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Contribution of Peripheral Chemoreception to the Depression of the Hypoxic Ventilatory Response during Halothane Anesthesia in Cats

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Background: **The effects of inhalational anesthetics on the hypoxic ventilatory response are complex. This study was designed to determine the contribution of peripheral chemoreception to the depression of hypoxic ventilatory response seen with halothane anesthesia.**

Methods: **Cats were anesthetized with pentobarbital sodium and α-chloralose and artificially ventilated. Respiratory output was evaluated by phasic inspiratory activity of the phrenic nerve. In 12 cats, this activity was measured during inhalation of an hypoxic gas mixture with halothane, 0, 0.1, and 0.8%, with intact or denervated carotid bodies. In 10 cats, a carotid body was isolated from the systemic circulation and perfused with hypoxic Krebs-Ringer solution equilibrated with halothane, 0, 0.1, and 0.8%.**

Results: **The hypoxic ventilatory response was depressed in a dose-dependent manner during halothane anesthesia. In carotid body perfusion studies, the response was significantly depressed only with halothane, 0.8%.**

Conclusion: **The hypoxic ventilatory response is depressed by a high dose of halothane through a peripheral effect at the carotid body. (Key words: Anesthetics; receptors; ventilation.)**

CONFLICTING data exist in the literature regarding the effects of inhalational anesthetics on the hypoxic ventilatory response.[1,2] The discrepancy may be the result of differences in methods, such as the technique used to induce hypoxia (short *vs.* long exposure). For instance, the hypoxic ventilatory response consists of two opposing time-dependent phases: an initial peripheral chemoreceptor-driven increase in ventilation, followed by a slower onset of central depression. Another problem in hypoxic ventilatory response measurement during administration of inhalational anesthetics is the possibility of masking the direct effect of inhalational anesthetics on peripheral chemoreceptors because of its simultaneous effect on the central nervous system. To separate the central and peripheral effects of hypoxia and inhalational anesthetics on ventilation, we developed an animal model with an isolated perfused carotid body (CB). Using this technique, the effect of inhalational anesthetics on the depression of the hypoxic ventilatory response *via* peripheral chemoreceptors independent of any central effect also can be studied.

The object of this study was to evaluate the contribution of peripheral chemoreception to the depression of the hypoxic ventilatory response during halothane anesthesia by comparing phrenic nerve activity during systemic halothane inhalation with halothane perfusion of an isolated CB.

Materials and Methods

Institutional approval for the study was obtained from the Animal Care and Use Committee of Chiba University School of Medicine in accordance with the *Guide for the Care and Use of Laboratory Animals.*[3] All experiments were performed at Chiba University, which is located 22 m above sea level.

Surgical Preparation

Thirty-one adult cats of both sexes (25 male, 6 female) weighing 2.9–5 kg (4.1 ± 0.95 kg [mean ± SD]) were used in the study. Each cat was anesthetized with pentobarbital (30 mg · kg^{-1} given intraperitoneally; Sigma Chemical Co., St. Louis, MO) and α-chloralose (20 mg · kg^{-1} given intravenously; Sigma Chemical Co.). The depth of anesthesia was judged by arterial blood pressure, heart rate, and reflex responses to stimuli. Eyelid reflex or paw withdrawal at interdigital pressure was not observed before paralysis. After paralysis, the depth of

