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Response of Muscular and Cutaneous Vessels to Physiologic Stimulation of Chemoreceptors (38505)

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Activation of chemoreceptors produces an increase in total peripheral resistance (1), which indicates vasoconstriction, but the constriction may not occur in all vascular beds. The concept that reflex stimuli produce a uniform sympathetic discharge (2), which would tend to produce vascoconstriction in different vascular beds, has been modified by the demonstration that some reflex stimuli produce profoundly different responses in different vascular beds (3-6). For example, a recent study indicates that pharmacologic activation of arterial chemoreceptors by nicotine or cyanide causes reflex vasoconstriction in muscle but reflex vasodilatation in skin (6). The purpose of this study was to determine whether physiologic stimulation of chemoreceptors causes different responses in blood vessels of skin and muscle.

Materials and Methods. Male mongrel dogs weighing 15-28 kg were anesthetized with chloralose (50 mg/kg) and urethane (500 mg/kg) and treated with decamethonium bromide (0.3 mg/kg). The animals were ventilated with room air and supplemental oxygen to maintain normal systemic arterial blood gases.

A carotid bifurcation was exposed. The internal carotid and all branches of the external carotid arteries were ligated, except for the occipital artery, preserving the blood supply to the carotid chemoreceptor. The common carotid and external carotid arteries were cannulated. Blood to perfuse the carotid was obtained from a femoral artery and flowed into a bubble oxygenator (Travenol regional perfusion oxygenator). The oxygenator was primed with 500 cc of dextran (average mol wt = 70,000). After passing through the oxygenator the blood was rewarmed and pumped at constant flow (100 ± 8.1 ml/min) past an oxygen electrode into the common carotid artery. Perfusion pressure in the carotid was 80 ± 5.5 mmHg (mean ± SE). Blood flowed out through a cannula in the external carotid artery and through a Starling resistor to a jugular vein. The Starling resistor maintained pressure constant in the carotid bifurcation. In most studies the contralateral carotid sinus was denervated and bilateral cervical vagotomy was done.

A gas mixture containing 13% oxygen, 5% carbon dioxide, and 82% nitrogen was bubbled through the oxygenator to maintain normal gas tensions. A mixture of approximately 10% carbon dioxide and 90% nitrogen was used to make the blood perfusing the carotid hypoxic and hypercapnic. One hundred percent nitrogen was used to make the blood hypoxic. These gas mixtures altered gas tensions in the blood perfusing the carotid-chemoreceptor without affecting systemic blood gases. Blood samples were analyzed for P_{O_2}, P_{CO_2}, and pH with an Instrumentation Laboratory ultramicro gas analyzer.

Responses to stimulation of chemoreceptors were observed in the gracilis muscle and hindpaw. The gracilis muscle was dissected free from surrounding tissues except for the gracilis artery, vein, and nerve. The cranial tibial artery to the hindpaw (which has a predominantly cutaneous vascular bed) was exposed about 4 cm upstream from the tarsus and collateral arteries at that level were ligated. The gracilis and cranial tibial arteries were cannulated and perfused separately at constant flow with heparinized arterial blood while perfusion pressure was recorded. Flow to the muscle was 16 ± 1.8 ml/min (mean ± SE) and flow to the paw was 39 ± 4.4 ml/min. With blood flow constant, changes in perfusion pressure reflected changes in vascular resistance in the muscle and paw. Systemic arterial pressure and heart rate also were measured.

Statistical comparisons were made by paired *t* tests.

Results. Blood gases. Bubbling 10% carbon

TABLE I. P_{O_2}, P_{CO_2}, AND pH IN BLOOD PERFUSING CAROTID CHEMORECEPTORS.[a]

	Control	Hypoxia + hypercapnia	Hypoxia
P_{O_2} (mmHg)	98 ± 2.7 (12)	32 ± 1.1 (12)	30 ± 2.4 (4)
P_{CO_2} (mmHg)	38 ± 0.7 (12)	78 ± 2.6 (12)	39 ± 1.4 (4)
pH	7.32 ± 0.02 (9)	7.10 ± 0.02 (9)	7.34 ± 0.03 (4)

[a] Entries represent mean values ± S.E. In parentheses are the number of dogs.

