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Inhibition by Guanethidine of Chemoreceptor Reflex-Induced Vasodilatation (39950)

EDMUND J. SYBERTZ AND BEN G. ZIMMERMAN

Department of Pharmacology, University of Minnesota, Minneapolis, Minnesota 55455

Sustained sympathetic vasodilatation has been demonstrated in the cutaneous vasculature of dogs (1-4). Activation of this response is brought about by peripheral sympathetic stimulation following blockade of the predominant adrenergic vasoconstrictor fibers (1-4) and by stimulation of sites in the central nervous system (5-7). The physiological significance of and the chemical mediator(s) released during sustained vasodilatation have not been defined (1, 3, 7).

Several reports suggest that in the dog this same vasodilator system may be activated by reflex means through stimulation of carotid body and/or aortic chemoreceptors with nicotine, cyanide, or hypoxia (8, 9). Others have been unable to demonstrate a chemoreceptor-induced reflex vasodilatation in the cutaneous vascular bed of dogs (10, 11) or cats (12), whereas vasodilatation in the rabbit's ear has been noted during hypoxia or asphyxia (13, 14). The present study was undertaken in an attempt to characterize the reflex response in the canine cutaneous vasculature elicited by stimulation of carotid body chemoreceptors and to determine if this response represents activation of sustained vasodilatation.

Materials and methods. Mongrel dogs of either sex (18-30 kg) were sedated with morphine (0.5-0.75 mg/kg, sc) and anesthetized by a warmed solution of α-chloralose (60 mg/kg) and urethane (480 mg/kg). Supplemental doses of anesthetic were given during the course of the experiment. Animals were immobilized with decamethonium bromide (0.25 mg/kg) and artificially respired at a volume of 15 ml/kg and rate of 10-12/min with a Harvard respirator. All animals receiving acute guanethidine treatment were respired with 95% O_2, 5% CO_2. All other animals were respired with room air. Heparin sodium (7.5 mg/kg) was administered at the start of the experiment to prevent blood clotting.

Carotid body chemoreceptors were stimulated with nicotine using a modification of the method of Calvelo *et al.* (8). No delay coils were used since no attempt was made to stimulate aortic chemoreceptors. A Y catheter was inserted in the carotid arteries, and nicotine tartrate (30-200 μg in a volume of 0.3-0.2 ml) was injected as a bolus into the catheter to elicit a chemoreceptor response. The cardiovascular effects, including reflex vasodilatation, evoked by intracarotid administration of nicotine in this dose range have been demonstrated to be of chemoreceptor and not central nervous system origin (8, 15, 16).

The right hind paw was perfused at constant blood flow with a Sigmamotor pump according to the method of Zimmerman (1). Flow was calibrated and set at the beginning of the experiment and was not changed during the experiment. Since flow was constant, changes in perfusion pressure directly reflect changes in vascular resistance. The range of flow was 24-30 ml/min in these experiments and was not significantly different in the various groups of animals.

Systemic blood pressure was measured from a catheter in the right carotid artery. This catheter did not interfere with blood flow to the right carotid body since perfusion of these chemoreceptors was derived from the left carotid artery via the Y catheter. Hind paw perfusion pressure was measured from a sidearm and catheter. Pressures were monitored with Statham P23AA pressure transducers and were recorded on a Gilson polygraph or a Beckman R511 dynograph.

In some experiments neurogenically mediated vascular responses were elicited in the paw by stimulation of the intact tibial nerve, employing a Grass S9 stimulator. Parameters of stimulation were 30 V, 1-msec duration, and a frequency of 0.3-3 Hz for 30 sec.

Adrenergic nerve endings were blocked

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by chronic treatment of animals for 3 days with 2.5, 5, and 5 mg/kg of guanethidine sulfate subcutaneously. Complete removal of sympathetic adrenergic vasoconstrictor tone in the hind paw by this treatment was demonstrated by the presence of vasodilatation upon tibial nerve stimulation and verified in six experiments by sectioning the tibial nerve. The latter procedure elicited a transient vasodilatation followed by a return of hind paw perfusion pressure to the presectioned control level, indicating an absence of adrenergic neurogenic vasoconstrictor tone (17). In one series of experiments acute blockade of adrenergic nerve endings was accomplished by administration of guanethidine (5 mg/kg, iv, slowly) during the experimental session.

