Important role of carotid afferents in control of breathing


Important role of carotid afferents in control of breathing. J. Appl. Physiol. 85(4): 1299–1306, 1998.—The purpose of the present study was to determine the effect on breathing in the awake state of carotid body denervation (CBD) over 1–2 wk after denervation. Studies were completed on adult goats repeatedly before and after bilateral CBD (n = 8), for 7 days after unilateral CBD (n = 5), and for 15 days after sham CBD (n = 3). Absence of ventilatory stimulation when NaCN was injected directly into a common carotid artery confirmed CBD. There was a significant (P < 0.01) hypoventilation during the breathing of room air after unilateral and bilateral CBD. The maximum PaCO2 increase (8 Torr for unilateral and 11 Torr for bilateral) occurred ~4 days after CBD. This maximum was transient because by 7 (unilateral) to 15 (bilateral) days after CBD, PaCO2 was only 3–4 Torr above control. CO2 sensitivity was attenuated from control by 60% on day 4 after bilateral CBD and by 35% on day 4 after unilateral CBD. This attenuation was transient, because CO2 sensitivity returned to control temporarily similar to the return of PaCO2 during the breathing of room air. During mild and moderate treadmill exercise 1–8 days after bilateral CBD, PaCO2 was unchanged from its elevated level at rest, but 10–15 days after CBD, PaCO2 decreased slightly from rest during exercise. These data indicate that 1) carotid afferents are an important determinant of rest and exercise breathing and ventilatory CO2 sensitivity, and 2) apparent plasticity within the ventilatory control system eventually provides compensation for chronic loss of these afferents.

HISTORICALLY, there have been different opinions on the contribution of carotid chemoreceptor afferents to the control of breathing. One view, that their contribution is minor, is based largely on the observed small decrease in breathing when chemoreceptor activity is attenuated acutely by hyperoxygenation (7, 9, 12, 32, 38). Another view of a greater role is based largely on hypoventilation after surgical carotid body denervation (CBD) (1-5, 16, 19, 27, 30, 34, 38). In most studies, the effects of CBD have been assessed immediately after CBD in the anesthetized state (25) or weeks later in the awake state (1-5, 16, 19, 27, 30, 34, 38). However, Bisgard et al. (2, 3) studied ponies in the awake state 7 and 14 days after CBD and found that, during the breathing of room air, arterial PCO2 (PaCO2) was 18 and 10 Torr, respectively, above pre-CBD values. These findings indicate a greater effect on breathing over the first few days after CBD than has been generally accepted. Because of the paucity of data over this time period (particularly CO2 sensitivity and the exercise hyperpnea), the purpose of the present study was to determine the effect on breathing in the awake state over the first 2 wk after CBD. We hypothesized hypoventilation at rest and during exercise and attenuated CO2 sensitivity over the first few days after bilateral CBD would be followed by a return of ventilatory control toward pre-CBD status. Furthermore, because there appears to be redundancy/plasticity within ventilatory control mechanisms (6, 36), we hypothesized that breathing at rest and CO2 sensitivity would not be altered by unilateral CBD.

METHODS

Four female and four male castrated adult goats (28–55 kg) were studied repeatedly before and over 15 days after surgical bilateral CBD. Five castrated male adult goats (28–35 kg) were studied before and for 7–10 days after surgical unilateral CBD. Finally, two female and one male adult goats (35–40 kg) were studied over 15 days after sham bilateral CBD. Goats were chosen for study because this species is commonly used for studies on the awake state. Goats were housed in an environmental chamber with ambient temperature and photoperiod adjusted seasonally. They had free access to hay and water except for periods of study.

An initial surgery was performed for bilateral elevation of the carotid arteries. Anesthesia was induced by using ketamine (Ketaset; 15 mg/kg im). After intubation, the goats were mechanically ventilated and anesthesia was maintained with 1–1.5% halothane in oxygen. Under sterile conditions, a 5-cm segment of each carotid artery was elevated subcutaneously. Two weeks were allowed for the goats to recover from this surgery before pre-CBD studies were begun.