TABLE II. CARDIOVASCULAR EFFECTS OF STIMULATION OF CAROTID CHEMORECEPTORS.

	Resting values	Responses to hypoxia + hypercapnia	Responses to hypoxia
Perfusion pressure (mmHg)			
Gracilis muscle	144 ± 10.7	+63 ± 10.6[a]	+25 ± 5.4[a]
Paw	99 ± 11.3	−16 ± 3.1[a]	−11 ± 2.5[a]
Mean arterial pressure (mmHg)	84 ± 2.7	+12 ± 4.8[a]	+3.3 ± 2.0
Heart rate (beats/min)	162 ± 6.2	−17 ± 4.0[a]	−8.7 ± 4.0
(*n*)	12	12	4

[a] $P < 0.05$, which indicates that responses to the stimuli were statistically significant.

dioxide and 90% nitrogen through the arterial blood perfusing the carotid chemoreceptors for 3 to 7 min resulted in severe local hypoxemia and hypercapnic acidosis (Table I). Bubbling 100% nitrogen through the blood perfusing the chemoreceptors resulted in severe hypoxemia without a change in P_{CO_2} or pH (Table I). Systemic arterial gases did not change: arterial P_{O_2} was 107 ± 5.8 mmHg (mean ± SE), P_{CO_2} was 35 ± 1.1 mmHg, and pH was 7.36 ± 0.01.

Responses to stimulation of chemoreceptors. Stimulation of carotid chemoreceptors by hypoxemia and hypercapnic acidosis produced a differential vascular response characterized by vasoconstriction in the muscle and vasodilatation in the paw (Table II, Fig. 1). Chemoreceptor stimulation also resulted in an increase in systemic arterial pressure and a decrease in heart rate.

Hypoxemia without hypercapnic acidosis also produced vasoconstriction in muscle and vasodilatation in paw (Table II). The responses to hypoxia tended to be smaller than the responses to the combination of hypoxia and hypercapnic acidosis (Fig. 2), but the differences did not achieve statistical significance.

The abrupt change in perfusion pressure during chemoreceptor stimulation (Fig. 1) suggested that the response was reflex rather than a response to a humoral stimulus. In addition, denervation of the carotid bifurcation in three dogs abolished the responses to chemoreceptor stimulation.

Discussion. This study indicates that stimulation of carotid chemoreceptors by the naturally occurring stimuli of hypoxia and hypercapnic acidosis results in differential effects in different vascular beds. Chemoreceptor stimulation produced vasoconstriction in muscle but vasodilatation in the paw, which has a predominantly cutaneous vascular bed.

If arterial baroreceptors were intact, the increase in systemic arterial pressure during chemoreceptor stimulation would activate baroreceptors and could contribute to vasodilatation in the paw. However in most of the studies (including the study in Fig. 1), pressure in the perfused carotid bifurcation was maintained constant and the contralateral carotid sinus and the aortic baroreceptors were denervated, so that aortic and carotid baroreceptor reflexes were not activated by the increase in systemic pressure. It appears that the vasodilatation in the paw is not the result of activation of arterial baroreceptors.

