HIGHLIGHTED TOPIC | Oxygen Sensing in Health and Disease

Effect of two paradigms of chronic intermittent hypoxia on carotid body sensory activity

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Peng, Ying-Jie, and Nanduri R. Prabhakar. Effect of two paradigms of chronic intermittent hypoxia on carotid body sensory activity. J Appl Physiol 96: 1236–1242, 2004. First published December 5, 2003; 10.1152/japplphysiol.00820.2003.—Reflexes arising from the carotid bodies may play an important role in cardiorespiratory changes evoked by chronic intermittent hypoxia (CIH). In the present study, we examined whether CIH affects the hypoxic sensing ability of the carotid bodies and, if so, by what mechanisms. Experiments were performed on adult male rats (Sprague-Dawley, 250–300 g) exposed to two paradigms of CIH for 10 days: 1) multiple exposures to short durations of intermittent hypoxia per day (SDIH; 15 s of 5% O<sub>2</sub> + 5 min of 21% O<sub>2</sub>, 9 episodes/h, 8 h/day) and 2) single exposure to longer durations of intermittent hypoxia per day (LDIH; 4 h of hypobaric hypoxia (0.4 atm/day) + 20 h of normoxia). Carotid body sensory response to graded isocapnic hypoxia was examined in both groups of animals under anesthetized conditions. Hypoxic sensory response was significantly enhanced in SDIH but not in LDIH animals. Similar enhancement in hypoxic sensory response was also elicited in ex vivo carotid bodies from SDIH animals, suggesting that the effects were not secondary to cardiovascular changes. SDIH, however, had no significant effect on the hypercapnic sensory response. The effects of SDIH on the hypoxic sensory response completely reversed after SDIH animals were placed in a normoxic environment for an additional 10 days. Previous treatment with systemic administration of O<sub>2</sub><sup>-</sup> radical scavenger prevented SDIH-induced augmentation of the hypoxic sensory response. These results demonstrate that SDIH but not LDIH results in selective augmentation of the hypoxic response of the carotid body and O<sub>2</sub><sup>-</sup> radicals play an important role in SDIH-induced sensitization of the carotid body.

hypoxic sensitivity; superoxide anions; oxidative stress

CHRONIC INTERMITTENT HYPOXIA (CIH) is encountered under many physiological and pathophysiological situations (15). Reported responses to CIH in experimental animals include increased blood pressure (3), augmented sympathetic nerve activity (7), elevated circulating catecholamines (1), enhanced long-term facilitation (LTF) of the respiratory motor activity (9, 11, 14), and augmented ventilatory response to hypoxia (9). Rats in which carotid bodies have been denervated show no increase in blood pressure as well as augmented sympathetic nerve activity in response to CIH (3). Enhanced hypoxic ventilatory response in animals exposed to CIH can be mimicked with electrical stimulations of the carotid sinus nerves (9). These studies led to the suggestion that cardiorespiratory changes in response to CIH are mediated in part from augmented carotid body sensitivity to hypoxia and/or from enhanced processing of carotid body inputs in the central nervous system (3, 9). Recently, our laboratory (13) examined the effects of acute intermittent hypoxia (AIH; 15 s of 12% O<sub>2</sub> followed by 5 min of hyperoxia, 10 episodes) on carotid body sensory activity in anesthetized rats that were exposed to 10 days of CIH or to normoxia. Carotid body sensory activity increased with each episode of hypoxia in both groups of animals. However, after AIH was terminated, sensory discharge remained elevated for 1 h in CIH but not in control animals. These observations suggested that CIH induces a novel form of functional plasticity in the carotid body manifested as sensory LTF (13). Although the magnitude of the sensory response to hypoxia tended to be higher in CIH animals (see Fig. 1 in Ref. 13), the paradigm of AIH did not allow determination of whether CIH affected the hypoxic sensitivity of the carotid body (i.e., stimulus-response relation). Because 1) hypoxic challenges were brief (15 s), 2) sensory response was studied with only one intensity of hypoxia (i.e., 12% inspired O<sub>2</sub>), and 3) baseline sensory activity progressively increased with multiple episodes of hypoxia, masking the estimate of the magnitude of the hypoxic response. Therefore, the first objective of the present study was to examine the effect of CIH on carotid body sensory response to graded isocapnic hypoxia and further to assess whether the effects of CIH are limited to hypoxia or whether they extend to hypercapnia.