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anesthesia was judged by changes in arterial blood pressure and heart rate. Although additional doses of α-chloralose (5 mg/kg given intravenously) were given between two different protocols when arterial blood pressure or heart rate increased by 10% above the baseline level obtained after the surgical procedure, no anesthesia supplement was given during any protocol. The right femoral vein was cannulated for continuous infusion of lactated Ringer's solution with 5% dextrose (10 $ml \cdot kg^{-1} \cdot h^{-1}$ during surgical preparation and thereafter maintained at 3 $ml \cdot kg^{-1} \cdot h^{-1}$). The right femoral artery also was cannulated to monitor arterial blood pressure and heart rate, whereas the left femoral artery was cannulated to withdraw blood samples for arterial blood gas analysis. After an endotracheal tube was inserted through the tracheostomy, the animal was paralyzed with pancuronium bromide (in a 0.2-mg/kg bolus dose, thereafter maintained at 0.05–0.08 $mg \cdot kg^{-1} \cdot h^{-1}$; Sankyo Chemical Industries, Tokyo, Japan) and artificially ventilated using a Harvard small animal respirator maintained at an inspiratory fraction of oxygen ($F_{I_{O_2}}$) of 1.0, at a fixed rate of 20 times/min. Continuous analysis of expired gases for concentrations of carbon dioxide and oxygen with an infrared gas analyzer (model 1H21A; Acoma, Tokyo, Japan) and of halothane (Takeda Chemical Industries, Osaka, Japan) with an anesthetic gas monitor (model 303; Atom, Tokyo, Japan), calibrated with appropriate gas mixtures of known concentrations, were performed. Halothane was administered by a vaporizer (Fluotec 3; Cyprane, Steeton, UK). The end-tidal carbon dioxide level ($P_{ET_{CO_2}}$) was maintained at 6.5%–7% throughout the test by adding small amounts of carbon dioxide into the inspired gas. This level of $P_{ET_{CO_2}}$, compared with the normocapnia value of 35 ± 0.5 mmHg (mean ± SEM) in awake cats,[4] represents hypercapnia in the cat; however, increased background chemical drive was needed to obtain vigorous inspiratory activity during anesthesia, because baseline anesthesia depresses the response.

Respiratory output was measured by phrenic nerve activity (IPHN), which is represented by the average of peak amplitudes of moving time averages during a period of 30 or 60 s. To record phrenic nerve activity, C5 branches of both phrenic nerves were exposed and cut. The proximal end of the left phrenic nerve was desheathed and placed on bipolar silver electrodes in a pool of warm liquid paraffin and prepared for subsequent recording of the whole nerve activity. The signal was preamplified (S1516; Nihon Koden, Tokyo, Japan) at a time constant of 30 ms, rectified, and integrated by a leaky integrator (EI-601G, Nihon Koden) to obtain the moving time average.

Carotid Body Perfusion

To perfuse the CB, the carotid sinus region was exposed by transecting the trachea and esophagus and reflecting the larynx and pharynx cranially. The right carotid sinus nerve and the sympathetic branch to the left CB arising from the superior cervical ganglion were identified and cut. Bilateral vagotomy was also performed at the middle cervical level. The perfusion system was similar to that described by Shirahata *et al.*[5] Before the left CB was prepared for *in situ* perfusion, heparin (2,000 U/kg; Sigma Chemical Co.) was administered intravenously in a bolus dose, followed by continuous infusion (400 $U \cdot kg^{-1} \cdot h^{-1}$) to prevent clotting. A loop catheter, connected to a pressure transducer (Transpac; Abbott Critical Systems/AP 601 G, Nihon Koden) and a three-way stopcock, was inserted in the left common carotid artery. The left lingual artery was also cannulated, and a variable resistance was attached around the catheter to control the CB perfusion pressure. All arteries, except the left common and external carotid arteries, and all veins between the loop and lingual catheters were tied. Krebs-Ringer (KR) solution, composed of 120 mM NaCl, 3.5 mM KCl, 1.8 mM $CaCl_2$, 0.6 mM $MgCl_2$, 0.6 mM NaH_2PO_4, 19 mM $NaHCO_3$, and 20 mM glucose, was recirculated continuously through the perfusion catheters using a peristaltic pump (MP-3; EYELA, Tokyo, Japan). When the perfusate was converted from arterial blood to KR solution, the common and external carotid arteries were occluded completely by snares, and the three-way stopcock was turned to allow perfusate flow into the lingual artery. The effluent KR solution was discarded. Variable resistance around the catheter in the lingual artery was controlled to keep the perfusion pressure close to the systemic arterial pressure at a constant perfusate flow. The KR solution was equilibrated with the desired gas mixture with or without halothane for at least 15 min before it was used in CB perfusion. Perfusion was continued for 90 s, followed by 30 min of perfusion by arterial blood.

Systemic arterial blood pressure, common carotid arterial pressure, raw and integrated phrenic nerve activities, and $P_{ET_{CO_2}}$ were monitored continuously and recorded on an eight-channel thermal array recorder (RTA 1200, Nihon Koden). Samples of arterial blood and KR solution were withdrawn periodically to measure *p*H and carbon dioxide and oxygen pressures (P_{CO_2} and P_{O_2}, respectively) at 37.5°C using a blood gas analyzer (model

Table 1. Overview of the Different Protocols to Which the Cats Were Subjected

Protocol	Perfusion of Carotid Body	Chemodenervation	Halothane Applied	Number of Cats
1	No	No	Inhalation*	6
2	No	Yes	Inhalation*	6
3	Yes	No	None given	5
4	Yes	No	Carotid body†	10
5	No	No	No	5

* Halothane is applied to overall system by inhalation.