Details on the CBD surgical procedure have also been presented elsewhere (31). Briefly, with the head rotated to a supine position, a midline incision was made. Blunt dissection accessed the carotid arteries, exposing the carotid bifurcation. One centimeter proximal to the bifurcation and dorsal to the carotid artery, a bundle of small vessels carrying the carotid sinus nerve was located. The nerve was dissected free, ligated at two points, and cut between the two points. This procedure was completed on both sides for bilateral CBD but only on one side for unilateral CBD. For sham CBD, the same procedure was followed except the ligation and cutting were omitted. The incisions were closed, and the goat was allowed

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RESULTS

Effect of CBD on ventilatory response to hypoxia. Within the first minute of exposure to 12.5% inspired O₂ (P_{aO₂} ~ 35 Torr), Vᵢ increased in carotid chemoreceptor-intact goats (Figs. 1 and 2). Vᵢ increased further in the second minute to ~35% above control. Over the next few minutes, Vᵢ decreased insignificantly (P > 0.05) to only 20% above control, with no consistent changes over the remaining hypoxic period. The hypopnea was accompanied by a 3- to 4-Torr decrease (P < 0.05) in P_{aCO₂} (inset, Figs. 1 and 2), and it was a result of small but insignificant (P > 0.10) increases in both f and VT (data not shown).

In both unilateral and bilateral CBD goats, Vᵢ did not change during the first minute of hypoxia (Figs. 1 and 2). Thereafter, average Vᵢ and P_{aCO₂} followed a pattern during hypoxia similar to chemoreceptor-intact goats. However, throughout the 15 days after bilateral CBD, there was no statistically significant (P > 0.05) change during hypoxia in Vᵢ and P_{aCO₂} (Fig. 1) nor in f and VT (data not shown). After unilateral CBD, significant (P < 0.01) hypopnea and hypocapnia were elicited by hypoxia (Fig. 2), but neither f nor VT changed significantly (P > 0.10) during hypoxia.

Effect of CBD on ventilatory response to venous NaCN. The ventilatory ratio for the intravenous response to NaCN was reduced significantly (P < 0.01) from 2.81 ± 0.26 to 1.56 ± 0.20 1–2 days after bilateral CBD (Fig. 3). In contrast, this ratio was not signifi-

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Fig. 1. Inspired pulmonary ventilation (Vᵢ) before and during 20 min of hypoxia before (●) and 1–8 (○) and 10–15 (□) days after bilateral carotid body denervation (CBD). Values are means ± 5E of 8 awake goats. Vᵢ increased significantly during hypoxia before CBD (P < 0.05) but not 1–8 (P = 0.09) and 10–15 days (P = 0.08) after CBD. Inset, group mean values of arterial blood gases measured at the indicated periods. Room-air blood-gas values in this inset do not correspond to Table 1 and Figs. 5 and 8 because the data in this inset are specific to hypoxia studies, whereas the data in Table 1 and Figs. 5 and 8 are specific to studies assessing CO₂ sensitivity or exercise. These 3 protocols were not all completed consistently on the same day in each animal, which contributes to the variation in arterial P_{aCO₂} (P_{aCO₂}) values between Table 1 and Figs 5 and 8. Pa_{aCO₂}, arterial P_{aCO₂}.

*Statistically significant difference from control, P < 0.05.

To recover. Ceftiofur sodium (2 mg/kg) was administered daily as an antibiotic for at least 1 wk after each surgery. At least one carotid artery was catheterized for 1 wk before and 2 wk after CBD surgery. In addition, a jugular vein was catheterized on 1 day before and after CBD. For most studies, a mask with attached breathing valve was securely taped to the goat’s snout. Breathing was monitored by connecting the valve to a Tissot spirometer that was connected to a Grass recorder. Arterial blood pressure was monitored by connecting the arterial catheter to a Statham transducer, which was connected to the Grass recorder.

One assessment of the carotid (or peripheral) chemoreflex was by determining the ventilatory response to intravenous or intra-arterial bolus injections of NaCN. While the goat was breathing room air, 100 µg/kg of NaCN were rapidly injected into the catheterized jugular vein. Breathing was continuously monitored, and the response to NaCN was expressed as inspired pulmonary ventilation (Vᵢ) between 10 and 30 s postinjection divided by Vᵢ for the minute preceding the infusion. Three such injections were made (at 5-min intervals) 1 day before and 1 or 2 days after CBD or sham CBD. In addition, 1 day before CBD, 1–2 days after CBD, and 7–15 days after CBD, we also rapidly injected NaCN (10 or 20 µg/kg) individually into one or both catheterized carotid arteries. The response to these injections was expressed as Vᵢ for the first five breaths after the injection divided by the control Vᵢ. Three to five such injections were made each day.