Hind paw vascular responses elicited by chemoreceptor stimulation and administration of nitroglycerin directly into the hind paw were determined in all untreated animals, animals treated acutely with guanethidine, and animals treated chronically with guanethidine. Data were analyzed using the unpaired t test (18), and differences were considered significant at $P < 0.05$.

Results. Systemic blood pressure in animals treated chronically with guanethidine was significantly lower than that in untreated animals (135 ± 6.0 vs 159 ± 6.5 mm Hg, $P < 0.05$). Hind paw perfusion pressures (164 ± 14.7 vs 186 ± 11.1) and vascular resistances (6.3 ± 0.64 vs 6.6 ± 0.33 mm Hg/ml) were not significantly different in guanethidine-treated and control animals. Figure 1 represents typical experiments from an untreated (A) and a guanethidine-treated (B) animal. Chemoreceptor stimulation in an untreated dog elicited a biphasic blood pressure response characterized by transient hypotension, followed by hypertension. A simultaneously occurring reflex vasodilatation in the hind paw was also evoked by chemoreceptor stimulation. Nitroglycerin injected directly into the hind paw exerted a vasodilator response. Figure 1B demonstrates that stimulation of carotid body chemoreceptors produces a fall in blood pressure in a guanethidine-treated animal, but fails to evoke reflex vasodilatation in the hind paw. Vasodilatation is elicited by nitroglycerin injection, and a sustained neurogenic vasodilatation is observed upon stimulation of the intact tibial nerve in the guanethidine-treated animal. The results of 12 control and 9 chronic guanethidine-treated animals are summarized in Fig. 2. Chemoreceptor stimulation with nicotine (100 μg) elicited reflex vasodilatation (response expressed as percentage change from control perfusion pressure) in the hind paw in 9 of the 12 control animals, while vasodilatation was observed in none of the 9 guanethidine-treated animals with doses of nicotine as high as 200 μg. Since no reflex vasodilatation was observed with doses of nicotine of 100 or 200 μg in guanethidine-treated animals, the data were pooled. It can be seen from Fig. 2 that the vasodilator responses to intraarterial administration of nitroglycerin were not significantly different in the two groups of dogs and vasodilatation was readily elicited by stimulation of the intact tibial nerve in guanethidine-treated animals. The reflex hypotension brought about by stimulation of carotid body chemoreceptors (nicotine, 100 μg) is not significantly different in control and guanethidine-treated animals (−13 ± 3.7 vs −24 ± 6.6

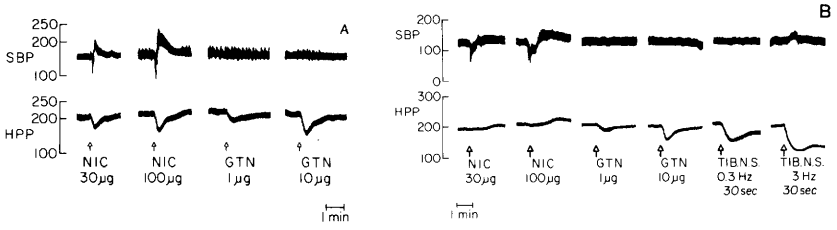

FIG. 1. (A) Typical experiment illustrating chemoreceptor-induced reflex vasodilatation in the hind paw of an untreated dog. Chemoreceptors were stimulated by intracarotid injection of nicotine (NIC). Nitroglycerin (GTN) was administered directly into the blood supply of the hind paw. SBP, systemic blood pressure; HPP, hind paw perfusion pressure. (B) Typical experiment demonstrating the absence of chemoreceptor-induced reflex vasodilatation in the hind paw of a guanethidine-treated dog. TIB. N.S., tibial nerve stimulation.

mm Hg, $P > 0.05$) and is abolished by atropine (0.25 mg/kg, iv).