† Halothane is applied to carotid body (CB) by selective perfusion of CB with KR solution saturated with halothane.

1302, Instrumentation Laboratories, Milan, Italy). Rectal temperature was monitored continuously and maintained at 37 or 38°C by wrapping the body in a circulating water blanket. The animal was kept supine throughout the experiment.

Experimental Protocols

Table 1 shows an overview of the experimental protocols.

Protocol 1: Response of Phrenic Nerve Activity to Inhalation of Halothane and the Hypoxic Gas Mixture. The effects of halothane inhalation on IPHN during inhalation of a hypoxic gas mixture were evaluated in six cats without CB perfusion. For this purpose, each cat was artificially ventilated with a hyperoxic gas mixture ($F_{I_{O_2}} > 0.95$) for 30 min at a constant $P_{ET_{CO_2}}$2 of 6.5–7%. The IPHN was measured for 1 min (control 1). After this procedure, $F_{I_{O_2}}$ was reduced abruptly to 0.05 by turning the three-way stopcock connected to the gas tank (nitrogen, 95%; oxygen, 5%) and maintained for 90 s. During this period, $P_{ET_{CO_2}}$ was kept constant at 6.5–7% by manual adjustment of the inspired carbon dioxide concentration. After recording IPHN during the last 30 s of hypoxia (hypoxia), the animal inspired the hyperoxic gas mixture ($F_{I_{O_2}} > 0.95$) for 3 min, and IPHN was sampled for the next 1 min (control 2). The same procedure was repeated with two different concentrations of halothane (0.1 and 0.8%) in each animal with an interval of 30 min. The order of halothane concentrations used in each experiment was randomized.

Protocol 2: Effect of Peripheral Chemodenervation on Phrenic Nerve Activity during Inhalation of Halothane and the Hypoxic Gas Mixture. Halothane-induced depression of the hypoxic ventilatory response also may result from the direct effect of the anesthetic on the central respiratory components. To test this possibility, after preparation of the animal, as described before, the carotid sinus nerves and aortic nerves separated from the vagus nerve near the nodose ganglion were sectioned bilaterally, and isocapnic hypoxic tests were repeated with or without halothane, 0.1 or 0.8%, in six cats. Measurements were recorded only after 1 or 2 h elapsed after peripheral chemodenervation to allow stable circulatory conditions.

Protocol 3: Effect of Carotid Body Perfusion on Phrenic Nerve Activity. The effect of perfusion itself on IPHN was assessed in five cats. The IPHN was measured before, during, and after perfusion of KR solution at three levels of perfusate P_{O_2} (PP_{O_2}) (hyperoxia, 250–350 mmHg; normoxia, 90–100 mmHg; hypoxia, 35–40 mmHg) at a constant perfusate P_{CO_2} (PP_{CO_2}) of 50–55 mmHg. The $F_{I_{O_2}}$ was adjusted to keep the levels of arterial oxygen tension (Pa_{O_2}) the same as each PP_{O_2} at a constant Pa_{CO_2}. After a 3-min exposure to each $F_{I_{O_2}}$ level, IPHN was measured for the next 1 min before perfusion (before perfusion). The CB was perfused with KR solution for 90 s, which was equilibrated with a predetermined gas mixture. The IPHN activity during perfusion was measured during the last 1 min of a 90-s perfusion period (during perfusion). After perfusion, the stopcock was returned to the original position and the CB was reperfused with arterial blood for 3 min. The IPHN activity was recorded after perfusion for the next 1 min (after perfusion). The order of use of solutions with differing PP_{O_2} was randomized.