A second assessment of the carotid chemoreflex was the ventilatory response to hypoxia. After the control data were obtained, the inspired O₂ for carotid intact goats was reduced to 12.5% for 20 min. After CBD, inspired oxygen was lowered to only 13–14%, thus providing the same arterial PO₂ (P_{aO₂}) as during the hypoxia in the intact condition. Breathing was monitored for at least 5 min before and continuously during the hypoxic period. Duplicate samples of arterial blood were withdrawn before and between 5 and 7 and between 18 and 20 min of hypoxia.

To assess ventilatory sensitivity to CO₂, inspired CO₂ was increased in 2.5% increments at 5-min intervals to a maximum of 7.5% (balance room air). Breathing was continuously monitored, and duplicate samples of arterial blood were withdrawn over the last 2 min at each CO₂ level.

To assess the effect of CBD on the exercise hyperpnea, arterial blood was withdrawn (n = 4) while the goats were standing on a treadmill and then at 15–, 30–, or 60-s intervals (n = 16) during 4 min of exercise at 1.8 miles/h (mph) and 5% grade and at 1.8 mph and 15% grade. Because of concern that instrumentation with a mask and breathing valve may affect the exercise hyperpnea, the goats were not instrumented other than with the arterial catheter. As in the past, we assessed the ventilatory response to exercise by the temporal pattern of P_{aCO₂}.

A Ciba-Corning analyzer (model 278) was used for determination of arterial blood gases and pH. Corrections were made between the temperature setting of the analyzer and the goat’s measured rectal temperature.

Linear regression analysis was used to compute ventilatory responsiveness to CO₂. ANOVA for repeated measures was used to determine whether Vᵢ, breathing frequency (f), tidal volume (Vₜ), P_{aO₂}, and P_{aCO₂} changed significantly during hypoxia; whether P_{aCO₂} changed significantly during exercise; and whether arterial blood gases, acid-base status, blood pressure, heart rate, and CO₂ sensitivity changed over days before and after surgery. Significant (P < 0.05) ANOVA was followed by the Newman-Keuls post hoc test. Paired t-tests were used to assess whether responses to NaCN injections were significantly altered by CBD.
significantly reduced (P > 0.05) 1–2 days after unilateral CBD (2.80 ± 0.33 vs 2.60 ± 0.30). For the three sham CBD goats, the average ventilatory ratio was 3.10 and 3.27 before and after surgery respectively.

**Effect of CBD on ventilatory response to carotid artery NaCN.** In intact goats, a 10 µg/kg bolus injection of NaCN into a carotid artery elicited a hyperpnea within the first breath after the injection, and the hyperpnea continued for three to five breaths. V̇l over these five breaths was usually about twice that of control. However, in both the bilateral and the unilateral CBD goats, there was no significant (P > 0.10) hyperpnea when NaCN was injected into a carotid artery where the sinus nerve had been cut (Fig. 4). This lack of response was observed 1–2 and 7–15 days after CBD. In contrast, in the unilateral CBD goats, injection of NaCN into the carotid artery contralateral to the denervated side elicited a ventilatory ratio of 1.76 ± 0.12. Finally, the ventilatory ratio for arterial NaCN injection was 1.90 and 1.83 before and after sham CBD, respectively (Fig. 4).

In intact awake goats, a 20 µg/kg bolus injection of NaCN increased the ventilatory ratio above the 10 µg/kg injection, and this dose often also resulted in a delayed “behavioral response” (head shaking, body movement), suggesting an effect within the brain. This latter effect was not consistently accompanied by a hyperpnea. After CBD, this higher dose did not elicit a significant ventilatory ratio, but there often was delayed behavioral response.

**Effect of CBD during the breathing of room air.** There was a significant (P < 0.01) hypoventilation during the breathing of room air over 15 days after bilateral CBD (Fig. 5). In a majority of goats, the hypopnea and hypercapnia were progressive over the first 4–7 days after CBD (Fig. 6). The maximum hypercapnia of 11 Torr above control occurred ~4 days after CBD (Fig. 5). However, beginning about 7 days after CBD, PaCO₂ began to return toward control, and, 15 days after CBD, PaCO₂ was only increased above control by 3.5 Torr.

