Effects of phrenicotomy and exercise on hypoxia-induced changes in phrenic motor output

KAREN B. BACH AND GORDON S. MITCHELL
Department of Comparative Biosciences and Center for Neuroscience, University of Wisconsin, Madison, Wisconsin 53706

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Bach, Karen B., and Gordon S. Mitchell. Effects of phrenicotomy and exercise on hypoxia-induced changes in phrenic motor output. J Appl Physiol 89: 1884–1891, 2000.—To investigate models of plasticity in respiratory motor output, we determined the effects of chronic unilateral phrenicotomy and/or exercise on time-dependent responses to episodic hypoxia in the contralateral phrenic nerve. Anesthetized (urethane), ventilated, and vagotomized rats were presented with three, 5-min episodes of isocapnic hypoxia (11% O2), separated by 5 min of hyperoxia (50% O2). Integrated phrenic (and hypoglossal) nerve discharge were recorded before and during each hypoxic episode, for the first 5 min after the first hypoxic episode, and at 30 and 60 min after the final episode. Of 36 rats, one-half were sedentary while the other one-half had free access to a running wheel; each of these groups was split into three subgroups: 1) unoperated, 2) chronic left phrenicotomy (27–37 days), and 3) sham operated. Neither unilateral phrenicotomy nor running wheel activity influenced the short-term hypoxic phrenic response (during hypoxia) or long-term facilitation (posthypoxia). Posthypoxia frequency decline was exaggerated in phrenicotomized-sedentary rats relative to unoperated-sedentary rats (change in burst frequency 23 ± 4 vs. 11 ± 5 bursts/min, respectively; 5 min posthypoxia; P < 0.05), an effect that was eliminated by spontaneous exercise. The results indicate that neither voluntary running nor unilateral phrenicotomy has major effects on time-dependent hypoxic phrenic responses, with the exception of an unexpected effect of phrenicotomy on posthypoxia frequency decline in sedentary rats.

respiratory control; plasticity; hypoglossal

SEVERAL TIME-DEPENDENT VENTILATORY responses are elicited by hypoxia in rats (14, 30), including 1) an acute increase in inspiratory neural activity observable within a single breath (11); 2) a progressive increase in nerve amplitude over 1–2 min, followed by a similar progressive decrease in amplitude when the stimulus is removed [short-term potentiation (STP)] (33); 3) a concomitant progressive decrease in nerve burst frequency during the first minute of hypoxia [short-term depression (STD)] (30) followed by 4) an abrupt decrease in burst frequency, below baseline values, during the first 5 min after the stimulus is removed [posthypoxia frequency decline (PHFD)] (2, 5); and 5) long-term facilitation (LTF), an enhancement of respiratory activity that persists for 1 h or more after episodic chemoafferent activation (1, 2, 24). LTF and PHFD depend, at least in part, on the activation of serotonergic and α2-adrenergic receptors, respectively (1, 2, 23). Recently, it has become clear that some of these time-dependent responses can be modified by perturbations of the system such as cervical dorsal rhizotomy (18) or chronic intermittent hypoxia (19). We were interested in investigating other, similar models of plasticity in time-dependent hypoxic ventilatory responses.

Our working hypothesis is that compensatory responses after neural injury or repeated system activation arise from a general mechanism involving monoaminergic nervous system function. In this study, we investigated unilateral phrenicotomy as a model of neural injury. Unilateral phrenicotomy paralyzes the ipsilateral hemidiaphragm and, under resting conditions, the contralateral hemidiaphragm and other accesso-ry inspiratory muscles increase their activity to maintain adequate ventilatory output (12, 31). During periods of increased respiratory muscle recruitment (e.g., exercise), it may become difficult to meet ventilatory demands. A functional deficit such as that caused by phrenicotomy necessitates increased respiratory drive to the remaining respiratory muscles, a process we propose would be facilitated by increased activity in descending monoaminergic pathways. On the basis of activity-dependent mechanisms, the descending monoaminergic pathways could become more robust as a result of an upregulation of rate-limiting enzymes (e.g., tryptophan hydroxylase) and a strengthening of nerve terminals and their connections.

