (Table I). The mean basal BP range was 117–121 mm Hg. For these four groups under control conditions, the calculated mean mesenteric vascular conductance was 20 mV/mm Hg. In Groups I–VIII, following each period of occlusion, peak VBF was significantly greater than basal VBF, and BP during peak RH was significantly less than basal BP, except in three cases (Table I). In control experiments, RH responses to 30-, 60-, and 120-sec arterial occlusions were similar to those reported previously (1,8). After release of the occlusion VBF increased to its peak value within 5 sec. Linear increments in peak VBF, C_h volume, and duration were observed in each group, as the period of occlusion was prolonged (Figs. 1–6; Tables I and II).

In Group I, the effects of periarterial application of capsaicin on the RH responses of the mesenteric vascular bed appear in Figure 1 and in Tables I and II. A response pattern similar to that of control was observed with capsaicin. However, capsaicin significantly reduced the C_h, volume, and duration responses to 30, 60, and 120 sec of arterial occlusion, compared with the corresponding control values.

In Group II, the effects of hexamethonium included significant enhancement of the C_h and duration responses to the different periods of occlusion and release (Fig. 2 and Table II). Further treatment with periarterial capsaicin did not significantly alter the effect of hexamethonium on C_h in response to 30, 60, and 120 sec of arterial occlusions.

In Group III, periarterial capsaicin alone induced changes in the RH response that were similar to those observed in Group I (Figs. 1 and 3; Tables I and II). Additional administration of hexamethonium, after treatment with periarterial capsaicin, significantly re-

[3] In our laboratory we check the effectiveness of capsaicin pretreatments with the ocular sensitivity-eye reflex test in the rat (Donnerer *et al.*, Naunyn-Schmiedeberg's Arch Pharmacol **340**:740–743, 1989). In some rats intra-arterial injections of capsaicin at the end of the experiment confirmed the functional sensory deficit (Donnerer and Lembeck, Naunyn-Schmiedeberg's Arch Pharmacol **320**:54–57, 1982).

Table I. Control and Experimental Hemodynamic Data for VBF and Arterial Blood Pressures in Rat Groups I–VIII[a]

