

Extent and Mechanism of Halothane Sensitization of the Carotid Sinus Baroreceptors

J. L. Seagard, Ph.D.,* F. A. Hopp, M.S.,† Z. J. Bosnjak, Ph.D.,* E. O. Elegbe, M.B.B.S.,‡
J. P. Kampine, M.D., Ph.D.§

The present study was performed to determine the extent and mechanism of carotid sinus baroreceptor sensitization due to halothane in an isolated, denervated carotid sinus in anesthetized dogs (thiopental 25 mg/kg; 5 mg · kg⁻¹ · h⁻¹, maintenance dose). Efferent sympathetic nerves to the sinus were sectioned to eliminate the contribution of these fibers to any sensitization observed. Halothane (H) administration was localized to the carotid sinus by an isolated perfusion system. The perfusion system was used to make standardized sine wave changes in carotid sinus pressure. Carotid sinus afferent nerve activity from single or few-fiber nerve preparations was recorded during carotid sinus pressure changes and the slopes of nerve activity *versus* carotid sinus pressure were used to determine the gain, or sensitivity, of the baroreceptors. The addition of 0.75% H and 1.5% H to the sinus perfusion produced a dose-dependent sensitization of the baroreceptors. A greater increase in carotid sinus afferent nerve activity for a given increase in sinus pressure was used as an indication of an increase in receptor sensitivity, or sensitization. In the presence of sodium nitroprusside, given in doses to maximally dilate the sinus prior to H administration, only 1.5% H produced baroreceptor sensitization. This suggests the changes in sinus wall tension due to halothane may have contributed to the sensitization seen during H administration. The remaining sensitization at 1.5% H was eliminated in the presence of nitroprusside and 7.5 mM Ca⁺⁺. This remaining sensitization therefore appears to be Ca⁺⁺-related and may be due to direct effects of H on the baroreceptors. (Key words: Anesthetics, volatile: halothane. Blood pressure: baroreceptor reflexes. Ions: calcium. Pharmacology: nitroprusside. Receptors: baroreceptors. Reflexes: baroreceptor.)

HALOTHANE HAS BEEN SHOWN to sensitize arterial baroreceptors,^{1,2} resulting in an increase in carotid sinus afferent activity for a given increase in sinus pressure. This action has been suggested as the possible mecha-

nism for the hypotension and bradycardia accompanying halothane anesthesia,^{1,3} in spite of the fact that the entire baroreceptor reflex is attenuated by the anesthetic.¹ This depression of the baroreceptor reflex by halothane has been reported for anesthetized humans and animals.³⁻¹⁰ The blunting of the baroreceptor reflex appears to be a result of the depressant effect of halothane on other components of the baroreflex arc, including the central nervous system, sympathetic ganglionic transmission, and cardiac chronotropic function. The net effect of halothane on these sites results in inhibition of the reflex in spite of baroreceptor sensitization.¹ The increased afferent input from the sensitized baroreceptors during anesthesia does appear to contribute to reduced sympathetic preganglionic efferent nerve activity,¹ an action which could affect reflex responses dependent on changes in sympathetic efferent tone.

The mechanism of the change in baroreceptor sensitivity in response to halothane is not known, but could be directly due to receptor stimulation, or indirectly due to changes in wall tension or changes in sympathetic efferent nerve activity to the sinus. Baroreceptor sensitivity has been reported to increase in response to sympathetic efferent stimulation¹¹⁻¹³ or application of norepinephrine to the sinus.¹⁴ Halothane, a smooth muscle dilator, appears to produce opposite changes in wall tension compared with sympathetic stimulation, yet it sensitizes the receptors. In addition, halothane has been found to decrease sympathetic efferent nerve activity. This is also an effect opposite that which has been reported to increase nerve activity.