Protocol 4: Effect of Carotid Body Perfusion with Hypoxic Krebs-Ringer Solution Equilibrated with Halothane. The direct effect of halothane on the CB was evaluated in a perfusion model in 10 cats. Each cat was ventilated artificially at a constant $P_{ET_{CO_2}}$ of 6.5–7% with a small amount of carbon dioxide in oxygen. After recording the IPHN before perfusion for 1 min (before perfusion), the CB was perfused for 90 s with a hypoxic KR solution equilibrated with 5% oxygen and 7% carbon dioxide in nitrogen. The IPHN during perfusion was sampled during the last 1 min of a 90-s perfusion (during perfusion). The CB was reperfused with arterial blood for 3 min and the IPHN after perfusion was recorded for the next 1 min (after perfusion). Before each perfusion, samples of KR solution and arterial blood were withdrawn and analyzed for P_{O_2}, P_{CO_2}, and *p*H. This protocol also was performed with a hypoxic KR solution equilibrated with two levels of halothane concentration (0.1 and 0.8%) at a 30-min interval. The order of use of

solutions with differing levels of halothane concentration was randomized.

Protocol 5: Time-Control Study. The effect of time during baseline anesthesia and mild hypercapnia on IPHN was evaluated in five cats. The measurements used in the first protocol, excluding exposure to halothane, were repeated three times at a 30-min interval.

Statistical Analysis

Data were expressed as the mean ± SD. Differences of IPHN between halothane concentration, Pa_{O_2} level, and with and without perfusion were tested for statistical significance using a two-way analysis of variance with repeated measures, and the Scheffé test was used to determine the significance of differences between mean values in the IPHN. A P value < 0.05 was considered significant.

Results

Protocol 1: The Response of Phrenic Nerve Activity to Inhalation of Halothane and Hypoxic Gas Mixture

The results were shown in figure 1A. Ratios of IPHN during hypoxia to hyperoxia (control 1) were 2.10 ± 0.26, 1.66 ± 0.22, and 0.98 ± 0.10 for 0, 0.1, and 0.8% halothane, respectively, revealing significant differences ($P < 0.05$). Levels of Pa_{CO_2} and pH revealed no changes at the three levels of halothane in each condition. The mean arterial blood pressure (MBP) increased significantly during hypoxia at 0 (118 ± 75 mmHg *vs.* 131 ± 5 mmHg; $P < 0.05$) and 0.1% (118 ± 6 mmHg *vs.* 130 ± 7 mmHg, $P < 0.05$; control 1 *vs.* hypoxia) halothane. Inhalation of halothane, 0.8%, significantly decreased MBP compared with that of halothane, 0 and 0.1%, regardless of the FI_{O_2} (control 1, 118 ± 7 mmHg, 118 ± 6 mmHg *vs.* 103 ± 6 mmHg; hypoxia, 131 ± 5 mmHg, 130 ± 7 mmHg *vs.* 114 ± 7 mmHg; control 2, 118 ± 8 mmHg, 119 ± 7 mmHg *vs.* 105 ± 6 mmHg; $P < 0.05$, respectively, for halothane, 0%, 0.1 *vs.* 0.8%).

Protocol 2: Effect of Peripheral Chemodenervation on Phrenic Nerve Activity during Inhalation of Halothane and the Hypoxic Gas Mixture (Fig. 1B)

There were no significant differences between ratios of IPHN obtained during hypoxia to hyperoxia (control 1); specifically, 0.95 ± 0.13, 0.81 ± 0.11, and 1.09 ± 0.30 for halothane, 0, 0.1, and 0.8%, respectively. There were no significant differences in the pH and Pa_{CO_2} at different levels of halothane in each condition. Hypoxia did not increase MBP, although inhalation of halothane, 0.8%, caused a significant decrease in MBP compared with that of inhalation of halothane, 0 and 0.1%, regardless of the FI_{O_2} (control 1, 144 ± 9 mmHg, 144 ± 7 mmHg *vs.* 124 ± 11 mmHg; hypoxia, 150 ± 11 mmHg, 147 ± 7 mmHg *vs.* 131 ± 11 mmHg; control 2, 145 ± 10 mmHg, 141 ± 9 mmHg *vs.* 127 ± 14 mmHg; $P < 0.05$, respectively, for 0%, 0.1 *vs.* 0.8% halothane).