Experimental group	Duration of occlusions (sec)	Basal VBF (V)	Peak VBF (V)	Basal arterial pressure (mm Hg)	Peak arterial pressure (mm Hg)
I. a. Control (n = 7)	30	2.4 ± 0.1	3.8 ± 0.2	119 ± 8	100 ± 7
	60	2.4 ± 0.1	4.5 ± 0.2	119 ± 8	101 ± 6
	120	2.3 ± 0.1	5.3 ± 0.3	119 ± 8	102 ± 5
b. After periarterial capsaicin (n = 7)	30	2.6 ± 0.1	3.9 ± 0.2	115 ± 7	99 ± 7
	60	2.5 ± 0.1	4.4 ± 0.2	115 ± 8	98 ± 7
	120	2.3 ± 0.1	4.6 ± 0.3	117 ± 8	93 ± 6
II. a. Control (n = 6)	30	2.7 ± 0.3	4.2 ± 0.4	117 ± 5	102 ± 5
	60	2.6 ± 0.3	4.8 ± 0.4	122 ± 5	102 ± 4
	120	2.4 ± 0.3	4.8 ± 0.6	124 ± 3	96 ± 5
b. After hexamethonium (n = 6)	30	2.0 ± 0.1	3.8 ± 0.2	95 ± 6	82 ± 5[b]
	60	2.0 ± 0.1	4.5 ± 0.3	104 ± 5	84 ± 5[b]
	120	1.9 ± 0.2	4.9 ± 0.4	104 ± 4[b]	87 ± 5
c. Hexamethonium with capsaicin (n = 6)	30	1.8 ± 0.2	3.4 ± 0.3	104 ± 6	85 ± 5[b]
	60	1.7 ± 0.2[b]	3.8 ± 0.4[c]	104 ± 9	82 ± 6[b]
	120	1.7 ± 0.2	4.1 ± 0.4	106 ± 8	83 ± 8
III. a. Control (n = 6)	30	2.4 ± 0.1	4.0 ± 0.3	119 ± 5	100 ± 4
	60	2.6 ± 0.2	4.8 ± 0.4	130 ± 5	103 ± 6
	120	2.5 ± 0.2	5.3 ± 0.5	130 ± 5	102 ± 4
b. After periarterial capsaicin (n = 6)	30	2.6 ± 0.2	3.8 ± 0.3	119 ± 4	104 ± 6
	60	2.6 ± 0.1	4.3 ± 0.3	123 ± 3	103 ± 2
	120	2.3 ± 0.1	4.5 ± 0.4	123 ± 4	103 ± 3
c. Capsaicin with hexamethonium (n = 6)	30	1.9 ± 0.1[b,c]	3.5 ± 0.2[b]	95 ± 5[c]	83 ± 13[b,c]
	60	1.9 ± 0.1[b,c]	3.9 ± 0.4[b]	103 ± 4[b,c]	86 ± 4[b,c]
	120	1.9 ± 0.1[b,c]	4.5 ± 0.4[b]	104 ± 6[b,c]	85 ± 5[b,c]
IV. a. Control (n = 8)	30	2.5 ± 0.1	4.2 ± 0.3	122 ± 6	99 ± 6
	60	2.5 ± 0.1	4.7 ± 0.3	121 ± 5	97 ± 6
	120	2.3 ± 0.2	5.1 ± 0.4	119 ± 6	92 ± 6
b. After intrajejunal capsaicin (n = 8)	30	2.6 ± 0.2	4.2 ± 0.2	119 ± 3	103 ± 4
	60	2.5 ± 0.2	4.7 ± 0.3	122 ± 4	107 ± 5
	120	2.3 ± 0.2	5.2 ± 0.4	121 ± 4	100 ± 4[b]
c. Capsaicin with hexamethonium (n = 6)	30	NA	NA	NA	NA
	60	2.0 ± 0.2[b,c]	3.4 ± 0.5[c]	106 ± 4[b,c]	87 ± 2[c]
	120	NA	NA	NA	NA
V. a. Littermate control (n = 6)	30	1.8 ± 0.2	3.6 ± 0.2	124 ± 9	94 ± 6
	60	1.8 ± 0.3	3.9 ± 0.4	131 ± 11	101 ± 8
	120	1.7 ± 0.2	4.1 ± 0.4	120 ± 10	90 ± 7
b. After periarterial capsaicin (n = 6)	30	1.6 ± 0.1	3.2 ± 0.2	92 ± 10[b]	81 ± 8
	60	1.5 ± 0.2	3.7 ± 0.2	90 ± 7[b]	82 ± 5[b]
	120	1.6 ± 0.1	3.8 ± 0.3	89 ± 6[b]	81 ± 3
VI. a. Neonatal capsaicin (n = 6)	30	2.0 ± 0.1	3.9 ± 0.3	100 ± 2[d]	86 ± 2
	60	2.0 ± 0.1	4.6 ± 0.3[d]	102 ± 3[d]	84 ± 2
	120	2.0 ± 0.1	4.6 ± 0.4	98 ± 5	82 ± 3
VII. a. Adult vehicle control (n = 6)	30	2.3 ± 0.2	3.6 ± 0.3	109 ± 10	91 ± 7
	60	2.2 ± 0.2	4.0 ± 0.4	108 ± 10	88 ± 7
	120	2.1 ± 0.3	4.2 ± 0.6	106 ± 11	91 ± 8
VIII. a. Adult capsaicin (n = 11)	30	3.7 ± 0.3[d]	5.8 ± 0.4[d]	98 ± 5	95 ± 5
	60	3.7 ± 0.3[d]	6.8 ± 0.4[d]	102 ± 5	94 ± 5
	120	3.6 ± 0.3[d]	7.0 ± 0.4[d]	106 ± 6	94 ± 6
b. After hexamethonium (n = 11)	30	3.1 ± 0.2[c]	5.3 ± 0.4	93 ± 4	88 ± 4
	60	3.1 ± 0.1[c]	6.1 ± 0.4	98 ± 5	89 ± 4
	120	3.0 ± 0.2[c]	6.6 ± 0.4	101 ± 5	90 ± 4

[a] Values shown are for VBF and arterial pressures before occlusion (basal) and pressures at the time of peak VBF during RH. Values for VBF are in volts output from the Doppler flowmeter (1 V = 2 kHz shift in the velocity of flowing blood). In every case, peak VBF was significantly greater than basal VBF ($P < 0.05$). In every case, peak arterial pressure was significantly less than basal arterial pressure ($P < 0.05$), except in the case of the 120-sec value for Group Vb and for 30-sec values for Group VIIIab. The n-values shown in parentheses apply to both Table I and Table II. NA, not available.