Several studies have reported enhanced hypoxic ventilatory responses in healthy human subjects exposed to several hours of hypoxia per day for a few weeks instead of brief episodes of hypoxia (lasting seconds to minutes) used in experimental animals. Katayama et al. (8) examined the ventilatory response to acute hypoxia in healthy male subjects to a simulated altitude of 4,500 m (1 h/day) for 7 days and found that the hypoxic but not hypercapnic ventilatory response was augmented. Other investigators (5, 6, 10, 18) also obtained similar results in healthy human subjects exposed to several hours of hypoxia per day for a few weeks. Although these studies implicated enhanced peripheral chemoreceptor reflexes to the augmented hypoxic ventilatory response, there are no studies demonstrating that chronic exposure to a few hours of hypoxia per day leads to enhanced hypoxic sensitivity of the carotid body. Consequently, the second objective of the present study was to investigate the effect of 4 h/day of hypobaric hypoxia...
for 10 days on carotid body sensory response to graded isocapnic hypoxia.

Recent studies suggest that oxidative stress plays an important role in respiratory changes caused by CIH (13, 14). Superoxide anion (O$_2^-$) levels increased in carotid bodies from CIH animals, as evidenced by downregulation of the aconitase enzyme activity, and CIH-induced sensory LTF in the carotid body was prevented by systemic administration of superoxide dismutase (SOD) mimetic, a potent scavenger of O$_2^-$ (13). Also, SOD mimetic prevented CIH-induced augmentation of LTF of the respiratory motor activity (14). If CIH leads to augmented hypoxic and/or hypercapnic sensitivity of the carotid bodies, then the third objective was to determine whether O$_2^-$ contributes to the enhanced chemosensitivity.

MATERIALS AND METHODS

Experiments were performed on male Sprague-Dawley rats weighing 250–350 g. The Institutional Animal Care and Use Committee of Case Western Reserve University approved the experimental protocols.

**Exposure to CIH**

Exposure to multiple short durations of intermittent hypoxia per day. Awake rats were exposed to a CIH paradigm consisting of 15 s of hypoxia followed by 5 min of normoxia for 9 episodes/h, 8 h/day as described previously (14) [short durations of intermittent hypoxia (SDIH)]. Briefly, animals housed in feeding cages were placed in a chamber for exposure to CIH. The animals were unrestrained, freely mobile, and fed ad libitum. The chamber was flushed with alternating cycles of pure nitrogen and compressed air so that inspired O$_2$ levels reached 5% O$_2$ during hypoxia within 68–75 s and 21% O$_2$ during normoxia within 70–85 s. Ambient O$_2$ levels in the chamber were continuously monitored with an O$_2$ analyzer (Beckman model OM-11) by sampling the air in the chamber. A continuous vacuum was created within the chamber to balance the pressure between in- and outflow of the gases. Inspired CO$_2$ levels were maintained at 0.2–0.5% and were monitored continuously by an infrared analyzer (Beckman model LB-2). The duration of the gas flow during each hypoxic and normoxic episode was regulated by timed solenoid valves. Animals exposed to alternating cycles of normoxia instead of hypoxia for 10 days served as controls. Animals were subjected to either intermittent hypoxia or normoxia between 9:00 AM and 5:00 PM for 10 consecutive days. Acute experiments were performed on the morning after the 10th day of the CIH exposure.

**Exposure to single, longer durations of intermittent hypoxia per day.** For the single, longer duration of intermittent hypoxia per day (LDIH) protocol, animals housed in feeding cages were placed in a hypobaric chamber. Animals were exposed to hypobaric hypoxia (0.4 atm) for 4 h/day (9:00 AM to 1:00 PM) for 10 days. Control animals were also placed in a similar chamber for 10 days but were subjected to normobaric normoxia. Acute experiments were performed on the morning after the final exposure.

**Preparation of animals for acute experiments.** Acute experiments were performed on rats anesthetized with urethane (1.2 g/kg ip) supplemented hourly with 15% of the initial dose. After tracheal intubation, a femoral artery and vein were cannulated for measurement of arterial blood pressure (Grass model P122) and for intravenous administration of fluids and drugs, respectively. Animals were paralyzed with pancuronium bromide (2.5 mg·kg$^{-1}$·h$^{-1}$ iv) to prevent spontaneous breathing and ventilated with a respirator (Harvard Apparatus). Arterial blood samples were collected from the femoral arterial catheter to determine blood gases [arterial P$_O_2$ and arterial P$_CO_2$ (Paco$_2$, and Paco$_3$, respectively) and pH (ABL-5, Radiometer, Copenhagen, Denmark). The rectal temperature of the animals was maintained at 38 ± 1°C by means of a heating pad. At the end of the experiments, animals were killed with intravenous administration of euthanasia solution.