In six additional animals, the response in the cutaneous vascular bed elicited by chemoreceptor stimulation with nicotine was determined before and after the acute administration of guanethidine (5 mg/kg, iv). Two of the animals were vagotomized. Guanethidine significantly decreased blood pressure (118 ± 14.5 to 85 ± 9.5 mm Hg, $P < 0.005$) and did not significantly change perfusion pressure (141 ± 15.3 to 180 ± 21.6 mm Hg, $P < 0.2$) in these animals. Chemoreceptor-induced reflex vasodilatation was observed in four of six animals, vasoconstriction in one, and no vascular response in one animal. Guanethidine abolished the reflex vascular responses in the hind paw associated with chemoreceptor stimulation in all animals (Table I), and did not significantly alter the vasodilator response to nitroglycerin 10 μg (−19 ± 2.6% during control vs −16 ± 1.9% after guanethidine).

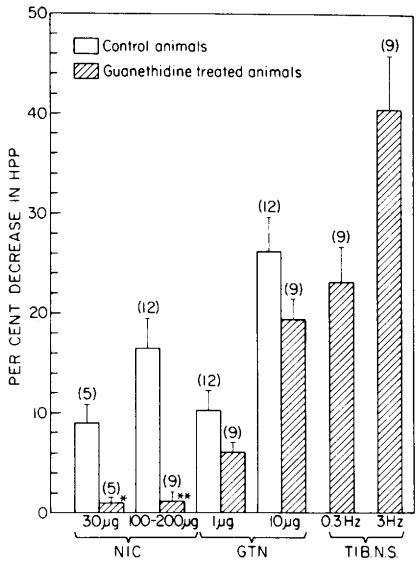

FIG. 2. Vascular responses in the hind paw evoked by chemoreceptor stimulation, nitroglycerin, and tibial nerve stimulation in 12 control and 9 guanethidine-treated dogs. Number of animals receiving a particular treatment is given in parentheses above bar. *, $P < 0.05$; **, $P < 0.001$.

The fall in systemic blood pressure mediated by reflex activation is not altered by guanethidine in animals with intact vagi. In vagotomized dogs the chemoreflex-induced hypotension is converted to a pressor response which is abolished by guanethidine (Table I, experiments 5 and 6).

Discussion. Stimulation of carotid body chemoreceptors elicits reflex cutaneous vasodilatation in the majority of control animals studied in this investigation, thus confirming the findings of others (8, 9). Reflex vasodilatation is, however, abolished by acute administration of guanethidine and is not present in animals treated for 3 days with guanethidine. These results obtained with guanethidine cannot be explained by a change in vascular reactivity caused by guanethidine since the treated animals exhibited vasodilator responses to nitroglycerin similar to those in the control group. Furthermore, neurogenically mediated vasodilatation is readily elicited in guanethidine-treated animals by stimulation of the intact tibial nerve, verifying the presence of

TABLE I. CHANGES IN HIND PAW PERFUSION PRESSURE AND SYSTEMIC BLOOD PRESSURE EVOKED BY CHEMORECEPTOR STIMULATION BEFORE AND AFTER ACUTE GUANETHIDINE ADMINISTRATION.

Experiment No.	Control				After guanethidine[a]			
	Nicotine, 30 μg		Nicotine, 100 μg		Nictoine, 30 μg		Nicotine, 100 μg	
	ΔHPP[b]	ΔSBP[c]	ΔHPP	ΔSBP	ΔHPP	ΔSBP	ΔHPP	Δ SBP
1	−8	−20	−13	−20	0	−10	−1	−18
2	14	−10	23	−30	0	−32	0	−37
3	−26	−40	−60	−47	0	−27	−2	−22
4	−10	−21	−14	−30	−1	−7	0	−10
5[d]	0	+36	3	+37	0	0	0	0
6[d]	−4	+ 9	−9	+28	0	0	0	0

[a] Guanethidine dose = 5 mg/kg iv.
[b] Hind paw perfusion pressure; values expressed as percentage change from resting perfusion pressure.
[c] Systemic blood pressure; values expressed as millimeters of mercury.
[d] Vagotomized dogs.

