Plasticity in Respiratory Motor Control
Invited Review: Plasticity in the control of breathing following sensory denervation

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Forster, H. V. Invited Review: Plasticity in the control of breathing following sensory denervation. J Appl Physiol 94: 784–794, 2003; 10.1152/japplphysiol.00602.2002.—The purpose of this manuscript is to review the results of studies on the recovery or plasticity following a denervation- or lesion-induced change in breathing. Carotid body denervation (CBD), lung denervation (LD), cervical (CDR) and thoracic (TDR) dorsal rhizotomy, dorsal spinal column lesions, and lesions at pontine, medullary, and spinal sites all chronically alter breathing. The plasticity after these is highly variable, ranging from near complete recovery of the peripheral chemoreflex in rats after CBD to minimal recovery of the Hering-Breuer inflation reflex in ponies after LD. The degree of plasticity varies among the different functions of each pathway, and plasticity varies with the age of the animal when the lesion was made. In addition, plasticity after some lesions varies between species, and plasticity is greater in the awake than in the anesthetized state. Reinnervation is not a common mechanism of plasticity. There is evidence supporting two mechanisms of plasticity. One is through upregulation of an alternate sensory pathway, such as serotonin-mediated aortic chemoreception after CBD. The second is through upregulation on the efferent limb of a reflex, such as serotonin-mediated increased responsiveness of phrenic motoneurons after CDR, TDR, and spinal cord injury. Accordingly, numerous components of the ventilatory control system exhibit plasticity after denervation or lesion-induced changes in breathing; this plasticity is uniform neither in magnitude nor in underlying mechanisms. A major need in future research is to determine whether “reorganization” within the central nervous system contributes to plasticity following lesion-induced changes in breathing.

receptors; recovery of function; redundancy; chemoreflexes; mechanoreflexes

DENERVATION OR LESIONING of a receptor or neural pathway that normally contributes to the regulation of a physiological function will result in loss of or altered function. Thereafter, a time-dependent recovery of function is a manifestation of plasticity within the regulatory system. The purpose of this review is to summarize research on this type of plasticity within the system regulating breathing. Lesions are one of several means of inducing plasticity; a review of these and a general discussion of plasticity are presented elsewhere (66). Nevertheless, it seems appropriate to emphasize here that recovery of function can be due to restoration of the same mechanism or substitution of another mechanism. Also, recovery refers specifically to the return of a function, whereas plasticity refers to the process or mechanism of the restoration (i.e., capability of building new tissue or formative). A related phenomenon, redundancy, refers to two or more mech-
organisms available to perform a function. Both mechanisms may be totally functional; thus loss of one mechanism does not compromise the function. As will be shown in this review, in some redundant systems one of the mechanisms is dominant, which when lost requires plasticity of the other before normal function is restored.

DENERVATION OF PERIPHERAL CHEMORECEPTORS

Plasticity in sensing low O2 by peripheral chemoreceptors. In 1937, Comroe and Schmidt (17) wrote “carotid body reflexes constitute an accessory mechanism, brought into action by emergencies such as foreign chemicals, anoxemia, and usually great increases in the CO2 tension of the blood.” Most contemporary physiologists do not view the carotid body as an accessory mechanism, but these receptors are still viewed as the major sensors for the excitatory effect on breathing of a few breaths or minutes (acute) of hypoxemia. In quantitating this excitatory effect (known as the peripheral chemoreflex), the response of only a few breaths or minutes of hypoxia is considered because, after a few minutes, the hypoxia-induced hyperpnea will result in hypocapnia, which, along with a depressant effect of hypoxemia on neurons, will dampen the hyperpnea due to the increased carotid stimulation (7).

Because of these time-dependent and multiple effects of hypoxia, the peripheral chemoreflex is often assessed by administering only a few breaths of low or high O2 or by intravenous bolus injection of sodium cyanide (NaCN), which transiently activates excitatory oxygen chemoreceptors. These assessments clearly show that, after carotid body denervation (CBD), the peripheral chemoreflex is attenuated or eliminated, but then there is a time-dependent recovery of the reflex (Fig. 1) (4, 8–11, 18, 25, 26, 31, 34, 43, 56, 57, 60, 74, 75, 80, 82, 83, 88).