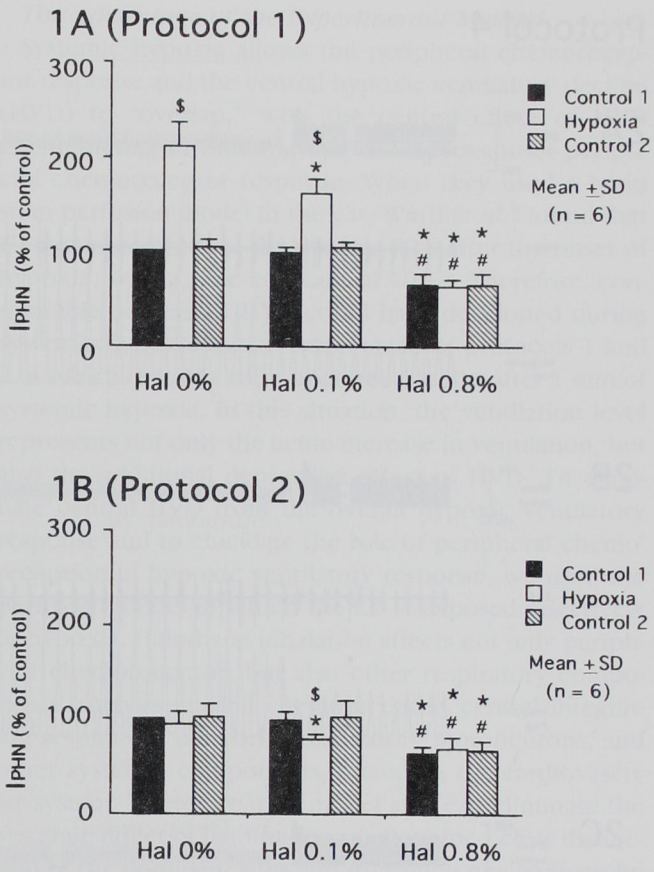

Fig. 1. Changes in phrenic nerve activity during systemic hyperoxia (controls 1 and 2) and hypoxia (hypoxia) at three levels of end-tidal halothane concentration with intact carotid sinus nerve (*A*) (protocol 1) and chemodenervation (*B*) (protocol 2). Phrenic nerve activity is expressed as a percentage of the value of control 1 at halothane, 0%. *P <0.05 compared with halothane, 0%. #P< 0.05 compared with halothane, 0.1%. $$P$ < 0.05 compared with controls 1 and 2.

Protocol 3: Effect of Carotid Body Perfusion on Phrenic Nerve Activity

There were no significant differences in IPHN activity before, during, and after perfusion of the CB with KR solution at three levels of PP_{O_2}. There were no significant