There is evidence that selective lesions induce long-lasting compensatory changes in neural circuitry that enhance the recruitment of intact respiratory musculature (20, 28). Cervical dorsal rhizotomy increases serotonergic innervation in the phrenic motor nucleus and enhances serotonin-dependent LTF of phrenic motor output after episodic hypoxia (18). In addition, chronic thoracic dorsal rhizotomy (TDR) increases the concentrations of serotonin and dopamine in cervical spinal cord segments associated with the phrenic mo...
METHODS

Enhance compensatory responses to phrenicotomy. Increased respiratory drive necessary for exercise might contribute to breathing efforts, especially during periods of increased respiratory drive (e.g., exercise). An upregulation of monoamine function in the phrenic motor nucleus could enhance diaphragmatic performance and offset the loss of intercostal function caused by the denervation. As yet, however, there is no direct demonstration of a causal, compensatory link.

In the present study, we investigated the effect of a selective neural injury on hypoxic ventilatory responses by examining the effect of chronic unilateral phrenicotomy on the phrenic nerve response to hypoxia in anesthetized rats. Specifically, we examined the effects of chronic unilateral phrenicotomy on the acute response to hypoxia, STP, STD, PHFD, and LTF of phrenic and hypoglossal nerve activity after hypoxia. We hypothesized that chronic unilateral phrenicotomy would upregulate serotonergic innervation of the contralateral cervical spinal cord, therefore enhancing contralateral phrenic LTF. Hypoglossal motor output was monitored as a comparison with the (intact) phrenic response.

Because exercise can increase the concentrations of central nervous system monoamines (22), one-half of the phrenicotomized animals were given voluntary access to running wheels. We hypothesized that the increased respiratory drive necessary for exercise might enhance compensatory responses to phrenicotomy.

EXPERIMENTAL GROUPS. Thirty-six male rats (364–454 g; Harlan Sprague Dawley colony 205, Madison, WI) were randomly separated into six equal groups. Sedentary groups included (each n = 6): 1) unilateral (right) phrenicotomy, 2) sham-operated and 3) unoperated rats. Identical groups (each n = 6) were allowed continuous access to a running wheel (fitted with a magnetic revolution counter from which distance traveled per day was recorded; Fisher Scientific, Pittsburgh, PA). Rats were familiarized with the wheels for 2 wk before phrenicotomy. Phrenicotomy and sham surgery did not appear to compromise the rats’ ability or desire to exercise on the running wheels, and, by the time experiments were conducted (~4 wk later), the rats had reached a steady state of revolutions per day (Fig. 1). We did not attempt to induce greater running through caloric restriction (8). All rats were housed separately and maintained under 12:12-h light-dark conditions.

Surgical preparation. Twenty-seven to thirty-seven days before acute experiments, phrenicotomies and sham operations were conducted under pentobarbital sodium anesthesia (55 mg/kg ip) after anesthetic induction with isoflurane. A ventral neck incision was made, and the muscles were gently separated and retracted to expose the phrenic nerve on the right side of the animal. The nerve was isolated and sectioned, and a small segment (1–2 mm) removed to discourage regrowth from the nerve stump. Phrenic nerve section was performed by visualizing changes in abdominal and rib cage movements associated with breathing. An equal number of sham surgeries were conducted in which the phrenic nerve was isolated but not cut. Rats recovered easily from both surgical procedures.

Experimental preparation. On the day of an experiment, rats were initially anesthetized with isoflurane (2.5–3.0% in 50% O2-balance N2) and then slowly converted to urethane anesthesia (1.6 g/kg iv in water vehicle) over a period of 15–30 min. The adequacy of anesthesia was assessed regularly by testing visual reflexes and blood pressure responses to toe pinch. Supplemental urethane was administered as needed through a catheter implanted in a femoral vein. A slow infusion of sodium bicarbonate (5.0%) and lactated Ringer solution (50:50, 1.7 ml·kg⁻¹·h⁻¹) was initiated 1–2 h after induction of anesthesia to maintain acid-base and fluid balance.

All rats were prepared with a tracheostomy through which they were artificially ventilated (rodent respirator, Harvard South Natick, MA) and tracheal pressure was measured (model P23-id pressure transducer, Statham). The lungs were hyperinflated periodically to minimize alveolar atelectasis. Rats were vagotomized bilaterally and paralyzed (2.5 mg/kg pancuronium bromide) to prevent spontaneous breathing efforts and entrainment of respiratory motor outflow with the ventilator. End-tidal CO2 was monitored with a flow-through capnograph (Novametrix, Wallingford, CT) with sufficient response time (~75 ms) to measure end-tidal PCO2. End-tidal CO2 values obtained from this capnograph closely approximated arterial PCO2 (Paco2; usually within 1–2 Torr). Blood samples were drawn from a catheterized femoral artery to determine blood gases and pH (model ABL-330, Radiometer, Copenhagen, Denmark). Blood-gas and pH values were corrected to the measured rectal temperature of each rat. Blood pressure was also monitored at the femoral artery (model P23-id pressure transducer, Statham). Rectal temperature was maintained between 37 and 38°C with a heated table.