![Image](https://via.placeholder.com/150)

Fig. 1. Arterial P\textsubscript{CO2} (P\textsubscript{aCO2}) (○) and the sodium cyanide (NaCN) response ratio (□) in awake ponies (n = 6) before and repeatedly over 52 mo after bilateral carotid body denervation (CBD). The NaCN response ratio is the pulmonary ventilation (VE) between 10 and 25 s after intravenous injections of 50 µg/kg NaCN divided by the control VE. Note that 1) CBD eliminated the NaCN response (peripheral chemoreflex) and induced marked hypventilation and 2) there was significant but <25% recovery of the NaCN response and complete recovery of P\textsubscript{aCO2}. (Data are from Refs. 8 and 9.)

- CAROTID RESPONSE
  - INTACT
  - CBD
  - 1.8
  - 1.0
- AORTIC RESPONSE
  - INTACT
  - CBD
  - 1.0
  - 2.7
- VENOUS RESPONSE
  - INTACT
  - CBD
  - 3.2
  - 2.1

The extent of recovery after CBD is not uniform among adult mammals. In cats (88) and rats (11, 60, 82), there is considerable recovery in the chemoreflex a few weeks after CBD and near total recovery a year later. In dogs (80), ponies (8, 9), and goats (31, 75), there is no significant or only a small recovery a few weeks after CBD, and in ponies there is less than 25% recovery 4 yr after CBD (Fig. 1). Similarly, in human asthmatic patients who underwent CBD, there is no or minimal recovery in the peripheral chemoreflex (42, 43, 58, 95, 96). It therefore seems that there is species variation in the extent of plasticity in the peripheral chemoreflex.

In contrast to adult goats who do not fully recover the peripheral chemoreflex a few weeks after CBD, goats denervated the first day after birth fully recover the reflex within 3 mo (56). Similarly, rats (82) and piglets (57, 83) denervated in the neonatal period also nearly recover the peripheral chemoreflex within 3 wk. These findings are consistent with the concept that plasticity is affected by age and is relatively enhanced in neonates (66).

Recovery of the peripheral O2 chemoreflex after CBD is not through reinnervation or resumption of carotid chemosensitivity; NaCN injections into carotid arteries of chronic CBD mammals does not stimulate breathing (Fig. 2) (8, 56, 57, 82, 83). Absence of a response after NaCN injections into carotid arteries also seems to rule out sites in the central nervous system (CNS) as possible mediators of an O2 chemoreflex after CBD. Consideration of a CNS site is warranted, however, because of recent data indicating O2-sensing mechanisms in the medulla (62, 89). The site of recovery appears to...
be in the proximal aorta or in other peripheral sites. This conclusion is based on findings that NaCN injections localized to the proximal ascending aorta of CBD rats (82) and proximal descending aorta of CBD piglets (57, 83) stimulates breathing (Fig. 2). Furthermore, sectioning the aortic, glossopharyngeal, and/or abdominal nerves attenuates or eliminates this plasticity in the peripheral chemoreflex after CBD (8, 60, 88).

Data from piglets suggest that this plasticity is due to resumption of function present at birth but lost during the neonatal period (31, 57). In carotid-intact piglets, NaCN injected into the proximal descending aorta stimulates breathing until they are ~8 days old. At older ages, NaCN injection at this site only stimulates breathing in CBD piglets. The response to aortic NaCN injections in CBD piglets is eliminated after denervation of this aortic region, but, in carotid plus aortic-denervated piglets, there is still a ventilatory response to intravenous NaCN injections, which appears due to activation of receptors in the left ventricle (83). These findings and the elimination of responses to hypoxia after sectioning abdominal nerves (60) indicate that there are multiple sites of functional peripheral chemoreceptors after CBD.

Serotonin (5-HT) appears to be involved in the aortic chemosensitivity after CBD. After CBD, in both piglets and rats, there is increased 5-HT immunoreactivity in the aortic segment that is chemosensitive. This increase is dependent on intact aortic innervation, as is the presence at this site of 5-HT5a receptors. Finally, pharmacological block of 5-HT5a receptor activity eliminates the ventilatory response to NaCN injection at this site in CBD piglets (83).

Current knowledge of plasticity in the peripheral chemoreflex can be summarized as follows. At birth, chemosensitivity exists at more than one site, but, within days, functional chemosensitivity becomes restricted to the carotid body. However, CBD results in the sustaining or regaining of the chemoreflex, particularly, but not exclusively, in the proximal aorta. The degree of plasticity in the chemoreflex varies between adult species, and it appears greater in neonatal than in adult mammals. Plasticity of aortic chemosensitivity is dependent on aortic innervation and an increase in 5-HT acting at 5-HT5a receptors.