We considered the possibility that the absence of a dilator response in the gracilis muscle might reflect a minimal reflex dilator capacity of these vessels. Other studies, how-

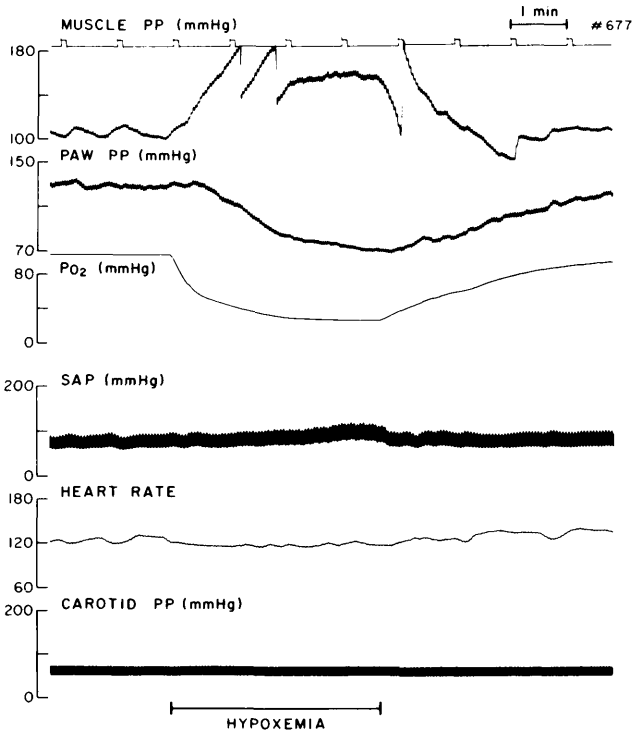

FIG. 1. The measurements are perfusion pressures in the gracilis muscle and paw, PO_2 in the blood perfusing the carotid chemoreceptor, systemic arterial pressure, heart rate, and perfusion pressure in the carotid. During the period marked "Hypoxemia" the blood perfusing the chemoreceptor was hypoxic, hypercapnic, and acidotic. The abrupt changes in perfusion pressure in the muscle occurred when we shifted the baseline to keep the recording within the scale. Physiologic stimulation of carotid chemoreceptors produced vasoconstriction in the gracilis muscle and vasodilatation in the paw.

ever, indicate that the vasodilator response to activation of carotid sinus and ventricular baroreceptors is greater in muscle than in skin (3, 4), which indicates that vessels in gracilis muscle have a profound reflex vasodilator capacity. The reflex vasodilator capacity of the gracilis muscle was demonstrated in one of the present experiments (Fig. 3); the vasodilator response to baroreceptor stimulation was much greater in muscle than in paw, but chemoreceptor stimulation nevertheless produced vasoconstriction in muscle and vasodilatation in paw.

We also considered the possibility that the absence of a constrictor response in the paw might reflect a minimal constrictor responsiveness of these vessels. The vasoconstrictor response to direct sympathetic nerve stimulation, however, is greater in paw than in muscle (7), which indicates that cutaneous vessels have a potent constrictor capacity.

The cardiovascular responses to stimulation of chemoreceptors by hypoxia, hypercapnia, and acidosis tended to be greater than the responses to hypoxia alone. It appears that hypercapnia added to hypoxia may potentiate the vasodilator response in

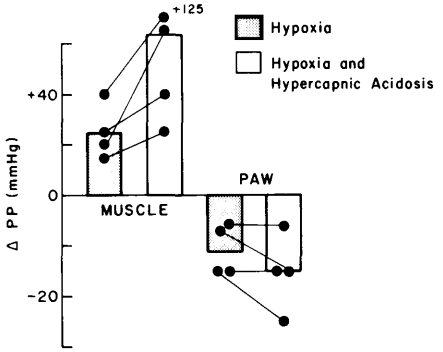

FIG. 2. Changes in perfusion pressure (ΔPP) in the gracilis muscle and paw in response to stimulation of carotid chemoreceptors by hypoxic blood (stippled bars) and by hypoxic, hypercapnic, and acidotic blood (clear bars). The bars indicate mean values from four dogs.