Phrenic and hypoglossal nerves were isolated unilaterally using a left-side dorsal approach, cut distally, and desheathed. The nerves were submerged in mineral oil and placed on bipolar silver recording electrodes. Nerve activity was amplified (>10,000; model BMA 831, CWE, Ardmore, PA), band-pass filtered (100 Hz to 5 kHz), and integrated (Paynter filter 821, CWE; time constant 100 ms). The integrated signal was digitized (Scientific Solutions, Lab Master DMA, Solon, OH) and processed with computer software developed in our laboratory.

Experimental protocols. After completion of the experimental preparation, 60 min were allowed for the nerve signals to stabilize in hyperoxia (inspired O2 fraction = 0.50; arterial was isolated but not cut. Rats recovered easily from both surgical procedures.

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Experimental protocols. After completion of the experimental preparation, 60 min were allowed for the nerve signals to stabilize in hyperoxia (inspired O2 fraction = 0.50; arterial
PO2 >150 Torr) and normocapnia (PaCO2 ~3 Torr above the CO2 apneic threshold; see Table 1). Baseline nerve activity was achieved by manipulating inspired CO2 and respiratory pump rate and/or volume while monitoring end-tidal CO2 levels until both phrenic and hypoglossal nerve activity attained low but stable levels of activity. The CO2 thresholds for hypoglossal vs. phrenic nerve activity were nearly the same in these rats (near 39 Torr for both nerves), unlike the results found in cats (16). The protocol began with a baseline arterial blood sample (0.3 ml drawn into a 0.5-ml heparinized glass syringe; unused blood was returned to the animal). All subsequent blood samples were compared with this initial baseline value. Baseline nerve activity was recorded, followed by three, 5-min episodes of isocapnic hypoxia (inspired O2 fraction 0.13–0.14), separated by 5 min of hyperoxic recovery. In all cases, data reported during an hypoxic episode were collected from the first hypoxic episode of a series.

Relative isocapnia was maintained throughout the stimulus protocol by monitoring end-tidal CO2 and adjusting inspired CO2 accordingly. Nerve activity was recorded throughout the entire protocol, and a blood sample was taken during the first hypoxic response to assess the level of hypoxia during the episodes. Blood samples were also taken at all posthypoxic data points (5, 30, and 60 min posthypoxia) to ensure that PaCO2 was within 1 Torr of the baseline value posthypoxic data points (5, 30, and 60 min posthypoxia) to during the episodes. Blood samples were also taken at all posthypoxic data points (5, 30, and 60 min posthypoxia) to ensure that PaCO2 was within 1 Torr of the baseline value during data collection (Table 1). At the conclusion of the protocol, the response to elevated levels of inspired CO2 was recorded in both nerves to obtain a measure of maximal (or at least a standardized hypercapnic “control”) nerve activity (end-tidal Pco2 = 80–95 Torr). All procedures were approved by the University of Wisconsin Animal Care and Use Committee.

Data analysis. Peak amplitudes and frequency (bursts/min) of phrenic and hypoglossal nerve activity were averaged over 50 bursts for each recorded data point or in 20-s bins during the first 5 min of the first hypoxic episode and during the first 5 min after the hypoxic episode. Averaged amplitude data were then normalized as a percent change from baseline (prestimulus control) activity and as a change, expressed as the percentage of the (CO2-stimulated) maximum nerve activity. The latter form of normalization obviates concerns about expressing data in terms of the percent increase above an arbitrary (low) baseline value (13). Statistical analyses were conducted by using repeated-measures two-way ANOVA and paired t-tests with the Bonferroni correction for multiple comparisons. Differences were considered significant if P < 0.05. Values are presented as means ± SE.

RESULTS

There was no significant difference between sham-operated and unoperated animals in any of our analyses. Therefore, these data were pooled in all figures and are regarded as a single group for purposes of discussion.