**Plasticity in other functions of peripheral chemoreceptors.** In 1937, Comroe and Schmidt (17) also wrote that the carotid body reflexes are not an “essential part of the normal respiratory regulating system; the control of breathing under ordinary conditions is accomplished entirely by the direct effects of chemical stimuli (mainly CO2) on the cells of the center.” Most contemporary respiratory physiologists do not adhere to this restrictive view. However, there are differences of opinion regarding the role of these receptors in the control of breathing (31, 74, 75, 80, 96).

After CBD, breathing and/or hypoventilation is shown to be initially reduced during room air breathing at rest (8, 9, 25, 26, 57, 75, 80, 83) (Fig. 1) and during exercise (74, 75, 77), but there is plasticity or recovery from the hypoventilation (Fig. 1 and Refs. 4, 8, 9, 31, 56, 57, 75, 82, 83). These findings support the view that these chemoreceptors normally provide a significant stimulus to maintain normal breathing at rest and during exercise (31). Although these receptors are important for breathing during exercise, the “exercise” stimulus for the hyperpnea is not carotid mediated (42, 58, 74, 96). The temporal pattern and extent of this plasticity differ between species. For example, after CBD in adult ponies (8), several months are required for eupneic arterial Pco2 (Paco2) to return to normal (Fig. 1); in adult dogs (Fig. 3) (80), there is only a small and insignificant recovery of eupneic Paco2 3 wk after CBD. In contrast, in adult rats (82) and goats (75) (Fig. 3), there is near complete recovery of Paco2 2–3 wk after CBD. Finally, in adult asthmatic humans who underwent CBD, eupneic and steady-state exercise, Paco2 levels are nearly normal months to years later (42, 43, 58, 96).

The Paco2 of rats (82), goats (56), and piglets (Fig. 3) (57, 83) denervated at 1–25 days of age fully recovers 3 wk to 3 mo later. Because the recovery 3 wk after CBD is incomplete for adult rats, these data indicate enhanced recovery/plasticity in the neonatal period.

Little information is available on the mechanism of plasticity in eupneic Paco2 after CBD. In less-than-5-day-old piglets, the plasticity might be partly due to the functional aortic chemosensitivity (Fig. 3), but, in older piglets, recovery of eupneic Paco2 does not differ between CBD and carotid plus aortic-denervated piglets (83). In addition, the near total recovery in eupneic Paco2 of CBD asthmatic humans (96) and CBD ponies (Fig. 1) (8) coincides with <25% recovery in peripheral chemosensitivity. Moreover, in adult goats, there is nearly total recovery of eupneic Paco2 before there is any appreciable recovery in the NaCN response (75).

![Fig. 3. Paco2 before and repeatedly after CBD in adult goats (•) and dogs (○) and in less than 5-day-old piglets that underwent CBD (△) or CBD plus aortic chemoreceptor denervation (AOD; ×). All data were obtained in the awake state. Note that 1) all animals hyperventilated after CBD; 2) on days 2, 3, and 4, CBD + AOD piglets hypoventilated more than CBD piglets, and 3) there was a time-dependent recovery of Paco2 in all animals but dogs. (Data are from Refs. 57, 75, 80, and 83.)](http://jap.physiology.org/DownloadedFrom/10.22033.5)
Two alternative conclusions appear warranted: 1) a small recovery in peripheral chemosensitivity is sufficient to fully recover rest and exercise \( P_{acO_2} \) or 2) mechanisms other than peripheral chemoreception contribute to the recovery in \( P_{acO_2} \).

After CBD, the minute-to-minute variation in \( P_{acO_2} \) is greater than normal, and the disturbance in \( P_{acO_2} \) caused by the onset of exercise and by resistive loading is accentuation by CBD (27, 74). Data such as these are consistent with the view that the peripheral chemoreceptors “fine-tune” alveolar ventilation to metabolic needs (31). It does not appear that there is plasticity in this function after CBD; there is an accentuated hyperventilation at the onset of exercise in ponies even 4 yr after CBD when eupneic \( P_{acO_2} \) has returned to the pre-CBD level (74).