Protocol 4

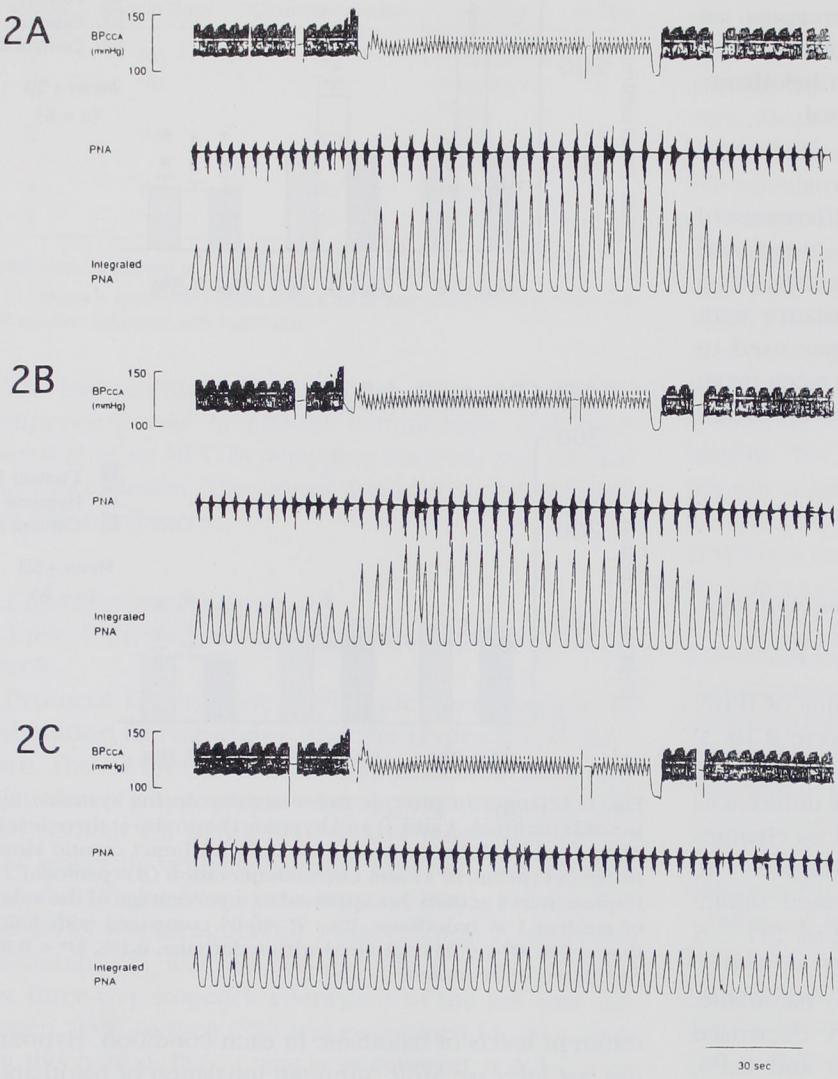

Fig. 2. Polygraphic records show changes in phrenic nerve activity during perfusion of the carotid body with hypoxic Krebs-Ringer solution (protocol 4). *A, B,* and *C* show records during the perfusion of solution equilibrated with halothane, 0, 0.1, and 0.8%. BPCCA = blood pressure measured in the left common carotid artery, PNA = phrenic nerve activity.

differences in gas tensions between arterial blood and KR solution at each level of oxygen tension.

Protocol 4: Effect of Carotid Body Perfusion with Hypoxic Krebs-Ringer Solution Equilibrated with Halothane

Figure 2 shows representative polygraphic recordings. Typically, the commencement of perfusion with hypoxic KR solution equilibrated with halothane, 0 and 0.1%, caused immediate increases in phrenic nerve activity (figs. 2A and B). In contrast, no change in phrenic nerve activity was noted when perfusion was performed by hypoxic KR solution equilibrated with halothane, 0.8% (fig. 2C). The hypoxia:hyperoxia ratios of IPHN (control 1) were 2.18 ± 0.20, 2.05 ± 0.12, and 1.06 ± 0.09 for halothane, 0, 0.1, and 0.8%, respectively (fig. 3). Compared with halothane, 0%, only the halothane, 0.8%, dose significantly depressed the CB-mediated hypoxic response. Table 2 shows the values of P_{O_2}, P_{CO_2}, and *p*H for arterial blood and KR solution before perfusion and the values of MBP and the mean perfusion pressure during selective perfusion.

Protocol 5: Time-Control Study

No significant differences were evident between the hypoxia:hyperoxia ratios of IPHN activity (2.15 ± 0.25,

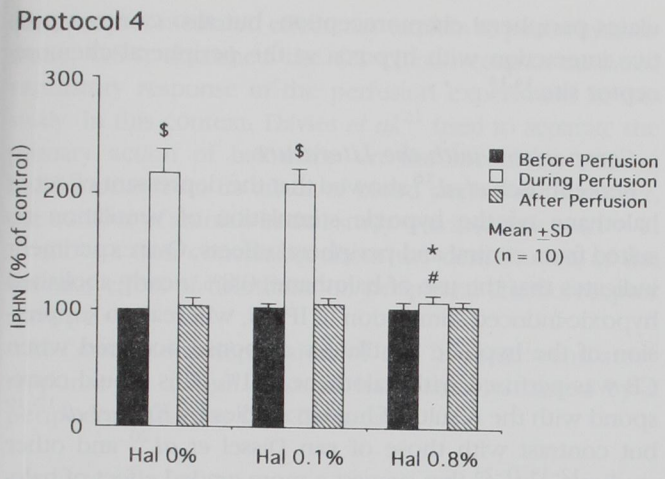

Fig. 3. Changes in phrenic nerve activity before, during, and after perfusion with hypoxic Krebs-Ringer solution equilibrated with three levels of halothane concentration (protocol 4). Phrenic nerve activity is expressed as the percentage of the value obtained during perfusion with the hyperoxic Krebs-Ringer solution equilibrated with halothane, 0% (control 1). *$P < 0.05$ compared with halothane, 0%. #$P < 0.05$ compared with halothane, 0.1%. \$$P < 0.05$ compared with before and after perfusion.

2.24 ± 0.21, and 2.22 ± 0.14 for first, second, and third measurements, respectively), or in blood gas data among these measurements of each condition. In the first and second measurements, MBP increased significantly during hypoxia compared with that during hyperoxia (first, 118 ± 10 mmHg *vs.* 132 ± 12 mmHg; second, 120 ± 7 mmHg *vs.* 138 ± 6 mmHg; $P < 0.05$, respectively, for control 1 *vs.* hypoxia), although not in the third measurement.