The present study was performed to examine the mechanism of halothane sensitization of the baroreceptors. Previous work had found that sensitization occurred when the whole animal was exposed to 1.5% inspired halothane. This study limited exposure of halothane to only an isolated carotid sinus, to determine whether halothane-induced sensitization was a local or central effect mediated through changes in efferent nerve activity. When sensitization was found to occur in the isolated sinus, efferent denervation of the sinus was performed to eliminate any neural component involved in halothane sensitization of the baroreceptors. Sensitization was still present after denervation, and, therefore, the local effects of halothane that could alter

* Assistant Professor, Departments of Anesthesiology and Physiology, The Medical College of Wisconsin.

† Biomedical Engineer, Department of Anesthesiology, The Medical College of Wisconsin.

‡ Lecturer/Consultant, Department of Anesthesiology, College of Medicine, University of Ibadan, Ibadan, Nigeria

§ Professor and Chairman, Department of Anesthesiology; Professor, Department of Physiology, The Medical College of Wisconsin.

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Address reprint requests to Dr. Seagard: Research Service 151, VA Medical Center, Wood, Wisconsin 53193.

baroreceptor sensitivity were examined. These effects included changes in smooth muscle tension in the sinus or direct stimulation of the receptors.

Materials and Methods

Twelve mongrel dogs were anesthetized with sodium thiopental (25 mg/kg) and placed on positive-pressure ventilation with oxygen. The right femoral artery was cannulated and connected to a Statham® pressure transducer for blood pressure recording. All pressures were recorded on a Vetter® FM tape recorder and displayed on a Grass® Model 7 recorder. The right femoral vein was cannulated for infusion of anesthetic. Anesthesia was maintained by constant infusion of thiopental at $5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ using a Harvard® pump. This method has been found in our laboratory to produce a stable level of anesthesia in dogs, evidenced by constant patterns of respiratory activity and sympathetic efferent nerve activity. The left carotid sinus and carotid sinus nerve were exposed via a midcervical incision. The sinus nerve was identified by extracellular nerve recording, utilizing tungsten carbide electrodes in series with a high gain preamplifier/filter amplifier system connected to a FM tape recorder, a monitoring oscilloscope, and an audio amplifier. Nerve activity was characteristically synchronous with each blood pressure wave. The nerve was traced to its junction with the glossopharyngeal nerve and cut. The distal end was desheathed and placed under warm mineral oil. When nerve recording was performed, the large sinus nerve was dissected into smaller bundles containing only one or two active fibers. In several dogs, larger multifiber recordings were obtained as well. To eliminate any role of sympathetic efferent nerve activity to the sinus in sensitizing the carotid baroreceptors, the cervical sympathetic trunk was sectioned and the superior cervical ganglion removed, eliminating sympathetic efferent innervation of the sinus.

Closed loop perfusion of the carotid sinus was performed by isolating the left common carotid artery and ligating all branches, including the internal and external carotid arteries, thyroid artery, occipital artery, and lingual artery. The common carotid artery then was cannulated in a rostral direction, while the external carotid artery was cannulated in a caudal direction, effectively isolating the carotid sinus between the two cannulae. The sinus was perfused at constant pressure with a solution of blood, mixed with heparinized dextran and lactated Ringer's solution, withdrawn from an oxygenator using a Sarn's roller pump. The perfusate was pumped through the common carotid artery to the sinus and withdrawn through the external carotid cannula. Perfusate was returned from the external carotid cannula to the oxygenator. Perfusion pressure, measured

at the tip of the common carotid cannula, was recorded on a FM tape recorder and directed to a servocontrol unit that was used to regulate the perfusion pressure. The servocontrol unit, with a response time of one second, utilized the error signal between actual and desired pressure to regulate the speed of the roller pump, thereby keeping perfusion pressure constant at 100 mmHg. Small pressure pulsations (20 mmHg, 0.5–0.8 Hz) produced by the occlusive roller pump were superimposed on the constant pressure perfusion. The servocontrol unit also provided on-line recordings of flow in pump RPMs and calculated resistance by electrically dividing perfusion pressure by flow. These readings were used to determine when equilibration had been achieved in the carotid sinus for each experimental procedure. Following the experiment, the flow signal was converted to ml/min by measuring actual flow/RPM ($\text{ml} \cdot \text{min}^{-1} \cdot \text{RPM}^{-1}$). The oxygenator in the closed perfusion circuit was aerated with 100% oxygen.