Unilateral CBD also resulted in a significant (P < 0.01) but transient hypventilation during the breathing of room air (Fig. 5). The increase in PaCO₂ was gradual over the first 4 days after CBD, reaching a peak 8 Torr above control. However, 7 days after CBD, PaCO₂ was (P > 0.05) only 3 Torr above control.

Sham CBD did not result in hypoventilation because PaCO₂ was within 2 Torr of control for 15 days after surgery (Fig. 5).
The hypoventilation and hypercapnia in CBD goats was accompanied by a significantly (P < 0.05) increased arterial HCO₃⁻ concentration (−3.5 meq/l) and in an insignificant decrease in arterial pH (Table 1). In the bilateral CBD goats, the hypoventilation also significantly (P < 0.05) reduced PaO₂ from 99 ± 3.8 to 85.7 ± 3.2 Torr (Table 1).

Bilateral and unilateral CBD did not significantly alter systolic or diastolic blood pressure but significantly (P < 0.05) increased heart rate by 8–15 beats/min (Table 1).

Effect of CBD on ventilatory sensitivity to CO₂. There was a significant attenuation of ventilatory sensitivity to CO₂ [ratio of change in V̇l to change in PaCO₂ (ΔV̇l/

\[ \Delta \text{PaCO}_2 \)] for several days after bilateral CBD (Fig. 7). For some goats, this attenuation was progressive over the first 4–7 days after CBD (Fig. 6). The nadir for the group in CO₂ sensitivity occurred 4 days after CBD when it was reduced 60% below control (1.55 ± 0.1 vs. 0.65 ± 0.05 l·min⁻¹·Torr⁻¹). About 7 days after CBD, the ΔV̇l/ΔPaCO₂ returned toward control, and 15 days after CBD it did not differ from control (Fig. 7).

After unilateral CBD, ΔV̇l/ΔPaCO₂ also decreased from a control of 1.15 ± 0.20 to a nadir of 0.75 ± 0.08 l·min⁻¹·Torr⁻¹ 12 days after CBD (Fig. 7). This decrease was not statistically significant.

Ventilatory CO₂ sensitivity did not change from control after sham CBD surgery.

Effect of bilateral CBD on exercise PaCO₂. Before CBD, PaCO₂ did not change significantly (P > 0.10) from rest during mild (1.8 mph and 5% grade) and moderate (1.8 mph and 13% grade) treadmill exercise (Fig. 8). Over about the first 7 days after CBD, PaCO₂ increased from rest during exercise in some goats (Fig. 9) and decreased from rest in other goats. As a group, over this period, PaCO₂ was ~10 Torr above pre-CBD at rest and during exercise, and PaCO₂ did not change from rest to exercise (Fig. 8). Between 10 and 15 days after CBD, PaCO₂ was increased from pre-CBD by 5 Torr at rest and 3 Torr during exercise. This 2-Torr difference between rest and exercise was statistically significant (P < 0.05).

DISCUSSION

The major finding in this study is that CBD results in transient rest and exercise hypoventilation and attenuated CO₂ sensitivity over 7–15 days after CBD.

NaCN and hypoxic chemoreception after CBD. Ventilatory responses to intravenous NaCN and to inhalation of low- or high-O₂ gas mixtures have been the traditional means of assessing peripheral chemoreception. Accordingly, all eight bilateral CBD goats of this study had attenuated peripheral chemoreception after CBD (Fig. 1 and 3). However, there was considerable variation among goats in this attenuation, and, in seven of these goats, V̇l responses to intravenous NaCN were not eliminated by CBD. These CBD goats had insignificant ventilatory stimulation when NaCN was injected directly into the carotid arteries at any time up to 15 days after CBD (Fig. 4); thus the residual peripheral chemoreception was not due to incomplete CBD or regeneration of responsiveness in the carotid region. This residual response could be due to O₂-sensing mechanisms recently shown to exist within several areas of the brain (23, 24). Indeed, with a 20 µg/kg injection of NaCN into a carotid artery, we often observed a behavioral response, which suggests a NaCN effect within the brain. However, in the CBD goats this response did not elicit a hyperpnea. We therefore believe it likely that aortic chemoreceptors mediated this residual response, which has been shown to explain a residual response in CBD ponies (2). In any event, there is redundancy in hypoxic and NaCN-sensing mechanisms even after bilateral CBD. More-
over, there is redundancy in carotid chemoreception because unilateral CBD did not significantly alter $V_i$ responses to intravenous NaCN injections.