a sympathetic vasodilator innervation in these dogs (Figs. 1B and 2). It is unlikely that guanethidine blocks the chemoreceptor-induced vasodilator response by altering afferent or central pathways of the chemoreflex because the hypotensive response to chemoreceptor stimulation is still present in guanethidine-treated animals. The fact that the chemoreflex-induced hypotension in these animals is a vagally mediated cardiac effect is suggested by our findings that no reflex hypotension is seen in vagotomized animals and atropine abolishes the hypotensive response.

The inhibition of the chemoreceptor-induced vasodilatation is most likely due to the elimination of sympathetic adrenergic vasoconstrictor tone brought about by guanethidine. The chronic doses of guanethidine employed in this study have been demonstrated to block the vasoconstrictor responses to sympathetic nerve stimulation, unmask sustained vasodilatation, and produce a more complete adrenergic blockade than that seen with bretylium (4). The chronic and acute doses of guanethidine employed in our studies have also been shown by others to produce sympathetic adrenergic blockade (19–21). Furthermore, the absence of neurogenic vasoconstrictor tone, as defined previously (17), was confirmed in this study by the failure of sectioning of the tibial nerve to produce a sustained fall in hind paw perfusion pressure in guanethidine-treated animals. The presence of vasodilatation upon tibial nerve stimulation in the chronic guanethidine-treated animals and the inhibition of chemoreflex-induced hypertension by acute guanethidine (Table I, experiments 5 and 6) also demonstrate an effective adrenergic neuronal blockade. The results therefore indicate that reflex vasodilatation associated with carotid body chemoreceptor stimulation is passive in nature, that is, due to the withdrawal of existing sympathetic neurogenic vasoconstrictor tone, and is not associated with activation of a cutaneous vasodilator system. This interpretation differs from that of others (8) who suggested that the cutaneous vasodilatation elicited by chemoreceptor stimulation was active in nature, that is, due to the neurogenic release of a vasodilator substance. Their conclusion was based on the finding that phentolamine at doses which markedly reduced responses to exogenously administered norepinephrine failed to block the reflex vasodilatation. No further evidence was presented to demonstrate the elimination of neurogenic vasoconstrictor tone. It is suggested by our study that the blockade of sympathetic vasoconstrictor tone achieved by chronic treatment with or acute administration of guanethidine is more complete than that obtained with phentolamine.

Pelletier and Shepherd (22) have demonstrated the existence of a chemoreceptor-induced venodilatation that is due to the passive removal of adrenergic vasoconstrictor tone. Iriki *et al.* (13) observed inhibition of sympathetic discharge to rabbit ear during asphyxia. Chalmers and Korner (14) noted that vasodilatation in the rabbit ear could be evoked by hypoxia only when the ear was cooled. The results of the present investigation support these previous findings and suggest that the cutaneous arterial vasodilatation elicited by chemoreceptor stimulation in the dog is likewise due to inhibition of adrenergic vasoconstrictor tone and does not represent a means of reflexly activating sustained sympathetic vasodilatation.

Summary. The vascular responses in the hind paw associated with stimulation of the carotid body chemoreceptor reflex were studied in morphine-sedated, chloralose-urethane-anesthetized dogs. Intracarotid arterial injection of nicotine (30–200 μg) elicited reflex vasodilatation in the perfused hind paw in control animals. In animals treated for 3 consecutive days with guanethidine (2.5, 5, and 5 mg/kg/day) chemoreceptor stimulation with nicotine failed to evoke reflex vasodilatation in the hind paw, whereas intraarterial administration of nitroglycerin and stimulation of the intact tibial nerve readily produced vasodilatation. Acute administration of guanethidine (5 mg/kg) also abolished chemoreceptor reflex-induced responses in the hind paw. The results of this investigation suggest that the chemoreceptor reflex-induced vasodilatation in the hind paw is due to an inhibition of sympathetic vasoconstrictor tone and does not represent activation of sustained vasodilatation.

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