To measure sensitivity of the baroreceptors, sine wave changes in blood pressure were imposed on the constant pressure perfusion using a signal generator to drive the servocontrol unit. Sine wave pressure changes which altered sinus pressure between threshold pressure, at which nerve activity first appeared, to saturation pressure, at which nerve activity plateaued, were used so that the entire curve of nerve activity response could be studied. A windkessel, or pressurized bottle, was placed into the circuit between the roller pump and the perfused artery during the pressure changes to minimize pulsations other than the desired sine wave changes in perfusion pressure. Carotid sinus afferent nerve activity, recorded during the standardized sine wave changes in sinus pressure, then was used to determine baroreceptor sensitivity. The slope of the curve plotting nerve activity *vs.* sinus pressure was determined as an index of sensitivity, as explained below.

The experiment was performed as follows. With only oxygen present in the perfusate, sine wave pressure changes driving sinus pressure from 70 to 200 mmHg were imposed on the isolated sinus, using the signal generator to control the servocontrol unit. Following control runs, halothane was introduced via a previously calibrated Fluotec® vaporizer into the oxygenator. The halothane concentrations in the perfusate, studied in random order, were 0.75% (1 MAC; 0.4 mM) and 1.5% (2 MAC; 0.87 mM). Halothane concentrations were determined using the gas chromatographic technique of Lowe.¹⁵ Following each change in the halothane concentration, 15 minutes were allowed for equilibration to occur within the system and the exposed sinus. Halothane concentrations, determined from samples of perfusate withdrawn at 5-min intervals, showed that halothane had equilibrated in the system by 10 min, with

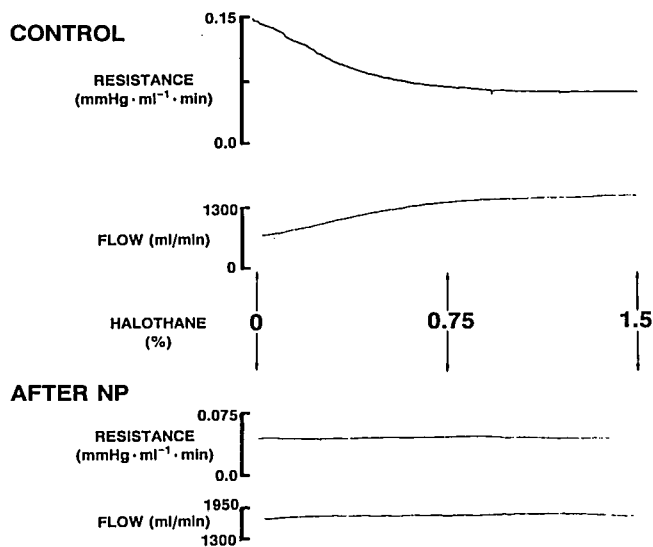


FIG. 1. Response of carotid sinus resistance and flow to halothane administration during constant pressure perfusion of the sinus before (control) and after administration of nitroprusside (after NP). The continuous on-line tracings were obtained from the servocontrol unit, with halothane concentrations equilibrated at the values indicated at each arrow. Note that following nitroprusside administration, the maximally dilated sinus did not dilate further with the addition of halothane. Time for the entire response shown is one hour.

no further changes in concentration. The sinus was perfused at a constant pressure of 100 mmHg during the halothane changes. The sinus then was subjected to the same dynamic pressure waves and nerve activity from the fiber again was recorded. This procedure was repeated for each level of halothane.