Another function of the carotid chemoreceptors is mediation of ventilatory acclimatization to hypoxia, which is the time-dependent increase in breathing with chronic hypoxia. After CBD, this acclimatization is attenuated and/or eliminated, and it remains attenuated even after the peripheral chemoreflex and eupneic \( P_{acO_2} \) have returned partially and completely to normal, respectively (8, 10, 25, 26). Thus there is no plasticity of this function, which is not unexpected from the evidence that acclimatization results from increased gain of the carotid chemoreceptors (7, 14, 71).

Within a few days or weeks after CBD in adult goats (75), dogs (4, 80), rats (82), and cats (88), CO2 sensitivity is initially attenuated by 20–60%, but subsequently there is a return to near normal in some species (goat) but not in others (dog). One conclusion from these findings is that the carotid chemoreceptors normally provide a major portion of the hypercapnic stimulus (80). This view is supported by the profound reduction in breathing with localized carotid body hypocapnia (86) and by the absence of plasticity in CO2 sensitivity more than 3 wk after CBD in dogs (80). An alternative conclusion is that the carotid chemoreceptors normally set the gain of the intracranial chemoreceptors or of other aspects of the ventilatory control system (31, 75). This view is supported by the initial uniform reduction in breathing (eupnea, hypocapnia, exercise) that occurs in goats after CBD followed by a uniform return of breathing to normal. All mammals (goats, piglets, and rats) denervated in the neonatal period have normal CO2 sensitivity 3 wk to 3 mo later, which again suggests enhanced plasticity in the neonatal period (56, 57, 82, 83). The mechanism of the plasticity in CO2 sensitivity is unknown, but it is not correlated with the recovery of the peripheral chemoreflex (75), and it occurs after carotid plus aortic denervation (83). Conceivably, intracranial chemoreceptors and/or other structures in the CNS underlie this plasticity.

In summary, after CBD, in several but not all species, there is recovery of breathing at rest, during steady-state exercise, and during CO2 inhalation; however, the fine-tuning of breathing and acclimatization to altitude have not recovered. For the plasticity that does occur, it appears unrelated and appears to occur by a mechanism different from the plasticity of the peripheral chemoreflex. A similar functional independence from peripheral chemoreception was found in studies in which rats were exposed to chronic hyperoxia during the neonatal period; the peripheral chemoreflex was permanently attenuated in these rats, yet there was no apparent change in eupneic breathing (54, 55, 66).

**DENERVATION OF RECEPTORS IN THE LUNG**

There are at least three different receptors in the lung: slowly adapting stretch receptors (SAR), rapidly adapting stretch receptors (RAR), and C-fiber endings (61, 99). The SAR, located in the lower airways, are activated by capsaicin, 5-HT, and other agents to elicit the so-called pulmonary chemoreflex, which consists of tachypnea, bronchoconstriction, bradycardia, and hypotension.

A major effect of lung denervation is prolonged inspiration, increased tidal volume, and reduced breathing frequency, all effects primarily of SAR denervation (15, 24, 30). These changes manifest the Hering-Breuer inflation reflex (HBIR), usually expressed as the increase in the ratio of inspiratory time (Ti) to total breathing cycle time (Ttot) (Fig. 4), the increase in expiratory duration as lung volume is increased, or the increase in the ratio of Ttot of an occluded breath divided by Ttot of unoccluded breath. The length of plasticity of the HBIR appears dependent on whether the denervation permitted regrowth of the vagal branches innervating the lung. In dogs, there is some plasticity after lung transplant or after selective hilar stripping (Fig. 4A) (15, 21, 81). However, in dogs (15) and ponies (Fig. 4B) (24, 30), there is no plasticity if regrowth is prevented by transection of the entire ventral vagal trunk caudal to the azygos vein. This absence of recovery was found in the anesthetized and awake (rest and exercise) state. In human lung transplant patients, there appears to be recovery of the HBIR in the awake but not the anesthetized state, and there is no apparent plasticity in the cough reflex of these patients (2, 44, 85).

Another change after lung denervation is attenuation of operational length compensation (OLC), which is the increased stimulation of the diaphragm that occurs when lung volume is increased. This reflex compensates for the reduced capability of the muscle fibers to generate force when they are at an unfavorable portion of their length-tension relationship. In ponies, the OLC reflex is reduced by nearly 50% 2 wk after lung denervation, but the reflex is normal 4 yr after lung denervation (Fig. 5) (12, 22). This plasticity is not due to reinnervation of the lungs. As summarized in
In summary, there is plasticity after lung denervation, which in some cases is due to reinnervation but in other cases seems due to an alternative system or mechanism providing some functions normally provided by lung receptors.