[b] Denotes $P < 0.05$ significant difference from corresponding control value in the same vertical column of the same group.

[c] Denotes $P < 0.05$ significant difference from the corresponding value in the preceding treatment group.

[d] Denotes $P < 0.05$ significant difference from the corresponding values of littermate or vehicle Groups V or VII for matched controls.

Table II. Control and Experimental Data for Reactive Hyperemia[a]

Experimental group	RH volume (ml) Occlusions			Duration of RH (s) Occlusions		
	30 s	60 s	120 s	30 s	60 s	120 s
I. a. Control	3.5 ± 0.6	7.2 ± 0.4	16.2 ± 1.8	78 ± 5	93 ± 6	178 ± 7
b. After periarterial capsaicin	3.2 ± 0.2	6.0 ± 0.4[b]	11.4 ± 1.0[b]	60 ± 3[b]	69 ± 2[c]	114 ± 12[c]
II. a. Control	4.4 ± 0.7	7.8 ± 1.7	11.9 ± 2.1	73 ± 5	89 ± 8	139 ± 14
b. After hexamethonium	3.5 ± 0.3	7.6 ± 0.8	13.4 ± 2.2	98 ± 9[c]	111 ± 11[c]	182 ± 14[c]
c. Hexamethonium with capsaicin	2.9 ± 0.2	6.4 ± 0.6[d]	12.7 ± 1.5	61 ± 6	96 ± 10	146 ± 10
III. a. Control	3.6 ± 0.8	5.9 ± 1.3	10.2 ± 2.1	66 ± 9	83 ± 11	119 ± 18
b. After periarterial capsaicin	2.3 ± 0.4[b]	4.4 ± 0.8	8.4 ± 1.8	42 ± 6[b]	52 ± 4[b]	72 ± 6[b]
c. Capsaicin with hexamethonium	3.0 ± 0.4[d]	5.6 ± 0.7[d]	11.2 ± 1.8[d]	82 ± 10[d]	89 ± 8[e]	107 ± 10[e]
IV. a. Control	3.5 ± 0.4	5.8 ± 0.7	12.2 ± 1.9	60 ± 5	70 ± 4	121 ± 13
b. After intrajejunal capsaicin	3.2 ± 0.3	5.8 ± 0.6	11.3 ± 1.4	46 ± 4[c]	58 ± 4[b]	88 ± 6[b]
c. Capsaicin with hexamethonium	NA	5.7 ± 0.5	NA	NA	63 ± 3	NA
V. a. Litter mate control	4.5 ± 0.4	6.2 ± 0.5	12.8 ± 2.6	137 ± 17	128 ± 15	221 ± 33
b. After periarterial capsaicin	2.9 ± 0.3[b]	6.0 ± 0.6	11.4 ± 1.8	73 ± 6[c]	100 ± 9	186 ± 29
VI. Neonatal capsaicin	4.0 ± 0.4	7.3 ± 1.0	11.2 ± 1.5	103 ± 11	118 ± 12	168 ± 26
VII. Adult vehicle control	3.8 ± 0.5	6.0 ± 0.9	11.2 ± 3.0	77 ± 5	96 ± 11	128 ± 10
VIII. a. Adult capsaicin	7.3 ± 0.8[b]	14.4 ± 2.5[b]	21.5 ± 1.8[b]	93 ± 3[c]	115 ± 9	174 ± 10[b]
b. After hexamethonium	6.0 ± 0.6	12.0 ± 1.4	23.5 ± 2.5	90 ± 6	106 ± 8	158 ± 12

[a] Values shown are for volume of excess blood accumulating during RH and the duration of reactive hyperemia in eight groups of rats. NA, not available.
[b] $P < 0.05$, indicating a significant difference from control.
[c] $P < 0.01$, indicating a significant difference from control.
[d] $P < 0.05$, indicating a significant difference from the immediately preceding treatment in the same group.
[e] $P < 0.01$, indicating a significant difference from the immediately preceding treatment in the same group.