To determine the importance of the vasodilator effect of halothane on baroreceptor sensitivity, sodium nitroprusside was added to the perfusion following sine wave changes at each level of halothane. The vasodilator was given in a supramaximal dose, as explained below, so that the carotid sinus would be maximally dilated and, thus, the addition of halothane would have no significant effect on wall tension. Maximal dilation was confirmed by flow and resistance readings for the perfusion system and did not change with the addition of more nitroprusside or halothane (fig. 1). After nitroprusside, therefore, any change in baroreceptor sensitivity caused by halothane could not be attributed to an indirect effect on wall mechanics, but rather to a direct effect of halothane on the receptors.

To test the effects of nitroprusside, in three dogs the halothane was eliminated by exposing the sinus to 0% halothane for 60 min prior to the administration of nitroprusside. Sodium nitroprusside (30 mg) was then added to the perfusate and additional 5-mg doses were given at 5-min intervals until flow and resistance readings for the perfused sinus did not change with addi-

tional doses. In this state, flow and resistance readings did not change significantly with increasing levels of halothane, suggesting that the dilation induced with nitroprusside was maximal and was not increased by halothane. In three additional dogs, nitroprusside was given prior to the first series of halothane exposures, after which halothane was administered as described previously. In all dogs, the nitroprusside was supplemented every 30 min to maintain the vasodilation.

In three additional dogs, Ca^{2+} was added to the perfusate after the addition of nitroprusside. Halothane has been reported to directly affect the flux of Ca^{2+} in smooth¹⁶ and cardiac¹⁷⁻²¹ muscle cells, and this type of action also may be important in receptor activation. Calcium administration therefore was used to eliminate effects on the receptor due to halothane alteration of Ca^{++} availability. CaCl_2 was added to the perfusate to bring the external Ca^{2+} concentration up to 7.5 mM, or three times the normal plasma concentration. Following the addition of Ca^{2+} , baroreceptor sensitivity was studied again for each level of halothane plus nitroprusside as described above. Carotid sinus nerve activity for each level of halothane, including halothane plus nitroprusside and Ca^{2+} , was analyzed in the range of pressures up to the pressure at which the response began to plateau, with no further increases in nerve activity despite increasing sinus pressures. The slopes of these curves, determined by linear least-squares fit, were used as an index of sensitivity of the baroreceptors. Regression analysis was performed and the mean slopes of carotid sinus nerve activity *versus* sinus pressure were determined for each experimental procedure. Only two regression lines, with correlation coefficients less than 0.7, were not used in the final analysis. Baroreceptor sensitivities for each level of halothane were statistically compared using a two-way analysis of variance. The slopes for the responses at each level of halothane plus nitroprusside were also compared with each other using

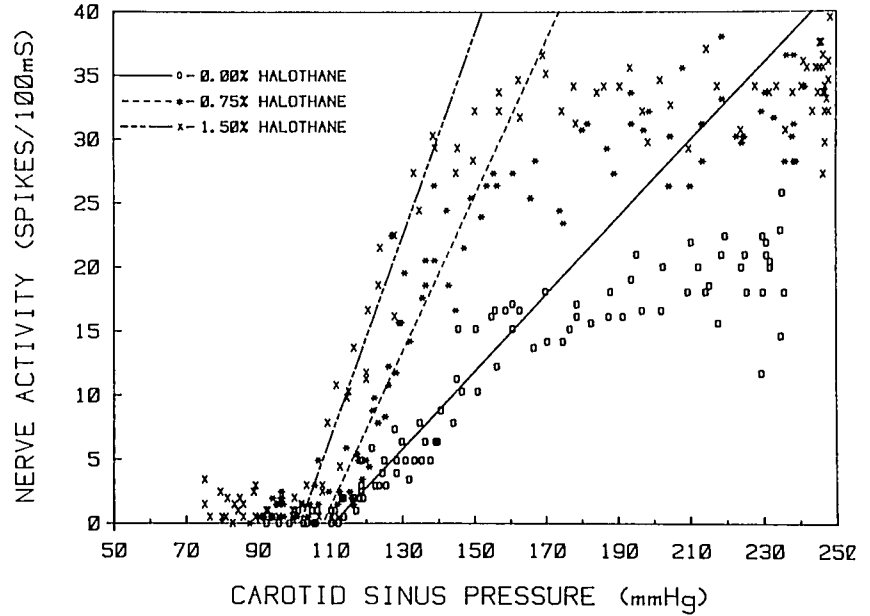
TABLE 1. Effects of Halothane, Nitroprusside, and Calcium on Baroreceptor Afferent Activity Presented as the Slopes of Nerve Activity *vs.* Carotid Sinus Pressure in Spikes $\cdot 100 \text{ ms}^{-1} \cdot \text{mmHg}^{-1}$