Carotid chemoreceptor contribution to breathing at rest. As pointed out by Comroe and Schmidt in 1938 (7) and Perkins in 1968 (32), there have been different views on the contribution of peripheral chemoreceptors to breathing at rest. One view is based largely on the finding that, when carotid chemoreceptor activity is transiently attenuated in awake humans or dogs by a few breaths of 100% O2, breathing decreases only 10% (7, 9, 12, 38). If the hyperoxia is sustained for several minutes, the reduced capacity of hemoglobin to buffer $H^+$, coupled with a slight reduction in cerebral blood flow, results in a slight increase in brain $H^+$ concentration. This acidosis increases intracrani al chemoreceptor activity, which offsets the reduction in carotid chemoreception resulting in a restoration of breathing to near normal. These data support the view that carotid chemoreceptors provide only a small portion of the total drive to breathing at rest in the awake state. Or, as stated by Comroe and Schmidt (7) in 1938, the “Carotid body reflexes constitute an accessory mechanism; . . . the control of breathing under ordinary conditions is accomplished entirely by the direct effects of chemical stimuli (mainly CO$_2$) upon the cells of the center.” And more recently, in 1997, Donnelly stated that the carotid bodies’ “primary mission in life is to detect and respond to hypoxia” (11).

Others have studied the contribution of carotid afferents by altering PO$_2$ and/or PCO$_2$ of blood perfusing the carotid region. Smith et al. (35) found that in awake dogs unilateral perfusion of an isolated carotid artery with hyperoxic (PO$_2$ >500 Torr) or hypocapnic (PCO$_2$ <10 Torr) blood reduced $V_i$ by 30%. Fitzgerald et al. (15) found in anesthetized dogs that bilateral carotid perfusion with hyperoxic (PO$_2$ >500 Torr) and hypocapnic (PCO$_2$ <10 Torr) blood reduced $V_i$ ~24%. Accordingly, these data seem to suggest a greater contribution of the carotid chemoreceptors to breathing at rest than indicated by the high-O2 breathing studies.

Data from CBD studies also suggest an important role of these chemoreceptors in breathing at rest. For

![Fig. 7. CO$_2$ sensitivity ($\Delta V_i/\Delta$PaCO$_2$) before and for several days after bilateral or unilateral CBD or sham CBD. Values are means ± SE; n, no. of animals. Note that both bilateral and unilateral but not sham CBD resulted in time-dependent attenuation of CO$_2$ sensitivity.](image)

![Fig. 8. PaCO$_2$ at rest and during exercise before and 1–7 and 10–15 days after bilateral CBD. Values are means ± SE. mph, miles/h. Note time-dependent hypercapnia at rest and during exercise after CBD. Note also that PaCO$_2$ changed significantly (P < 0.05) from rest to exercise only in 10- to 15-day post-CBD period.](image)
example, in anesthetized cats in which carotid chemoreceptors had been blocked chemically, bilateral CBD transiently reduced \( V_I \) by \(-30\%\) (25). From these data, Katsaros (25) concluded "that carotid sinus nerves conduct an important respiratory drive which is independent of chemical and pressure stimuli." Supporting this conclusion are most studies that have found hyperventilation in the awake state after CBD in goats, dogs, ponies, rabbits, cats, and humans (2–5, 16, 19, 21, 27, 30, 34, 37). Most of these data were obtained at least 2 wk after CBD, when the hypercapnia at rest ranged between 3 and 12 Torr above pre-CBD. However, Bisgard et al. (2, 3) found that, in ponies 1 wk after CBD \( P_{a\text{CO}} \) was 18 Torr above pre-CBD, but 1 wk later and thereafter, \( P_{a\text{CO}} \) was \(<10\) Torr above control. This latter study suggested time-dependent changes in breathing at rest after CBD; thus, in the present study, we focused on the changes that occurred over the first 1–2 wk after CBD.