Phrenic and hypoglossal burst amplitudes are expressed as a percentage change from prehypoxic baseline values in Fig. 2. Burst amplitude increased acutely in both neurograms at the onset of hypoxia. However, the increase in hypoglossal burst amplitude during hypoxia reached twice the magnitude of phrenic burst amplitude (a maximum increase of 194 ± 27% in the hypoglossal neurogram vs. a maximum increase of 109 ± 17% in the phrenic neurogram; P < 0.0001). Hypoglossal burst amplitude was also significantly elevated above phrenic burst amplitude for the first 3 min after the hypoxic stimulus was removed (P < 0.008), but both had returned to prehypoxic baseline levels at 5 min posthypoxia. To minimize normalization artifacts caused by variable baseline nerve activities, mean data were also expressed as a change from baseline, expressed as a percentage of the CO2-stimulated nerve burst amplitude (data not shown). Analyzed in this way, the results were qualitatively similar: hypoglossal nerve burst amplitude was significantly greater than phrenic nerve burst amplitude during and after hypoxia, indicating that hypoglossal nerve activity is affected more profoundly by isocapnic hypoxia than phrenic activity in urethane-anesthetized rats.

Table 1. PaCO2 and PaO2 values in 6 experimental series

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Time Poststimulation</th>
<th>Baseline</th>
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<tr>
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<td>PaCO2 = 39.0 ± 2.3 Torr</td>
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<td>Exercised</td>
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Values are means ± SE given in Torr for 6 rats per group. There were no significant differences between time points in any group. PaCO2, arterial PCO2; PaO2, arterial PO2. At all posthypercapnic time points, PaCO2 was actively maintained within 1 Torr of the baseline value or respiratory nerve activities were not included in the analysis.
Chronic phrenicotomy and/or exercise had no effects on phrenic nerve activity during hypoxia. Figure 3A illustrates mean changes from baseline of nerve burst frequency during the 5-min hypoxic episode. Burst frequency increased acutely and then decreased significantly to a new steady-state level even though the stimulus was unchanged (i.e., STD; P < 0.05). No significant differences were detected between any of the treatment groups consisting of 1) unoperated-sedentary rats, 2) phrenicotomized-sedentary rats, 3) unoperated-exercised rats, and 4) phrenicotomized-exercised rats. Mean phrenic burst amplitude, expressed as percent change from baseline values, increased similarly in all treatment groups (Fig. 3B); similar results were obtained when expressed as percentage of maximal nerve activity (not shown).

On termination of the hypoxic stimulus, there was a significant decrease in respiratory nerve burst frequency below prestimulus control values in all treatment groups, representing the PHFD (Fig. 4A; P < 0.001). In unoperated-sedentary animals, nerve burst frequency decreased by 6.5 ± 4.6 bursts/min 1 min after the hypoxic stimulus was removed and by 11.5 ± 5.3 bursts/min 5 min posthypoxia. PHFD was enhanced by chronic phrenicotomy in sedentary rats, resulting in a greater decline in nerve burst frequency. Burst frequency in phrenicotomized-sedentary rats decreased by 12.5 ± 2.1 bursts/min at 1 min and by 23.5 ± 4.0 bursts/min at 5 min after the hypoxic stimulus was removed (P < 0.04 relative to sedentary controls). In animals that exercised after phrenicotomy, an exaggerated PHFD was not apparent. In these phrenicotomized-exercised rats, nerve burst frequency decreased by 9.5 ± 1.8 bursts/min at 1 min and by 9.5 ± 2.8 bursts/min at 5 min after termination of the hypoxic stimulus. PHFD in animals treated with phrenicotomy and exercise was significantly different from animals treated with phrenicotomy alone (P < 0.05) but was not significantly different from unoperated-sedentary and unoperated-exercised animals.

Phrenic nerve burst amplitude progressively decayed toward baseline at the termination of the hypoxic episode (i.e., STD; Fig. 4B). There were no differences in STD between unoperated and phrenicotomized-exercised rats. However, in phrenicotomized-exercised rats, phrenic nerve burst amplitude was significantly elevated relative to phrenicotomized-sedentary rats (P < 0.02) when expressed as percent change from baseline (16 ± 9% above baseline vs. 32 ± 22% below baseline 5 min posthypoxia, respectively). When these data were expressed as a change in percent of the CO₂-stimulated maximal nerve burst amplitude, the results were similar (P < 0.01).