Halothane Concentration	Halothane (H)	Halothane plus Nitroprusside (H + NP)	Halothane plus Nitroprusside and Calcium (H + NP + CA)
0.00%	0.278 \pm 0.050	0.374 \pm 0.082§	0.204 \pm 0.014¶
0.75%	0.438 \pm 0.074*	0.435 \pm 0.075 ns	0.197 \pm 0.007**
1.50%	0.555 \pm 0.066†	0.543 \pm 0.075‡	0.211 \pm 0.007††

Significance within groups H, H + NP, and H + NP + CA: * $P < 0.05$ *vs.* 0% H; † $P < 0.01$ *vs.* 0% H and 0.75% H; and ‡ $P < 0.01$ *vs.* 0% H + NP and $P < 0.05$ *vs.* 0.75% H + NP.

Significance between groups H, H + NP, and H + NP + CA: § $P < 0.01$ *vs.* 0% H; ¶ $P < 0.05$ *vs.* 0% H and $P < 0.025$ *vs.* 0% H + NP; ** $P < 0.005$ *vs.* 0.75% H and 0.75% H + NP; and †† $P < 0.005$ *vs.* 1.5% H and 1.5% H + NP.

FIG. 2. Single-fiber carotid sinus afferent nerve activity vs. carotid sinus pressure at 0.0%, 0.75%, and 1.5% halothane. The lines indicate the slopes of the responses up to the point of saturation. The slopes are all significantly different from each other ($P < 0.05$ or less).



a two-way analysis of variance. Finally, the baroreceptor sensitivities in the presence of halothane plus nitroprusside and Ca^{2+} were analyzed in a similar manner to the other responses. Significant differences between means were determined in all three cases using Duncan's Multiple Range Test. Differences between groups were examined using an unpaired t test. In all cases, significance was set at the $P < 0.05$ level.

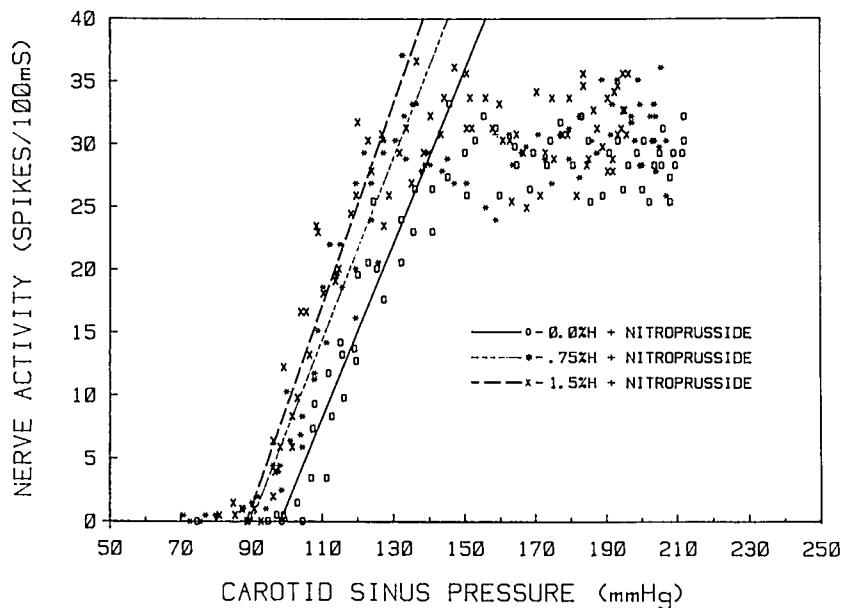
Results

Analysis of the slopes of nerve activity *versus* sinus blood pressure indicated a significant dose-dependent

increase in baroreceptor sensitivity with the addition of both 0.75% ($P < 0.05$) and 1.5% ($P < 0.01$) halothane, as compared with control (0% halothane) [table 1, fig. 2]. In addition, the slope of the response at 1.5% halothane was significantly greater than at 0.75% halothane.