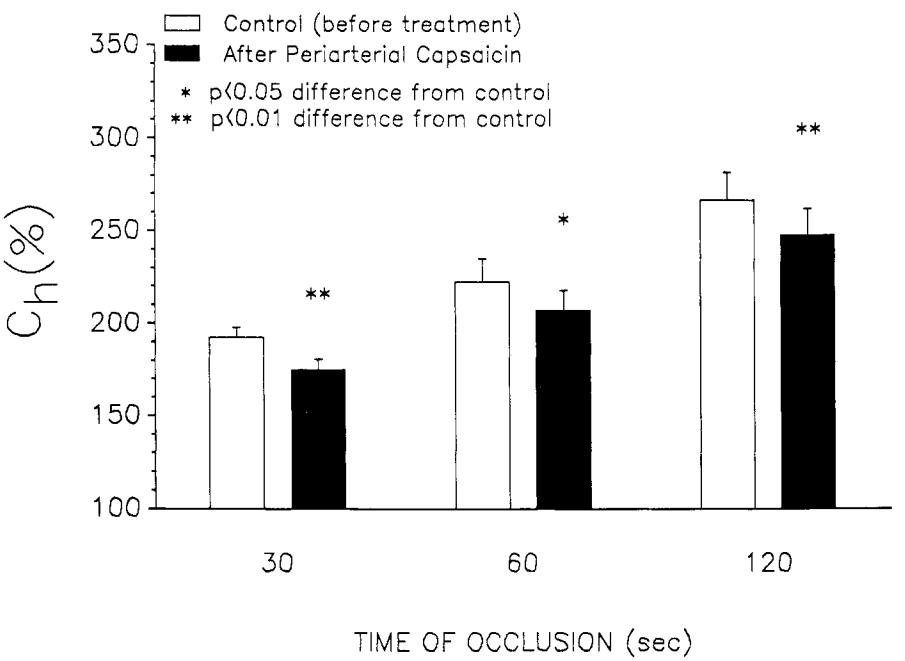

Figure 1. Periarterial capsaicin reduced peak conductance changes (C_h) during RH following 30, 60, and 120 sec of mesenteric occlusion in seven rats.

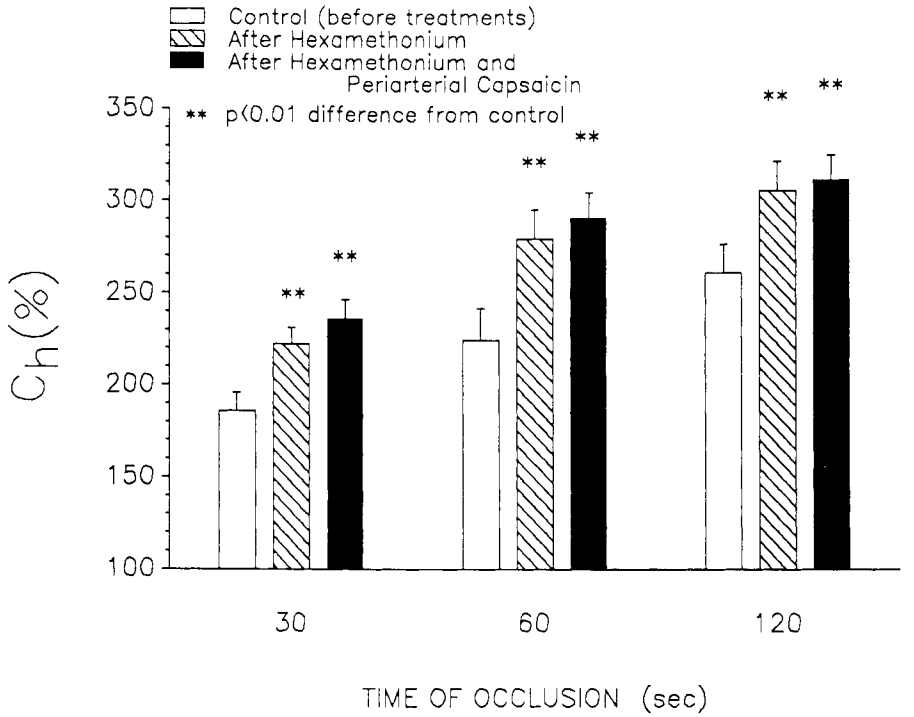

Figure 2. C_h values were increased by hexamethonium after each time of occlusion in six rats. Subsequent treatment with capsaicin was without significant effect on the response to hexamethonium.