Thirty and sixty minutes after the third and final hypoxic episode, LTF was evident in both phrenic and hypoglossal motor output. Phrenic and hypoglossal nerve burst amplitudes are expressed as percent changes from prestimulus baseline values in Fig. 5. Sixty minutes after the final hypoxic episode, phrenic burst amplitude was increased by 46 ± 5% and hypo-
A glossal burst amplitude was increased by 26 ± 14% (average of all 4 treatment groups; both P, 0.0001). Frequency also exhibited a small, but significant, increase 30 and 60 min posthypoxia (P, 0.05; Fig. 5C). There were no significant differences between any of the treatment groups, illustrating that chronic phrenicotomy and/or exercise had no significant effects on LTF of phrenic or hypoglossal nerve amplitude.

DISCUSSION

We found no evidence to support the hypothesis that chronic (unilateral) phrenicotomy enhances LTF of contralateral phrenic motor output. Instead, the data suggest that chronic phrenicotomy exaggerates PHFD, an effect that is offset by 1 mo of spontaneous exercise. Furthermore, unilateral phrenicotomy exaggerated the posthypoxia return of phrenic burst amplitude to baseline values (i.e., decreased STP), an effect similarly offset by exercise. These results imply a complex interplay between phrenicotomy and exercise in a mechanism possibly associated with α2-adrenergic receptor activation (2).

Phrenic and hypoglossal motor output: responses to hypoxia. In these studies, we recorded hypoglossal nerve activity as an indicator of changes in respiratory motor output not specifically associated with phrenic activity. Previous studies in cats (4) and rabbits (3) have shown that hypoglossal motor output is preferentially stimulated by hypoxia compared with phrenic motor output, suggesting that ventilatory drive is heterogeneously distributed among respiratory-related motoneuron pools. Recording from the phrenic and hypoglossal nerves of cats is problematic, however, because the CO2 apneic threshold for nerve activity is higher in the hypoglossal nerve (10). Thus, for any given level of CO2, hypoglossal motor output is stimulated more by hypoxia than phrenic motor output when analyzed as a percent change from (a lower) baseline nerve activity. In the present study, the CO2 apneic thresholds for phrenic and hypoglossal motor output...
were virtually identical. This allowed us the unique opportunity to compare hypoglossal and phrenic motor output in response to hypoxia without the confounding effects of variable CO₂ apneic thresholds. Our results in rats confirm that the hypoglossal nerve is more responsive to hypoxia both during and immediately after the hypoxic exposure. This finding suggests that inputs to respiratory-related motoneuron pools may be heterogeneous in response to a given stimulus.

**STD.** STD of nerve burst frequency within an hypoxic episode (14, 30) was unaltered by phrenicotomy and/or chronic spontaneous exercise. STD of burst frequency was present in all treatment groups. This contrasts with Hayashi et al. (14), who observed STD of phrenic burst frequency during carotid sinus nerve stimulation but not during hypoxia in anesthetized rats. The difference between the two studies (both conducted in our laboratory) can probably be attributed to alterations in the gas-delivery system. A slow time course of hypoxic gas delivery, caused by low flow rates through long tubes, could effectively mask STD by blunting the acute increase in frequency that accompanies the onset of hypoxia. The present study coupled higher flow rates with shorter tubes than those used by Hayashi et al. to minimize gas dilution and maximize the speed of hypoxic gas delivery. These modifications resulted in an acute increase in burst frequency in response to hypoxia, followed by a gradual reduction in burst frequency toward a new steady-state level, similar to that observed after carotid sinus nerve stimulation (14).

**PHFD and STP.** PHFD is a time-dependent decrease in nerve burst frequency below initial baseline values after exposure to 5-min of moderate to severe hypoxia. STP is a progressive increase in nerve burst amplitude during the first 1–2 min of hypoxia as well as a progressive decrease in burst amplitude when hypoxia ceases. PHFD can be blocked by electrical lesions of the ventrolateral pons in the A5 noradrenergic area (5). The response is also sensitive to α₂-adrenergic-receptor antagonists (2), although there is controversy surrounding this issue (6). Chronic unilateral phrenicotomy enhanced the PHFD of phrenic and hypoglossal motor output and blunts STP of phrenic burst amplitude after hypoxic exposure. These effects suggest that unilateral phrenicotomy alters the mechanism underlying PHFD and STP in rats, possibly through denervation-induced changes in the noradrenergic nervous system.

Neural injury or denervation can result in changes in noradrenergic inputs to the spinal cord. Mitchell et al. (26), observed an increase in spinal norepinephrine concentrations after chronic TDR in goats. It has also been demonstrated that rat noradrenergic perivascular neurons sprout into neighboring dorsal root ganglia after sciatic nerve lesion (21). Thus plasticity in noradrenergic neurons can occur at sites not directly affected by the neural injury.