**DENERVATION OF RECEPTORS IN RESPIRATORY MUSCLES**

Muscle spindles and Golgi tendon organs in respiratory muscles (like other skeletal muscles) provide sensory, afferent information regarding muscle length and tension (20, 45). This feedback information is thought to be of importance to the control system that efficiently maintains blood-gas homeostasis over a range of mechanical conditions of the airways, lungs, and chest wall. It has also been shown that C-fiber endings in respiratory muscles, sensing for example a lactacidosis, are important to reflex adjustments in breathing in conditions of respiratory muscle fatigue (78, 94).

Denervation of receptors in respiratory muscles through dorsal rhizotomy has a minimal effect on breathing of awake animals during normal, unstressed conditions (22, 28). However, reflexes in response to stress are altered. For example, cervical dorsal rhizotomy (CDR) (diaphragm deafferentation) attenuates the OLC reflex, which is eliminated by subsequent lung denervation (Fig. 5) (22). In addition, CDR or thoracic dorsal rhizotomy (TDR) (intercostal muscle deafferentation) attenuates reflex adjustments to changes in airway resistance or dead space (65). Dramatic demonstrations of these effects are data showing that TDR goats responded normally to exercise when airway resistance was normal, but respiratory failure occurred (in a dose-dependent manner) during exercise when airway resistance or dead space was increased (65).

After TDR in goats, there was recovery/plasticity observed as early as within 1 wk, but this was highly variable among the goats (51, 63). A critical element in the recovery was repeated exposure to the stress (i.e., exercise plus increased airway resistance or dead space). Recovery could be observed with repeated trials within 1 day, but increasing the stress would again require several trials before respiratory failure was not observed. It appeared therefore that “recovery of function was related to the number of trials rather than time, indicating that recovery was experience rather than time dependent” (63). Postmortem visual exami-
nation and immunohistochemistry revealed no evidence of regrowth of dorsal roots in any studies. The mechanism of the plasticity after TDR appears to involve increased phrenic motoneuron neuromodulation by the descending 5-HT system (65). In goats killed 4–15 mo after TDR, 5-HT levels at C5 and C6 were 122% greater than those in sham-operated goats, and TDR also increased 5-HT-immunoreactive terminal density. Thoracic levels of norepinephrine and dopamine were also relatively elevated in the TDR goats. Subsequently, it was found that, 1 wk after CDR in rats, brain-derived neurotrophic factor and neurotrophin-3 expression were increased in C3 to C5 and T3 to T6 ventral horn motoneurons (47). These findings form the basis of a hypothesis that plasticity after CDR and TDR results from 5-HT- and neurotrophin-mediated increases in phosphorylation of glutamate receptors (i.e., upregulation), which increases phrenic motoneuron responses to descending respiratory drive. In other words, attenuation of sensory or afferent inputs to the ventilatory control system is compensated by increased responsiveness on the efferent limb.

Data from a recent study (32) suggest another mechanism of plasticity following CDR. Crossed spinal pathways to phrenic motoneurons are ineffective in normal rats, but they are effective in rats 1 wk after CDR. The 5-HT antagonist methysergide had no effect on this effectiveness, indicating that 5-HT is not critical to sustain this response. These data thus reveal another strategy to improve motor function following spinal injury.

The attractiveness of these 5-HT-mediated hypotheses is that key elements of the mechanism have been found in plasticity after TDR, CDR, and episodic hypoxia, which suggests that the mechanism could underlie plasticity after other sensory denervation or lesions and therefore be a generalized mechanism of plasticity (51, 52, 64). For example, loss of tonic carotid chemoreceptor input after CDR resulting in hypoventilation (51, 52, 64). Subsequently, it was found that, 1 wk after CDR in rats, brain-derived neurotrophic factor and neurotrophin-3 expression were increased in C3 to C5 and T3 to T6 ventral horn motoneurons (47). These findings form the basis of a hypothesis that plasticity after CDR and TDR results from 5-HT- and neurotrophin-mediated increases in phosphorylation of glutamate receptors (i.e., upregulation), which increases phrenic motoneuron responses to descending respiratory drive. In other words, attenuation of sensory or afferent inputs to the ventilatory control system is compensated by increased responsiveness on the efferent limb.