Discussion

Four major findings resulted from the current study: (1) Inhalation of 0.8% halothane significantly depressed IPHN during systemic hyperoxia. (2) The ratio of IPHN during systemic hypoxia:hyperoxia was depressed in a dose-dependent manner during halothane anesthesia. (3) During inhalation of the hypoxic gas mixture, IPHN was significantly depressed by inhalation of halothane in a dose-dependent manner with or without chemodenervation. (4) Perfusion of the CB with hypoxic KR solution was associated with a significant depression of IPHN activity when the solution was equilibrated with halothane, 0.8%, although not with halothane, 0.1%. Based on these results, we conclude that depression of the hypoxic ventilatory response by a high dose of halothane is caused by a suppression of activity at the CB.

The Advantage of the Experimental Method

Systemic hypoxia allows the peripheral chemoreceptor response and the central hypoxic ventilatory decline (HVD) to "overlap," with the central effect of HVD counteracting or masking the full expression of peripheral chemoreceptor response. When they used a brain stem perfusion model in the cat, Ward *et al.*[6] found that HVD commenced on the average 32 s after the onset of hypoxia, with a time constant of 105 s. Therefore, considerable degrees of HVD could have developed during systemic hypoxic experiments, such as protocols 1 and 2 in which the data were obtained for 30 s after 1 min of systemic hypoxia. In this situation, the ventilation level represents not only the acute increase in ventilation, but also the additional depressant effect of HVD. To eliminate central HVD from the overall hypoxic ventilatory response and to elucidate the role of peripheral chemoreception in hypoxic ventilatory response, we used the perfusion model in which the CB is exposed selectively to hypoxia. Halothane inhalation affects not only peripheral chemoreceptor, but also other respiratory components, such as central chemoreceptor, central integrating respiratory networks, respiratory motoneurons, and other systemic components, including the cardiovascular system. Therefore, this model also can eliminate the systemic effect of halothane and allow for a clear distinction of the dominant sites and prevailing mechanisms by which halothane causes its effect in whole-system studies such as protocol 1.

In studies of peripheral chemoreception, it is important to control the CB perfusion because chemoreception depends critically on blood flow to the chemore-

Table 2. Values of P_{O_2}, P_{CO_2}, and *p*H for Arterial Blood and Krebs-Ringer (KR) Solution, and Mean Arterial Blood Pressure (MBP) and Mean Perfusion Pressure (MPP) during Selective Perfusion of Carotid Body with the Hypoxic KR Solution in Protocol 4

Halothane	0%	0.1%	0.8%
Arterial blood			
Pa_{O_2}	396 ± 43	384 ± 40	384 ± 30
Pa_{CO_2}	50 ± 3	50 ± 3	51 ± 4
*p*H	7.36 ± 0.03	7.36 ± 0.04	7.36 ± 0.03
MBP	115 ± 6	117 ± 6	100 ± 7
KR solution			
P_{O_2}	39 ± 2	40 ± 3	40 ± 3
P_{CO_2}	50 ± 3	49 ± 4	49 ± 3
*p*H	7.33 ± 0.06	7.34 ± 0.05	7.34 ± 0.05
MPP	115 ± 4	116 ± 5	101 ± 6

Values are mean ± SD (n = 10). There were no significant differences between three levels of halothane concentration.

ceptors.[7–9] In addition, it has been shown that there is a major central interaction between baroreceptor and chemoreceptor reflexes, so changes in baroreceptor activity modulate ventilatory responses to chemoreceptor stimulation.[9] Therefore, perfusion of the carotid sinus region must be controlled to exclude the effect of changes in blood pressure and blood flow on ventilation. Although the distribution of the perfusate or local vasodilation within the CB during artificial perfusion may differ from that of natural blood perfusion, the perfusion flow was kept constant in this study by a roller pump with variable resistance. Blood flow through the common carotid artery ranges in cats from 2–10% of cardiac output[10] (4–20 ml/min). Thus, the constant flow of the perfusion system was adjusted to 5–8 ml/min based on these data and the size of cats used in our experiments.