An upregulation of α₂-receptors in regions of the brain and spinal cord relevant to respiratory control could be involved in the enhanced PHFD observed after phrenicotomy. Similarly, α₂-receptors are upregulated in dorsal root ganglia after peripheral nerve injury (34). Further experiments are needed to determine whether α₂-receptor densities increase in neural structures relevant to the generation of respiratory rhythm or in spinal segments affected by phrenicotomy.

One month of chronic voluntary exercise completely blocks the exaggerated PHFD and the blunted STP of phrenic burst amplitude (posthypoxia) caused by chronic phrenicotomy, indicating that physical activity can alter injury induced plasticity. Spontaneous exercise may affect monoaminergic function directly, helping to offset the effects of phrenicotomy on PHFD and STP. In the literature, chronic exercise has inconsistent effects on resting central nervous system levels of monoamines (22). Monoamines increase, decrease, or remain unaltered depending on the type and duration of exercise and whether the exercise was spontaneous or forced. For example, whole brain norepinephrine concentrations increased in rats trained (forced) to swim regularly for 17 wk (29). The synthesis and metabolism of brain stem serotonin also exhibited a significant increase after 4 wk of regular swimming (9). This increase was evident even 1 wk after termination of the training protocol. In contrast, rats that ran voluntarily for 7 wk showed no significant increase in brain tissue serotonin levels (15), raising the possibility that increased brain monoamine levels in rats trained (forced) to exercise may be caused by factors other than exercise per se (e.g., stress hormones).

**LTF.** LTF of respiratory motor output is a long-lasting enhancement of phrenic and hypoglossal nerve burst amplitude and frequency observed after episodic exposure to isocapnic hypoxia (20, 30). LTF was unaffected by chronic phrenicotomy and/or exercise. This finding does not rule out the possibility that chronic phrenicotomy and/or exercise might enhance LTF under different circumstances. For example, it was difficult to control the distance and intensity of the rats physical activity because they exercised spontaneously. Exercise intensity could have been increased through dietary restriction (8) or a “forced” exercise regime. Alternatively, bilateral phrenicotomy would have completely denervated the diaphragm, increasing the overall functional deficit and, perhaps, the ensuing compensatory response. In addition, we conducted all experiments 1 mo after phrenicotomy. This recovery period was chosen on the basis of previous studies that demonstrated monoaminergic system alterations after 1 mo of recovery from cervical dorsal rhizotomy (18). Had the experiments been conducted at a different time postphrenicotomy, different findings may have been obtained.

**Comparison with previous LTF studies.** Overall, both LTF of phrenic and hypoglossal motor output and PHFD were reduced compared with previous studies on Sprague-Dawley rats (1, 17). This “blunted” short- and long-term response to hypoxia may be attributable to fundamental genetic differences between rat substrains used in different studies. Earlier experiments
used Sprague-Dawley rats obtained from Sasco (Madison, WI) (1), whereas the present study used Sprague-Dawley rats obtained from Harlan. Morphological differences exist between the noradrenergic innervation of the spinal cord in Sasco vs. Harlan Sprague-Dawley rats (7, 32). In Sasco Sprague-Dawley rats, the locus coeruleus projects to the ventral horn (ipsilaterally), and in Harlan Sprague-Dawley rats, the locus coeruleus projects to the dorsal horn (bilaterally). This striking difference suggests that locus coeruleus neurons serve different physiological functions in these two substrains of rats and raises the possibility that other anatomic and, possibly, functional differences exist.

In summary, we discovered an unexpected model of ventilatory plasticity in respiratory motor output (exaggerated PHFD after 1 mo of recovery from unilateral phrenicotomy). Although our experimental preparation is unphysiological (anesthetized, paralyzed, vagotomized, ventilated rat) it allows us to examine and manipulate monoamine-dependent plasticity in the ventilatory drive. This study illustrates that the balance between the two can be shifted, sometimes in favor of the inhibitory (possibly noradrenergic) mechanism between the two can be shifted, sometimes in favor of the inhibitory (possibly noradrenergic) mechanism (unilateral phrenicotomy) or against it (spontaneous ventilation). This study was supported by National Heart, Lung, and Blood Institute Grants HL-36780 and HL-53319 and by Neuroscience Training Program Grant GM-07507.

REFERENCES