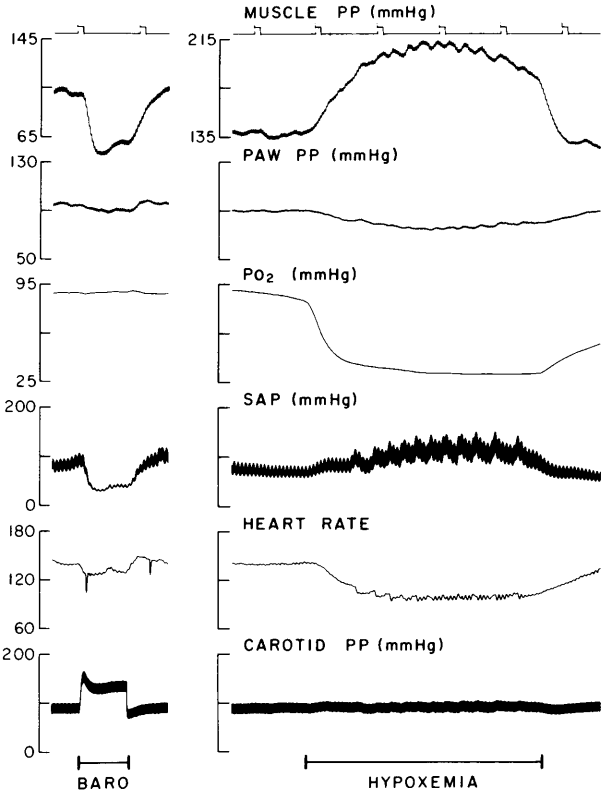

FIG. 3. During the period marked "Baro" in the left panel, perfusion pressure in the carotid was raised (by increasing outflow resistance in the Starling resistor) to stimulate carotid sinus baroreceptors. Stimulation of baroreceptors produced profound vasodilatation in the muscle and a minimal response in the paw. During the period marked "Hypoxemia" in the right panel, carotid chemoreceptors were stimulated with hypoxic, hypercapnic, and acidotic blood. Stimulation of carotid chemoreceptors produced vasoconstriction in the muscle (despite the profound reflex vasodilator capacity demonstrated during baroreceptor stimulation) and more marked vasodilatation in the paw than that observed during baroreceptor stimulation. Time lines at the top of the record indicate 1 min. The scale for muscle perfusion pressure was changed between the left and right panels as indicated.

the paw as well as the vasoconstrictor response to chemoreceptor stimulation (8).

This study was done to examine vascular responses to physiologic stimulation of chemoreceptors. A previous study in our laboratory evaluated efferent pathways which mediate the vascular response to pharmacologic stimulation of chemoreceptors (6). The vasoconstrictor response in the gracilis muscle was mediated by adrenergic constrictor fibers. The dilator response in the paw appeared to be produced by activation of efferent sympathetic dilator fibers, and not by withdrawal of sympathetic constrictor tone; the dilatation was not mediated through release of acetylcholine, histamine, or bradykinin. The chemical mediator of the dilatation in the paw was not identified.

Thus, physiologic stimulation of carotid chemoreceptors does not produce a uniform vascular response. In contrast to vasoconstriction in skeletal muscle, there is vasodilatation in cutaneous vascular bed. These responses would tend to redistribute blood flow away from skeletal muscle and toward skin. This could provide a mechanism for conservation of oxygen during hypoxemia, by redistributing blood flow away from skeletal muscle (which has a moderately high rate of oxygen consumption) and toward skin (which has a lower rate of oxygen consumption).

Summary. Experiments were performed to determine whether physiologic stimulation of carotid chemoreceptors produces different responses in blood vessels of skin and muscle. Carotid chemoreceptors of anesthe-

tized dogs were stimulated with hypoxic and hypercapnic blood and responses were observed in the isolated, perfused gracilis muscle and hindpaw. Chemoreceptor stimulation produced vasoconstriction in the muscle and vasodilatation in the paw (a predominantly cutaneous vascular bed). Responses to hypoxia without hypercapnic acidosis tended to be less pronounced. The study indicates that physiologic stimulation of carotid chemoreceptors produces contrasting responses in different vascular beds.

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