**Carotid body sensory activity in vivo.** Sensory activity from the carotid body was recorded in anesthetized rats as described previously (2). Briefly, carotid bifurcation was isolated, and the carotid sinus nerve was transected at the point where it joins the glossopharyngeal nerve. Afferent activity was recorded with a monopolar platinum-iridium wire electrode with a reference electrode placed in a nearby neck muscle. Electrical activity was amplified by an AC amplifier (Grass P511), with a bandwidth of 100–3,000 Hz, and displayed on an oscilloscope (Tektronix 5B12N). Clearly identifiable action potentials above the baseline noise were converted to standardized pulses with a window discriminator (Winston RAD II-A). An example of action potentials recorded from carotid sinus nerve and setting of the window discriminator is shown in Fig. 1A, inset. The output from the window discriminator (standard pulses) was fed into a rate meter (CWE RIC-830) to display the magnitude of the discharge. Signals from the rate meter, raw action potentials from the amplifier, and blood pressure signals were continuously recorded on a chart recorder (Astro-Med). Carotid body activity was identified by prompt augmentation of sensory discharge in response to hypoxia and prompt decrease in response to hyperoxia (100% O$_2$). Reducing the pressure in the carotid sinus by occluding the common carotid artery for 10 s caused no change or an increase in sinus nerve activity but never a decrease, indicating that the sensory activity is of carotid body rather than baroreceptor origin.

**Carotid body sensory activity ex vivo.** Carotid bodies and the sinus nerves were harvested from anesthetized animals and placed in ice-cold physiological saline. Carotid bodies and sinus nerves were placed in a recording chamber and superfused with warm physiological saline (36.5°C) at a rate of 2 ml/min. The composition of the superfusing medium was as follows (in mM): 125 NaCl, 5.3 KCl, 1.8 CaCl$_2$, 2 MgSO$_4$, 1.2 NaH$_2$PO$_4$, 25 NaHCO$_3$, 10 n-glucose, and 5 sucrose, pH 7.4. The medium was continuously bubbled with either 95% O$_2$ + 5% CO$_2$ (normoxia) or 6% O$_2$ + 5% CO$_2$ (hypoxia). We recorded afferent activity from the sinus nerve with a suction electrode, using the amplification protocols described above.

**Experimental Protocols**

**Group I.** The effect of acute hypoxia on carotid body sensory activity was examined in SDIH-conditioned rats (n = 8). Parallel experiments were performed on animals exposed to intermittent normoxia for 10 days (controls, n = 8). Also, after exposure to 10 days of SDIH, an additional seven rats were placed in room air for 10 days, and on the 11th day carotid body sensory activity was examined. The carotid body sensory activity was recorded in anesthetized, paralyzed, and mechanically ventilated animals. The effects of the three levels of inspired O$_2$ (100, 21, and 12% O$_2$) were examined while maintaining P$_{ACO}_2$ at ~33 Torr. All gases were administered via a needle placed in the inspiratory port of the respirator. Each gas challenge was maintained for 2 min. After hypoxic challenge, inspired gas was switched back to hyperoxic gas mixture and 10 min were allowed before the protocols were repeated to ensure that baseline was not altered. In additional experiments, the effect of hyperoxic hypercapnia (5 and 7% CO$_2$ with balance O$_2$) was examined in SDIH and control rats (n = 6 each). Hypercapnic challenges were given for 5 min. Arterial blood samples were collected at the end of each gas challenge. Hypoxic and hypercapnic challenges were repeated twice in a given experiment. At the end of the experiment, chemoreceptor response to asphyxia (by stopping the respirator for 2 min) was recorded. Sensory response to hypoxia and hypercapnia were normalized as percentage of asphyxia response. In the same experiments, we also examined the effect of systemic administration of sodium cyanide (NaCN; 90 µg/kg iv) on carotid body sensory activity.
Group II. The effect of acute hypoxia was examined in ex vivo carotid bodies harvested from control (n = 10 carotid bodies) and SDIH-conditioned animals (n = 8 carotid bodies). Baseline carotid body activity was recorded for 5 min while the carotid bodies were superfused with medium equilibrated with 95% O₂-5% CO₂. The medium was then switched to that equilibrated with hypoxic gas (medium PO₂ = 46 Torr) for 3 min followed by hyperoxic medium. Hypoxic challenges were repeated at least twice in a given experiment. At the end of the experiment, superfusion of the carotid body was interrupted for 3 min and the effect of stop-flow on the sensory activity (maximum excitation) was recorded. Sensory response to hypoxia was normalized as percentage of response to stop-flow.