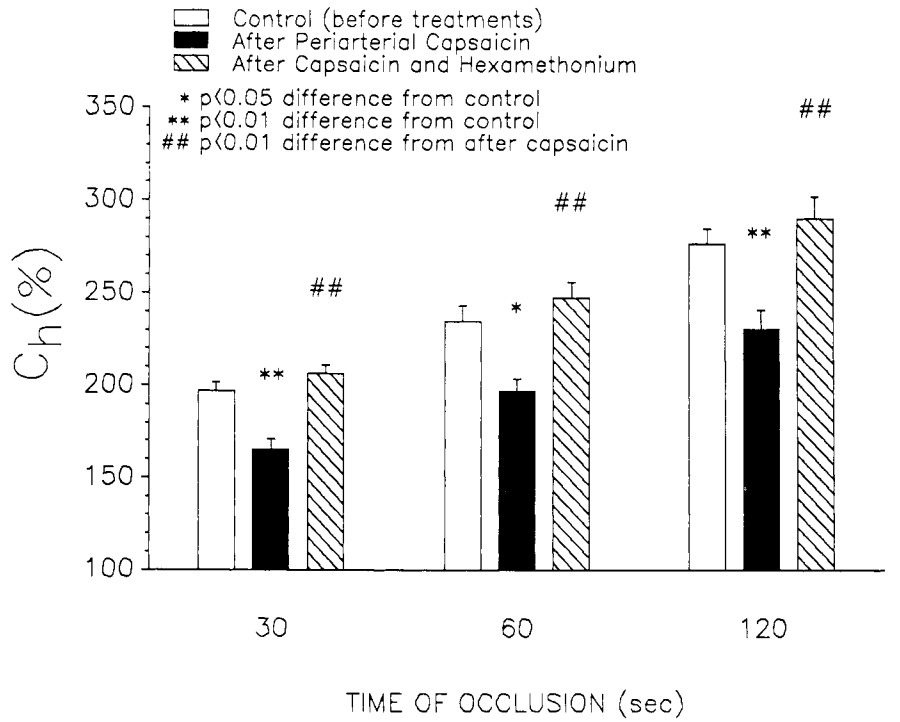

Figure 3. C_h values were reduced by periarterial capsaicin in six rats. The capsaicin-induced depression of peak conductance values was reversed to control values by subsequent administration of hexamethonium.

duced basal VBF and BP values below capsaicin-treated values (Table I). However, addition of hexamethonium did increase C_h, volume, and duration values compared with the capsaicin-treated values (Fig. 3 and Table II).

In Group IV, intrajejunally applied capsaicin significantly reduced the duration of RH for all periods of arterial occlusion, as well as C_h after 60 sec of occlusion (Fig. 4 and Table II). Subsequent administration of hexamethonium reduced both VBF and BP values following 60 sec of arterial occlusion (Table I).

In Group V, the effects of periarterial capsaicin on C_h responses in animals from the same litter were