The addition of nitroprusside, which maximally dilated the sinus (resistance change of 0.042 ± 0.017 mmHg \cdot ml $^{-1}$ \cdot min), significantly increased the activity of the baroreceptors at 0% halothane ($P < 0.01$) [table 1, fig. 3]. The slope of the nerve activity-blood pressure curve for 0% halothane plus nitroprusside increased towards that for 0.75% halothane plus nitroprusside, elim-

FIG. 3. Single-fiber carotid sinus afferent nerve activity vs. carotid sinus pressure at 0.0%, 0.75%, and 1.5% halothane, after maximal dilation of the sinus with nitroprusside. The slope at 1.5% halothane is significantly different from the slopes at 0.0% and 0.75% halothane ($P < 0.05$).



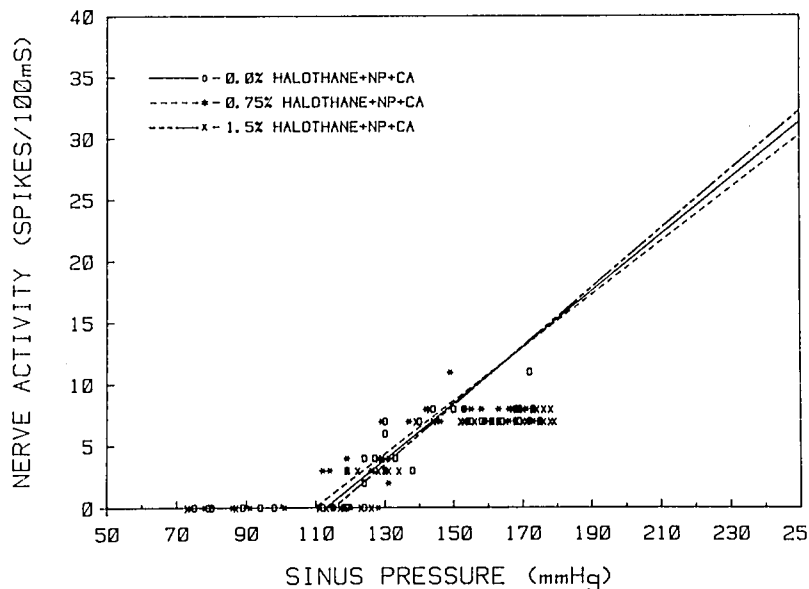


FIG. 4. Single-fiber carotid sinus afferent nerve activity vs. carotid sinus pressure at 0.0%, 0.75%, and 1.5% halothane after prior administration of nitroprusside and 7.5 mM CaCl_2 to block the local sensitizing effects of halothane. There are no significant differences between slopes.

inating the significant difference between the two responses. The slope for 1.5% halothane plus nitroprusside was still significantly different from 0% ($P < 0.01$) and 0.75% ($P < 0.05$) halothane plus nitroprusside.

The addition of Ca^{2+} significantly decreased responses at all levels of halothane ($P < 0.05$ to 0.005) [table 1, fig. 4]. The slopes for each level of halothane after the addition of nitroprusside plus Ca^{2+} were not significantly different from each other, but were significantly less than the slopes at the same level of halothane and halothane plus nitroprusside.