Group III. Carotid body sensory responses to hypoxia were determined in LDIH-conditioned animals for 10 days (n = 7). Parallel experiments on animals exposed to 10 days of normobaric normoxia served as controls (n = 7). The protocols for assessing the sensory response to acute hypoxia were the same as those described for group I.

Group IV. These experiments were performed on animals exposed to 10 days of SDIH. One group of animals (n = 7) received manganese(III) tetraakis(1-methyl-4-pyridyl)porphyrin pentachloride (MnTMPyP; Alexis), a potent scavenger of O₂· anions, via an intraperitoneal route each morning (5 mg·kg⁻¹·day⁻¹) before they were subjected to SDIH. MnTMPyP was given for 10 days. The protocols were repeated in another group of SDIH animals that received saline (vehicle control, n = 8). The effect of hypoxia on carotid body sensory activity was recorded in vivo in both groups of animals as described above.

Data Analysis

The following variables were analyzed: 1) chemoreceptor activity (impulses/s), 2) mean arterial blood pressure (mmHg); and 3) PaO₂, PaCO₂, and pH. In the in vivo experiments, chemoreceptor activity (impulses/s) and mean blood pressure (mmHg) were quantified during baseline (hyperoxia) room air, hypoxia, and hypercapnia. Because there are variations in basol sensory activity in different experiments, the magnitude of the sensory response to either hypoxia or hypercapnia was normalized to percentage of asphyxia response and plotted against arterial PaO₂ and PaCO₂. In ex vivo carotid body preparation, sensory activity (impulses/s) was analyzed during baseline and hypoxia. The magnitude of the response was normalized to response to stop-flow. Average data are expressed as means ± SE. Two-way ANOVA with repeated measures followed by Tukey’s test was used to evaluate the statistical significance. P values of <0.05 were considered significant.

RESULTS

Effect of CIH on Carotid Body Response to Hypoxia

Effect of SDIH. Carotid body sensory activity increased in response to hypoxia in both SDIH and control animals. However, as illustrated in Fig. 1A, the magnitude of increase was greater in SDIH animals. Average data (normalized to % of asphyxia response) showed that the sensory response to hypoxia (PaO₂ = 35–36 Torr) was significantly enhanced in SDIH compared with control animals (P < 0.001; Fig. 1B), whereas sensory activity was comparable at less severe hypoxia (PaO₂ = 81–82 Torr) between both groups. To determine whether SDIH-induced enhancement of the hypoxic response is a reversible phenomenon, after 10 days of exposure to SDIH, animals were placed in a room air environment for another 10 days. Subsequently, carotid body sensory activity was recorded under anesthetized conditions. Sensory response to hypoxia in SDIH animals exposed to 10 days of normoxia was nearly the same as that for control animals (Fig. 1B).

Effect of LDIH. In sharp contrast to SDIH, sensory response to hypoxia was not augmented in LDIH compared with control animals (Fig. 2). Average data showed no significant differences in the sensory response (expressed as % of asphyxia response) at all three levels of PaO₂ tested between control and LDIH animals (Fig. 2B).

Arterial blood pressure and blood-gas values in SDIH and LDIH animals are summarized in Table 1. Arterial blood pressure was significantly elevated in SDIH but not in LDIH animals compared with controls. During acute hypoxia, arterial blood pressure decreased, and the magnitude of decrease was comparable in all groups of animals (P > 0.05; Table 1).
Changes in arterial blood gases during acute hypoxic challenges were comparable between all groups of animals (Table 1).

The results described above demonstrate that SDIH but not LDIH augmented the hypoxic sensory response. Therefore, the following series of experiments were performed to further assess the effects of SDIH on carotid body activity.

Sensory Response to Hypoxia in Ex Vivo Carotid Bodies

To determine whether the enhanced sensory response to hypoxia is secondary to cardiovascular alterations, experiments were performed on ex vivo carotid bodies from SDIH and control animals, wherein the influence of cardiovascular changes on sensory activity is effectively absent. Hypoxia increased ex vivo carotid body sensory activity in both groups of animals (Fig. 3A). The magnitude of hypoxic response (normalized to % of stop-flow response) was significantly greater in SDIH than in control carotid bodies ($P < 0.001$; Fig. 3B).