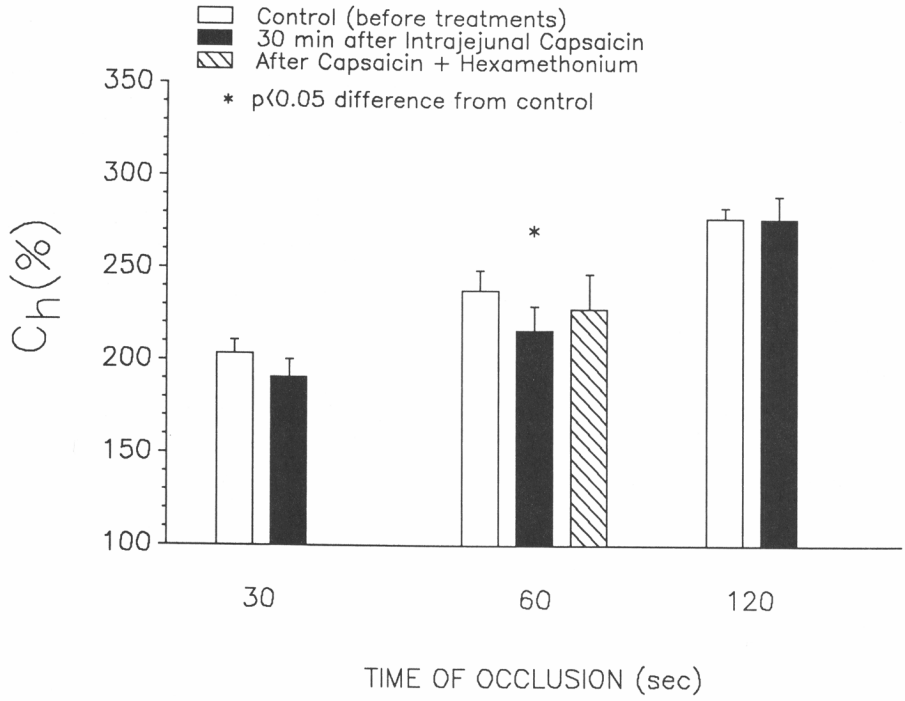

Figure 4. C_h values were reduced by intrajejunal administration of capsaicin after only one period of occlusion in eight rats. Further treatment with hexamethonium did not reverse the effect following 60 sec of occlusion.

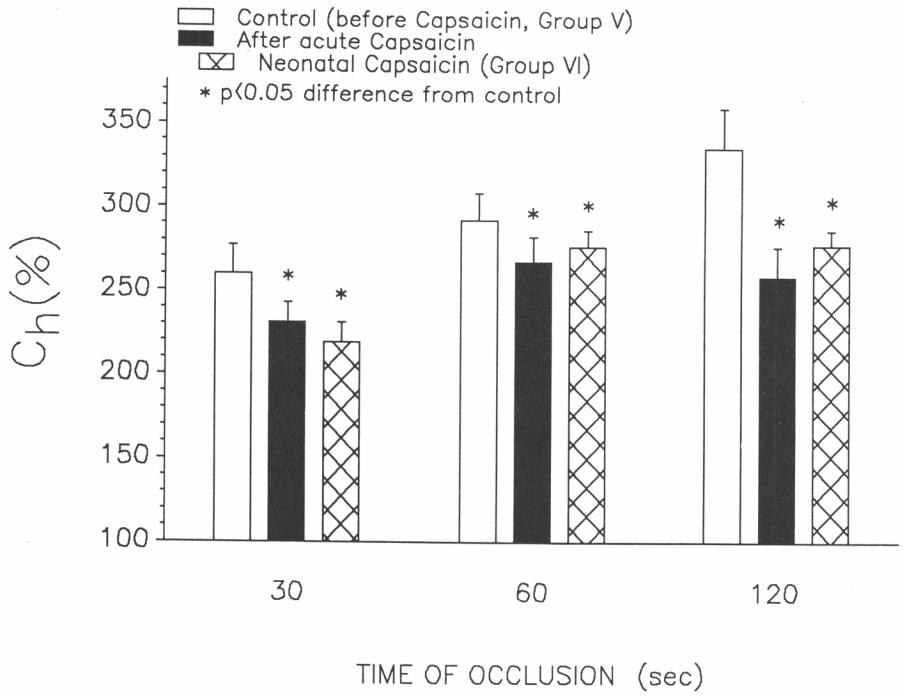

Figure 5. Comparison of C_h values in two groups of six littermate rats each. Group V animals were vehicle treated after birth and had acute periarterial treatment with capsaicin in adult life. Group VI rats were treated with capsaicin in neonatal life. Both acute, periarterial capsaicin and chronic, neonatal capsaicin significantly reduced the peak conductance during RH.

essentially the same as in Groups I and III (Figs. 1, 3, and 5), but there was less consistent inhibition of volume and duration values. In addition, BP values were reduced after treatment with capsaicin.

In Group VI, animals that were pretreated in neonatal life with capsaicin showed the following control values: basal VBF, 2.0 ± 0.1 V; and basal mean BP, 100 ± 2 mm Hg. These pressure values were lower than basal values in Group V controls. RH responses observed in these chronically treated rats were not significantly less than those observed in Group V (Tables I and II).