We have confirmed the previous finding of time-dependent changes in breathing at rest after CBD. In a majority of both unilateral and bilateral CBD goats, \( P_{a\text{CO}} \) did not reach a maximum until the fourth to seventh day after surgery (Figs. 5, 6, and 9). The maximum values were sustained for a few days, after which \( P_{a\text{CO}} \) decreased such that by 7 (unilateral) and 15 (bilateral) days after surgery \( P_{a\text{CO}} \) was within 3 Torr of pre-CBD. Most previous studies on chronic CBD thus did not obtain data during the period of maximal effects, and therefore these studies underestimated the contribution of the carotid chemoreceptors to breathing at rest. Our data do indeed confirm that carotid chemoreceptors provide an important contribution to ventilatory control mechanisms. These data support the conclusions of Katsaros (25) and Smith et al. (35) and our previous conclusion "that the carotid chemoreceptors may influence breathing through tonic facilitation of medullary centers." (31).

Carotid chemoreceptor contribution to \( CO_2 \) sensitivity. There have also been differing opinions on the role of the carotid chemoreceptor in ventilatory sensitivity to \( CO_2 \) (see Ref. 10 for review). There seems little doubt that carotid chemoreceptor activity and \( V_I \) increase with hypercapnia and decrease with hypocapnia. Several studies have shown, however, that the increase in \( V_I \) with hypercapnia remains after CBD and that \( CO_2 \) sensitivity is reduced only \( 10–40\% \) when measured weeks after CBD (1, 20, 25). Data from several other studies in which different techniques were used to separate peripheral and central chemoreception in intact animals also suggest a modest but definite contribution of carotid chemoreception to \( CO_2 \) sensitivity (1, 10, 32). Mitchell (28) thus proposed a "unified control theory" whereby the ventilatory response at any stage of respiratory and metabolic disorders is the algebraic sum of inputs from peripheral and central \( H^+ \) chemoreceptors.

On the other hand, the classic cerebral ventricular-cisternal perfusion studies by Fend et al. (14) led them to conclude that the hyperpnea during respiratory as well as metabolic acidosis is mediated entirely by the intracranial chemoreceptors (14). This conclusion is supported by data in awake (33) and anesthetized cats (29) showing that \( CO_2 \) sensitivity can be nearly abolished by lesions on the ventral lateral medullary surface.

In many previous CBD studies on chronic awake animals, \( CO_2 \) sensitivity was not assessed. However, the observed hypercapnia during eupnea (as high as 18 Torr above control) strongly suggests that \( CO_2 \) sensitivity was reduced \( >10–40\% \). Indeed, in the present study, on the fourth day after bilateral CBD, a 20% increase in \( P_{a\text{CO}} \) during the breathing of room air (39–49 Torr) coincided with a 60% reduction in \( CO_2 \) sensitivity (1.55–0.65 l·min\(^{-1}\)·Torr\(^{-1}\)). However, as with the hypercapnia during the breathing of room air, the \( CO_2 \) attenuation was not sustained, and, by 15 days post-CBD, \( CO_2 \) sensitivity did not differ from pre-CBD (Figs. 6 and 7). The attenuated \( CO_2 \) sensitivity was less in magnitude and duration in the unilateral compared with the bilateral CBD goats. Accordingly, these data indicate that carotid afferent activity has a major influence on ventilatory \( CO_2 \) sensitivity that temporally corresponds with \( P_{a\text{CO}} \) during the breathing of room air.

Carotid chemoreceptor contribution to the exercise hyperpnea. The mechanism underlying the exercise hyperpnea remains controversial (26). Moreover, there has been a controversy over the role of the carotid chemoreceptors in this hyperpnea (7, 21, 30, 37). However, recent findings suggest that these chemoreceptors do not provide the primary stimulus for the hyperpnea and that their role is to “fine tune” alveolar ventilation to minimize during exercise the deviation of \( P_{a\text{CO}} \) and \( P_{a\text{CO}} \) from resting levels (17, 30). The data from the present study are in agreement with this view. Bilateral CBD did not have an effect on the primary exercise ventilatory stimulus, as indicated by the finding that exercise \( P_{a\text{CO}} \) did not significantly change from rest either before or the first week after CBD. In other words, metabolic rate and alveolar ventilation changed from rest proportionally the same during exercise.
both before and after CBD. There was, however, considerable variation among goats, because some were slightly hypercapnic (Fig. 8), whereas others were hypocapnic during exercise. During the second week after CBD, exercise $P_{acO_2}$ decreased significantly from rest. Accentuated hypocapnia during exercise has previously been observed after CBD (30), which supports the concept that intact chemoreceptors fine tune alveolar ventilation in addition to their role of tonic facilitation of medullary centers.