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DENERVATION OF HINDLIMB RECEPTORS

Over the past century, numerous theories regarding mechanism(s) mediating the exercise hyperpnea have been tested, but there is no unequivocal evidence in support of any of the theories. One of the theories is that pressure, stretch, and/or chemoreceptors in the exercising muscles or limbs are activated by exercise and through dorsal spinal afferent pathways providing the “exercise” signal to the medullary respiratory control centers (50, 76). Elegant studies in reduced preparation and immunohistochemistry revealed no evidence of regrowth of dorsal roots in any studies. The mechanism of the plasticity after TDR appears to involve increased phrenic motoneuron neuromodulation by the descending 5-HT system (65). In goats killed 4–15 mo after TDR, 5-HT levels at C5 and C6 were 122% greater than those in sham-operated goats, and TDR also increased 5-HT-immunoreactive terminal density. Thoracic levels of norepinephrine and dopamine were also relatively elevated in the TDR goats.

Subsequently, it was found that, 1 wk after CDR in rats, brain-derived neurotrophic factor and neurotrophin-3 expression were increased in C3 to C5 and T3 to T6 ventral horn motoneurons (47). These findings form the basis of a hypothesis that plasticity after CDR and TDR results from 5-HT- and neurotrophin-mediated increases in phosphorylation of glutamate receptors (i.e., upregulation), which increases phrenic motoneuron responses to descending respiratory drive. In other words, attenuation of sensory or afferent inputs to the ventilatory control system is compensated by increased responsiveness on the efferent limb.

Thus these studies did not provide data directly supporting plasticity of an apparent hindlimb exercise ventilatory stimulus. However, there clearly was plasticity in posture and locomotion, and if reliable assessments could have been made during the recovery phase, plasticity may also have been found in the exercise ventilatory stimulus. Unfortunately, during the recovery phase, the anxiety of the ponies and other technical problems during exercise trials did not permit a valid assessment of the exercise ventilatory stimulus. These studies underscore the fundamental difficulty of maintaining physiological conditions in studies on the exercise hyperpnea, control of breathing, and the plasticity of ventilatory control. This difficulty is a major reason why there is incomplete understanding of these control mechanisms.

LESIONS WITHIN THE CENTRAL NERVOUS SYSTEM

Plasticity after pontine lesions. Over 75 yr ago, Lumsden (59) found in anesthetized cats that transection at the rostral border of the pons had no effect on breathing but that transection at the midpons level increased the Ti and reduced breathing frequency. Subsequently, the pontine nucleus parabrachialis medialis (NPBM), also known as the pneumotaxic center, was established as an important determinant of respiratory timing. For example, St. John et al. (93) found in anesthetized cats that bilateral NPBM lesions increased Ti from 1.1 to 2.8 s and reduced breathing frequency from 16.6 to 10.5 breaths/min (Fig. 6). Lesions outside the NPBM had no effect on Ti and breathing frequency. Three months later, Ti while awake and under anesthesia did not differ between NPBM-lesioned and control cats, and Ti did not differ between awake and anesthetized states. There was thus recovery or plasticity after NPBM lesions. This plasticity appeared dependent on vagal afferents, as subsequent vagotomy increased Ti from 2.3 to 29.2 and from 2.2 to 6.9 s in NPBM-lesioned and control cats, respectively.

This apneustic breathing pattern waned over the sub-
sequent hours as the cats recovered from the anesthe-
sia, and 24 h later in the awake state, Ti was 3.0 and
2.5 s in lesioned and control cats, respectively. The cats
were then anesthetized, which increased Ti to 28.5 and
4.0 s, respectively. These data thus dramatically dem-
strate that plasticity within the timing elements of
the ventilatory control system is markedly greater dur-
ing the awake than during the anesthetized state.

St. John (92) also found that the NPBM was vital for
the tidal volume (VT) response to hypercapnia. In
awake cats, the hyperpnea while breathing 7% CO2
results primarily from an increased VT. NPBM lesions
greatly reduce this response, but 1 wk after the lesions
were introduced, the VT response to 7% CO2 returns to
normal. This plasticity is dependent on suprapontine
mechanisms, as subsequent decerebration again re-
duces the VT response to 7% CO2. Decerebration in
control cats has no effect on the VT response to 7% CO2.

In summary, there is plasticity after NPBM lesions
that have altered respiratory timing and the VT re-
sponse to CO2. This plasticity is dependent on the
awake state and/or on suprapontine mechanisms.