Effect of SDIH on Sensory Response to Hypercapnia and Cyanide

To determine whether the effects of SDIH were confined only to hypoxia or whether effects extended to other stimuli,
carotid body responses to graded hypercapnia (5 and 7% CO₂-balance O₂) were examined. Hypercapnia caused a small but significant increase in sensory activity in SDIH and control animals, and the magnitude of the response to a given hypercapnia was comparable between both groups (P > 0.05; n = 6 each; Fig. 4A). Arterial blood-gas values during hypercapnia were comparable between both groups (Table 1). Carotid body response to systemic administration of NaCN (90 μg/kg iv) was examined in the same animals as above. The magnitude of sensory response to NaCN was significantly greater in SDIH animals (Fig. 4, B and C).

**SOD Mimetic Prevents SDIH-Induced Enhanced Hypoxic Sensory Response**

To test whether O₂· radicals are involved in SDIH-induced augmentation of the hypoxic sensory response, rats were given MnTMPyP (5 mg/kg ip), a membrane-permeable, stable SOD mimic (a potent scavenger of O₂·), every morning before they were subjected to 8 h of SDIH exposure. Parallel experiments were performed on SDIH animals that received vehicle (saline). The magnitude of hypoxic sensory response (normalized to % of asphyxia response) was significantly less in SDIH + SOD mimetic-treated compared with vehicle-treated SDIH animals (P < 0.01, Fig. 5). Changes in arterial blood pressure and blood gases during hypoxia were comparable between groups of animals (Table 1).

**DISCUSSION**

A major finding of the present study is that carotid body sensitivity to hypoxia was augmented with SDIH but not with LDIH, although both paradigms resulted in intermittent hypoxia. However, it should be noted that, although the duration of

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Fig. 3. A: representative tracings showing the changes in carotid sinus nerve activity (imp/s) from carotid bodies harvested from a control rat and a rat conditioned with 10 days SDIH. Time calibration = 40 s. Hypoxic challenges are marked under the tracings as solid bars, and PO₂ levels during hypoxic challenges are indicated under the bars. B: average data showing carotid body chemoreceptor sensory activity in response (expressed as %response to stop-flow) to hypoxia in ex vivo preparations taken from control (n = 10) and SDIH-conditioned (n = 8) rats. **P < 0.01, significantly different compared with control rats.

Fig. 4. A: average data showing the relationships of carotid body sensory activity (expressed as % of asphyxia response) against PaCO₂ while PaO₂ was maintained at ~250 Torr in control (n = 6, ○) and SDIH-conditioned (n = 6, ●) rats. B: representative tracings showing the changes in carotid body sensory discharges (imp/s) in response to intravenous injection of 90 μg/kg sodium cyanide (NaCN) in a control rat and a rat conditioned with 10 days of SDIH. Time calibration = 20 s. NaCN injections are marked under the tracings as solid bars. C: average data showing carotid body chemoreceptor sensory activity in response (expressed as % of baseline) to NaCN in control (n = 8) and SDIH-conditioned (n = 8) rats. *P < 0.05, significantly different compared with control rats.
ambient $O_2$ reached this level as well when it returned to existing $PaCO_2$, i.e., the greater the arterial $CO_2$, the greater the response to a given hypoxic challenge critically depends on the number rather than the absolute length of effects of intermittent hypoxia on the chemosensory activity (activity-dependent plasticity), which would explain the enhanced processing of carotid body inputs at the central neurons (adaptive sensitization of the carotid body might have triggered enhanced sensitivity to low $O_2$. Several factors in alternating cycles of normoxia did not exhibit enhanced carotid body sensory response to repetitive hypoxia because control animals exposed to hypoxic episodes.