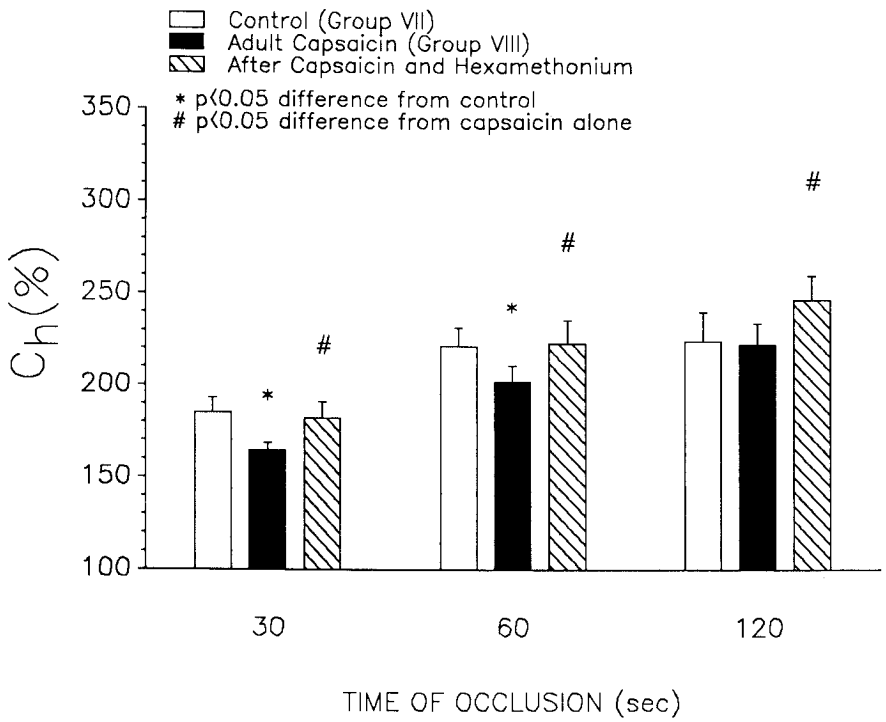

Figure 6. Chronic pretreatment of 11 adult rats (Group VIII) with capsaicin reduced C_h values following each period of occlusion, compared with responses of six control rats (Group VII).

In Group VII, vehicle-treated adult rats exhibited RH responses that were comparable to those of other control groups (Tables I and II).

In Group VIII, adult rats pretreated with capsaicin for 1 week, starting 9 days before the experiments, exhibited the following control values: basal VBF, 3.7 ± 0.3 V; and basal systemic arterial pressure, 102 ± 5 mm Hg. Compared with Group VII control, there was some reduction in C_h values (Fig. 6), but a significant increase in both volume and duration values (Table II). Treatment with hexamethonium did not further potentiate RH responses.

In Group IX, repeated arterial occlusions for 60 sec, performed at zero time, 40, and 104 min later, demonstrated no significant changes in RH parameters among the three time periods. For example, peak VBF values following release from occlusion were 4.2 ± 0.4 V, 4.2 ± 0.8 V, and 4.1 ± 0.6 V, respectively, at each of the three times that occlusions were performed. Similarly, the respective volume values for the three elapsed times were 6.8 ± 0.7 ml, 7.0 ± 0.7 ml, and 7.2 ± 0.4 ml.

In Group X, basal portal venous pressure values were 7–8 mm Hg and increased by 1–3 mm Hg at peak RH. Calculation of C_h during RH following occlusions lasting 30, 60, and 120 sec, with or without subtracting mean portal pressure values from mean BP values, yielded values that were not significantly different among modes of calculation. Thus, C_h values at 30, 60, and 120 sec in computations using BP values only were (respectively) 213 ± 10%, 249 ± 12%, and 269 ± 32%. The corresponding C_h values from computations in which portal pressure values were subtracted from BP values were 220 ± 20%, 239 ± 11%, and 257 ± 28% (respectively).