Discussion

Sensitization of the baroreceptors has been reported during electrical stimulation of sympathetic efferent nerves innervating the carotid sinus,¹¹⁻¹³ by anesthetics including ether, cyclopropane, chloroform, and halothane,^{13,22-24} by topical application of norepinephrine^{14,24} and angiotensin,²⁵ and by alterations in plasma sodium, potassium, and calcium.²⁶⁻²⁸ The mechanisms of sensitization are not clearly known, but may involve direct stimulation of the receptors or changes in sinus wall tension, leading indirectly to changes in receptor tension, or sensitivity. Anesthetics also could produce changes in sympathetic efferent activity to the sinus, leading to neurally mediated changes in receptor activity. Results from this study, performed in the absence of efferent sinus innervation, indicate that neural control is not required for halothane-induced sensitization, but that effects on carotid sinus wall tension or direct effect on receptors may be involved.

Halothane has been reported to decrease the slow inward Ca^{2+} current in cardiac muscle, altering cardiac cell action potentials and tension development.¹⁷⁻²¹ Al-

terations of slow Ca^{2+} currents in smooth muscle have been proposed as the mechanism for smooth muscle relaxation produced by both halothane¹⁶ and sodium nitroprusside.²⁹ If a change in sinus wall tension is involved in halothane-induced sensitization of the baroreceptors, this effect of halothane may be altered by nitroprusside because of the previous relaxation produced by the vasodilator. The increased diameter of the sinus due to the vasodilation may result in a greater degree of wall tension for a given pressure, according to Laplace's law ($\text{Pressure} = \text{tension} \cdot \text{radius}^{-1}$).

The results of the present study suggesting that vasodilation produced sensitization of the baroreceptors appears to conflict with previous studies that found that increased sympathetic activity to the sinus or topically applied norepinephrine-produced receptor sensitization. These procedures generally result in vasoconstriction,³⁰ although decreased sinus wall strain has been reported for topically applied norepinephrine.³¹ Halothane appears to produce changes in wall tension opposite to those produced by norepinephrine or sympathetic stimulation, yet all have been found to sensitize the baroreceptors. The answer may lie in the possibility that norepinephrine may directly stimulate the receptors^{11,12} and that the accompanying vasoconstriction does not play a role in the sensitization.

An additional effect of sodium nitroprusside and halothane may directly involve the receptors. Decreased extracellular $[\text{Ca}^{2+}]$ has been found to increase atrial receptor activity evoked by stretch of an isolated atrial wall segment.³² In addition, decreases in extracellular $[\text{Ca}^{2+}]$ were found to lower threshold and increase sensitivity of carotid and aortic baroreceptors.^{27,28} Increased $[\text{Ca}^{2+}]$ produced opposite results. The changes in baroreceptor activity produced by alterations in

[Ca²⁺] occurred without any changes in vessel wall distensibility or diameter.²⁷ It is conceivable that the decreases in Ca²⁺ current seen in vascular smooth muscle in the presence of halothane or nitroprusside also may reduce Ca²⁺ availability for the receptors. Alternatively, halothane may directly alter a Ca²⁺ flux important for receptor activation. Andresen *et al.*²⁷ proposed that the changes in aortic baroreceptor sensitivity due to alterations of extracellular [Ca²⁺] were due to actions of the ion at the receptor membrane or the spike initiating zone. Kunze²⁸ similarly has proposed that [Ca²⁺] affects threshold pressure at the spike-initiating zone of the carotid baroreceptors. The reduction in Ca²⁺ flux may lower the threshold for spike initiation, thereby increasing the receptor discharge for a given amount of stretch. Thus, [Ca²⁺] may play a stabilizing role for the receptor, and this effect is reduced by both halothane and/or nitroprusside.

In the presence of nitroprusside and Ca²⁺, 1.5% halothane did not significantly increase baroreceptor activity. This lack of sensitization suggests that the mechanisms of halothane-induced sensitization were eliminated by the addition of the two agents. The present study suggests that the mechanisms involved result from both changes in sinus wall tension and direct receptor activation. The effects of nitroprusside on carotid baroreceptor sensitivity may potentiate its direct effect on vascular smooth muscle.

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