We believe that the effects of SDIH are due to brief exposures to repetitive hypoxia because control animals exposed to alternating cycles of normoxia did not exhibit enhanced carotid body sensitivity to low $O_2$. Several factors influence carotid body sensory response to hypoxia. For example, sensory response to a given hypoxic challenge critically depends on existing $PaCO_2$, i.e., the greater the arterial $CO_2$, the greater the response to hypoxia and vice versa (17). It is possible that the enhanced sensitivity to hypoxia is secondary to altered sensitivity of the carotid body to $CO_2$. However, such a possibility seems unlikely because carotid body sensory responses to two levels of hypercapnia were unaffected in SDIH-conditioned animals. Changes in $PaO_2$ were comparable between SDIH and control animals, indicating that the enhanced sensitivity to hypoxia was not due to differences in arterial $O_2$ levels during hypoxia. The observation that the sensory response to NaCN (histotoxic hypoxia) was also augmented, whereas the response to hypercapnia was unaffected, suggests that SDIH selectively affected the hypoxic sensitivity of the carotid body. Enhanced sensory response to hypoxia was also seen in ex vivo-superfused carotid bodies from SDIH animals, implying that the effects were not secondary to acute alterations in carotid body blood flow. We have recently reported that SDIH had no significant effect on carotid body morphology either in terms of number of glomus cells (putative $O_2$-sensing cells) or the volume of the glomus tissue (13). Thus the enhanced hypoxic sensitivity seems unlikely due to changes in gross morphology of the carotid body.

SDIH animals exhibited elevated blood pressures compared with controls. There are conflicting reports on the effects of CIH on blood pressure in experimental animals. Fletcher et al. (3), using an SDIH paradigm very similar to that described in the present study, reported elevated blood pressures after 30 days of CIH but not with 10 days in rats; Sica et al. (19), however, observed increases in systolic blood pressure in rats within 7 days of CIH with a SDIH paradigm similar to that employed by Fletcher et al. (3). It is known that moderate hypertension augments carotid body sensory response to hypoxia in rats (4). It is possible that the increased blood pressure and/or elevated circulating vasoactive hormones during SDIH might have contributed in part to the enhanced sensory response to hypoxia. Systemic administration of SOD mimic, a potent scavenger of $O_2^*$, prevented SDIH-induced augmentation of the hypoxic sensory response. These observations suggest that the enhanced carotid body sensitivity involves increased generation of $O_2^*$ and support the idea that CIH with multiple brief exposures to hypoxia represents a form of oxidative stress, as suggested previously (14, 16). The mech-

![Fig. 5](image-url). A: representative tracings showing the changes in carotid body sensory discharges (imp/s) in response to hypoxia in a vehicle control (SDIH + saline) rat and a superoxide dismutase (SOD) mimetic-subjected, SDIH-conditioned (SDIH + SOD) rat. Time calibration = 40 s. Hypoxic challenges are marked under the tracings as solid bars, and $PaO_2$ levels during hypoxic challenges are indicated under the bars. B: average data showing the relationships of carotid body sensory activity (expressed as % of asphyxia response) against $PaO_2$ while $PaCO_2$ was maintained close to 35 Torr in SDIH + saline ($n = 8$, ○) and SDIH + SOD ($n = 7$, ●) rats. **$P < 0.01$, significantly different compared with control rats.
anisms by which reactive oxygen species participate in the heightened carotid body sensitivity to hypoxia are beyond the scope of the present study and require further investigation.

What might be the significance of SDIH-induced augmentation of carotid body sensitivity to hypoxia? Previous studies (3) reported that chronic sectioning of sinus nerves prevents elevated blood pressures and augmented sympathetic nerve activity caused by CIH. Also, Ling et al. (9) reported that the neural respiratory response to hypoxia was greater after CIH at PaO₂ between 25 and 45 Torr but not at higher PaO₂, and suggested that CIH-induced enhanced hypoxic ventilatory drive is due to enhanced carotid body sensitivity to hypoxia and/or due to increased processing of sensory inputs from carotid body at the central nervous system. By recording the carotid body sensory activity, our study provides direct evidence for heightened hypoxic sensitivity of the carotid body in response to SDIH. Also, consistent with the ventilatory studies by Ling et al. (9), we also found that the carotid body sensitivity is enhanced with PaO₂ of <40 Torr but not at higher PaO₂. Thus it is likely that the enhanced carotid body sensitivity to hypoxia contributed in part to the augmented ventilatory sensitivity to hypoxia as well as to the enhanced sympathetic activity and increased blood pressure associated with CIH (3, 7, 19).

In summary, the present study demonstrates that, although intermittent hypoxia was performed in both the SDIH and LDIH protocols, only SDIH leads to enhanced hypoxic sensitivity of the carotid body. Our data further suggest that increased generation of reactive oxygen species plays an important role in SDIH-induced sensitization of the carotid body response to hypoxia.

GRANTS
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