Carotid afferent tonic facilitation of medullary centers. Katsaros (25) speculated that the function of a nonspecific, tonic carotid “drive seems to consist mainly in keeping the threshold of the respiratory centers at a low level, so that they can respond more efficiently to the adequate respiratory stimuli, CO₂ and H⁺.” In other words, for a period after CBD, CO₂/H⁺ chemoreception per se is probably minimally affected, but the capability of the medullary centers to respond to chemoreceptor input is greatly attenuated. Similarly attenuated are the responses to all stimuli that determine breathing at rest and during exercise. Accordingly, the carotid afferents are not an “accessory mechanism” (7) “primarily responding to low $O_2$” (11), but they provide an important, major input that determines normal ventilatory responsiveness.

The mechanism by which carotid tonic facilitation influences the gain or threshold of medullary centers is speculative. One possibility is suggested by the findings of Hoop et al. (22), who found that CBD in anesthetized dogs decreased glutamate turnover in the medulla during normoxia and increased GABA turnover, particularly during hypoxia. Because neuronal membrane conductances are determined by the balance between glutamate facilitation and GABA inhibition, the net effect of CBD is to reduce neuronal excitability. There also could be a comparable shift in the balance between the density of glutamate and GABA receptors. Such changes in neurotransmitter turnover and/or receptor density would seemingly be time dependent, which could account for the finding that the greatest effect on breathing of CBD is not immediate. Furthermore, the recovery toward normal breathing at rest and CO₂ sensitivity was also gradual over days suggesting a time-dependent metabolic or ultrastructural change in medullary neurons. These changes might be inherent to the neurons, or they might result from increased tonic facilitation from other sources, such as the retrotrapezoid nucleus, which appears to serve a tonic facilitatory function in respiratory control similar to carotid afferents (18, 29). Whatever the mechanism, the return of normal function demonstrates a high degree of plasticity in respiratory control mechanisms.

Notable is that after bilateral CBD there was considerable intergoat variation in peripheral chemoresponsiveness, but the effect of CBD on breathing at rest and CO₂ sensitivity was remarkably consistent over all goats. Moreover, unilateral CBD did not alter peripheral chemoresponsiveness, but it did cause hypoventilation during the breathing of room air and attenuated CO₂ sensitivity. These findings suggest a mechanistic distinction between carotid/peripheral chemoresponsiveness and carotid tonic facilitation of medullary centers.

Clinical relevance. The data from the present study are relevant to the clinical applicability of carotid body autotransplants in Parkinson’s disease. Recently, in a rat model of hemi-Parkinson’s disease, Espejo et al. (13) found that autotransplants of carotid body cell aggregates into the rat’s substantia nigra nearly abolished motor asymmetries and deficits of sensorimotor orientation. These behavioral effects were observed within days after transplants; they were sustained for at least 3 mo, and they were associated with dopamine secretion by the implanted glomus cells. Accordingly, it was concluded that these findings “should stimulate research on the clinical applicability of carotid body autotransplants in Parkinson’s diseases.” The relevance of the data in the present study is that with such autotransplants there would be only small and transient effects on the control of breathing when one carotid body is eliminated from its normal function.

Redundancy and/or plasticity, as presently demonstrated, is probably a general characteristic of the central nervous system, and, as such, it may underlie recovery from temporary dysfunctions caused by head trauma and other injuries. Careful investigation and documentation of redundancy/plasticity and insights into mechanisms should be useful in the management of neurologically impaired patients.

Summary. CBD results for a few days in hypoventilation at rest and during exercise and attenuated ventilatory sensitivity to CO₂. These data are consistent with the concept that carotid afferents tonically facilitate medullary respiratory neurons to influence their responsiveness to other stimuli (CO₂, exercise, etc.). The hypoventilation and attenuated CO₂ sensitivity are transient; thus chronic loss of carotid afferent facilitation appears to be compensated, which emphasizes the plasticity within the ventilatory control system.

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