Discussion

The neurogenic tone of intestinal blood vessels is determined by extrinsic autonomic innervation and by intrinsic nerves of the enteric nervous system (22, 23). The extrinsic innervation of mesenteric vessels is primarily adrenergic. However, there are examples of nonadrenergic and noncholinergic innervation of the mesenteric vasculature (24, 25). In addition, it has been shown that intestinal vessels are innervated by visceral, sensory, afferent nerves (C fibers). These unmyelinated C fibers contain a variety of well-recognized peptides, such as substance P, vasoactive intestinal polypeptide, somatostatin, CCK, and CGRP (19, 20, 26). Such peripheral peptide-containing fibers appear to participate in the transmission of sensory impulses (19, 20), in intestinal thermoreflexes (13), in intestinal postprandial hyperemia (27), and in autoregulatory escape (11). It was, therefore, of interest to determine whether or not peptidergic, afferent neurons participate in intestinal RH. The hemodynamic characteristics of RH observed in the present study are similar to previous findings from our laboratory (7, 28) and to those reported by others (1, 8). Furthermore, we found that RH responses did not vary significantly during the

elapsed time of our experiments.

In order to determine the influence of afferent activity on mesenteric RH responses, the physiological function of C fibers was impaired using the neurotoxin, capsaicin, administered by different routes (11–13, 16–20, 27, 28). Our findings with acute application of capsaicin suggest that afferent C fibers play a significant role in the modulation of RH. When the neurotoxin was applied periarterially, it was more effective in inhibition of RH than was the case with intrajejunal administration of the agent. These quantitative differences in the effects of capsaicin administered via different routes on RH may be due to differences in accessibility to C fibers. The involvement of capsaicin-sensitive afferent neurons in the modulation of RH was further substantiated by the fact that in animals acutely or chronically treated with capsaicin (Fig. 5), the vascular conductance at peak RH was significantly reduced.

The current findings are consistent with our previous work, showing that sensory neurons play a modulatory role in intestinal autoregulatory escape (11). The present findings with an autonomic, ganglionic blocking agent confirm our previous studies about the role of adrenergic innervation in the modulation of RH (7). However, our experiments with periarterial capsaicin treatment did not demonstrate any significant interaction between capsaicin and the peripheral adrenergic system, as was observed in recent electophysiological experiments (14). The lack of effects of capsaicin on RH after hexamethonium could be related to potent vasodilation that could not be counteracted by the relatively weak vasoconstriction following depletion of vasodilatory peptides. Experiments with intrajejunal capsaicin indicate that interaction between capsaicin and adrenergic nerves can occur at a peripheral level, because hexamethonium was without effect on RH, after intrajejunal capsaicin administration. However, the inconsistent effects of hexamethonium in adult capsaicin-treated rats (Group VIII) could also have resulted from a decrease in resting adrenergic activity in these animals. This latter finding is supported by earlier studies that have demonstrated that chronic pretreatment with capsaicin inhibits adrenergic activity (9, 15).

The preceding experimental findings suggest that there is a sensory nerve-dependent component of RH in the mesenteric circulation of control rats. However, at present, there is no direct evidence that this modulation is due to either the presence of a resting sensory influence or to an increase in activation of sensory afferents during mesenteric artery occlusions. It is possible that tissue hypoxia and local production of metabolites during the occlusion period may stimulate the C fibers to release vasodilatory peptides (29). Available evidence indicates that substance P, vasoactive intestinal polypeptide, and CGRP can be released near splanchnic vessels by the stimulation of afferent C fibers (13, 27, 30, 31). These peptides induce vasodilation of the vasculature through interaction with specific receptors on the vessel wall (16, 21, 24). In addition, RH may involve activation of C fibers in response to adrenergic vasoconstriction in the gut (11, 32). Recently, such a negative feedback response to sympathetic activity has been described for capsaicin-sensitive nerves in the guinea pig mesenteric artery by electrophysiological and pharmacological techniques (14).

It is also possible that capsaicin modulates circulatory responses indirectly via effects on other intestinal functions, i.e., motility or absorption. For example, if capsaicin were to inhibit active cotransport of sodium and glucose across the intestinal epithelium, thereby reducing oxygen consumption, this effect might also reduce RH responses. Another alternative consideration may involve a change in vascular reactivity to other endogenous vasodilators by unknown interactions with capsaicin thereby reducing vessel conductance or compliance responses. However, neither the present investigations nor other studies of which we are aware provide evidence to support this possibility.

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