The CB activity may be influenced indirectly by halothane through its effect on the sympathetic nerve supply. McCloskey[11] showed that stimulation of sympathetic discharge increases the CB activity by modifying the blood supply. In the current study, sympathectomy was performed to exclude the effect of sympathetic activity. In this context, Ponte and Sadler[12] suggested that chemodepression is unlikely to occur through a reduction in sympathetic tone, because sympathectomy did not alter chemodepression secondary to inhalational anesthetics.

Finally, any effect resulting from a deterioration in the general status of our preparation should be considered. Despite the invasive nature of the *in situ* preparation, little or no change in response was noted in the perfusion system check study (protocol 3) and the time control study (protocol 5), indicating the absence of significant deterioration in the preparation itself during the course of the experiment.

Limitations of the Experimental Method

Although it would be preferable to evaluate IPHN activity during halothane administration without baseline anesthesia, a baseline anesthetic was necessary because of the invasive nature of our study. All halothane-mediated changes in the hypoxic ventilatory response were superimposed on the baseline anesthesia. Although it has been shown that baseline anesthesia with pentobarbital does not affect peripheral chemoreceptor discharge,[13] phrenic nerve activity, which reflects the overall neural output of the central respiratory system, may be affected by baseline anesthesia. In this context, a hypercapnic condition to enhance system excitability was needed to obtain adequate IPHN activity during baseline anesthesia. However, it might be possible that the hypercapnic condition not only stimulates peripheral chemoreception, but also causes a positive interaction with hypoxia at the peripheral chemoreceptor site.[14,15]

Comparison with the Literature

Berkenbosch *et al.*[16] showed that the depressant effect of halothane on the hypoxic stimulation of ventilation resulted from central and peripheral effects. Our experiment indicates that the use of halothane, 0.8%, nearly abolished hypoxic-induced stimulation of IPHN, whereas no suppression of the hypoxic ventilatory response occurred when CB was perfused with halothane, 0.1%. This would correspond with the results of human studies by Knill *et al.*[17–19] but contrast with those of van Dissel *et al.*[20] and other studies[12–13,21–23] that suggest a more graded effect of halothane on the peripheral chemoreceptor. In an experiment using an artificial brain stem perfusion technique, van Dissel *et al.*[20] showed that halothane, 0.8–1.2%, depresses but does not abolish the hypoxic stimulation of ventilation. Davies *et al.*[21] showed that inhalation of halothane, 0.5–1%, by decerebrate cats reduced impulse activity recorded from the carotid sinus nerve during hypoxia to 58% of the control response. In cats, Biscoe and Millar[13] found that halothane did not depress impulse activity from the carotid sinus nerve during hypoxia, but it depressed it during normoxia and hyperoxia. In rabbits and cats, Ponte and Sadler[12] showed that the impulse activity during hypoxia less than 40 mmHg was not depressed severely by halothane and enflurane. In goats, Koh and Severinghaus[22] showed that halothane at a 0.5% end-tidal concentration (approximately 0.5 minimum alveolar concentration) did not depress ventilation during hypoxia. Stuth *et al.*[23] found that the phrenic nerve activity during an acute, moderately severe isocapnic hypoxic stimulus is depressed dose dependently but not abolished by surgical doses of halothane (0.5–2 minimum alveolar concentration). It is possible that the discrepancy in animal studies results from different species, different preparations and protocols, different indexes of respiratory output, and the presence of other anesthetics. In this study, the combination of halothane inhalation and baseline anesthesia might have shown the synergistic effect on phrenic nerve activity and induced a considerable depression of IPHN during inhalation of halothane, 0.8%. In addition, the discrepancy in the results between different studies may be explained by the effect of halothane on the cardiovascular system. Although moderate hypotension usually has little effect on carotid chemoreceptor activity in itself, evidence suggests that the activity of baroreceptors is influenced by perfusion pressure, which in turn influences ventilation.[9] The absence of this

baroreceptor-mediated effect may explain in part why halothane, 0.8%, abolished the CB chemoreceptor-mediated ventilatory response in the perfusion experiment in this study. In this context, Davies *et al.*[21] tried to separate the primary action of halothane on the receptor's sensing mechanisms from its effect of blood perfusion. However, the number of animals in that study was insufficient (n = 1) to allow a firm conclusion about the contribution of the vascular effect of halothane on peripheral chemoreceptor activity.

In conclusion, depression of the hypoxic ventilatory response by a high dose of halothane is caused by a peripheral effect at the CB in cats.

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