Plasticity after medullary lesions. Lumsden’s studies
(59) referred to earlier established findings that neu-
rons in the medulla were vital to sustain breathing;
transection at the juncture of the medulla and spinal
cord in anesthetized cats resulted in sustained apnea.

Subsequent studies identified respiratory neurons in
the medullary nucleus tractus solitarius, in the nu-
cleus ambiguus, and in a column of neurons near or
rostral to the nucleus ambiguus. These neurons appear
to be part of neural circuits involving several other
medullary, pontine, and cerebellar nuclei that provide
important functions such as respiratory rhythmogen-
esis, pattern generation, and intracranial chemorecep-
tion (6, 23). However, despite advancements in knowl-
edge, controversy remains regarding the exact site and
mechanism mediating these and other functions. Most
of the studies have been utilizing acute, anesthetized
preparations; thus relatively little information is avail-
able regarding plasticity after the creation of lesioned-
induced deficits in function. However, it seems intuiti-
tive that, for a vital behavior such as breathing, there
would be redundancy and/or plasticity in the basic
regulatory mechanisms thought to exist in the me-
dulla. Indeed, extensive plasticity/redundancy might
be why lesions of a postulated important pathway or site
have only a slight effect on breathing in the awake
state. This plasticity appears to be state dependent, as
lesions at some sites cause terminal apnea in anesthe-
tized mammals but only modest changes in breathing
in awake mammals (1, 29, 68-70, 98). As a result, to
prevent death, Berger and Cooney (3) mechanically
ventilated cats for 24 h after bilateral kianic acid
lesions in the nucleus tractus solitarius. Eight weeks
later, baseline breathing and CO2 sensitivity of these
cats were attenuated (compared with prelesion values),
more in the anesthetized state than while awake.

Other investigators have also mechanically venti-
lated anesthetized animals after creating neurotoxic
lesions in medullary respiratory nuclei. Indeed with
lesions in the Bötzinger complex (90) or the retrotrap-
zeid nucleus (69), phrenic nerve activity was absent
for over 1 h in some animals, but eventually the activity
returned. These findings may indicate plasticity.
However, the cause of the initial phrenic quiescence is
not known. Particularly with the ibotenic acid injection
into the Bötzinger complex, the quiescence could have
been because of prolonged, intense activation of neu-
rons that inhibit inspiration. Eventually, these neu-
rons died, which resulted in alleviation of the inhibi-
tion and a return of phrenic activity. Thus the data
from these studies may not provide evidence of plastic-
ity.

Possible evidence of plasticity after medullary le-
isions is from studies on goats after bilateral implanta-
tion of microtubules in rostral medullary nuclei (98).
For days thereafter, the goats hyperventilated and had
a reduced CO2 sensitivity, but gradually over 2 wk,
eupneic breathing and CO2 sensitivity returned to nor-
mal. However, the initial change could be related to
neurosurgery rather than the lesion created by the
microtubule. Subsequently, ibotenic acid-induced le-
isons also altered CO2 sensitivity, but there was min-
imal recovery (Fig. 7). This absence of plasticity is
surprising given the supposed widespread distribution
of intracranial chemoreceptors (5, 16, 48) and the plas-
ticity that occurs in CO2 sensitivity after lesions in the
NPBM (92) and after CBD (75). Another medullary site
where lesions have been made is the pre-Bötzinger
complex, which is a site that is involved in respiratory
timing (73, 87, 91). These lesions had a profound effect
on respiratory rhythm (39), but the rats were not

Fig. 6. Ti in cats (n = 6) before (prelesion) and on several occasions
after bilateral lesions placed in the pontine nucleus parabrachialis
medialas (NPBM) (□) or in pontine regions other than the NPBM (○).
The cats were studied 1 mo after the pontine lesions, and then all
cats were vagotomized and subsequently studied at various times as
they recovered from the anesthesi a and surgery. Twenty-four hours
after vagotomy, the cats were studied while awake and then while
anesthetized. Note 1) the initial effect on Ti but subsequent recovery
after the NPBM lesion and 2) the marked effect on Ti of vagotomy in
the NPBM-lesioned cats, which was greater in the anesthetized than
in the awake state. (Data are from Ref. 93.)
studied long enough to indicate whether there was any recovery.

In summary, there is minimal evidence of plasticity after deficits in functions caused by lesioning of medullary nuclei.

Plasticity after spinal cord injury. This topic will be reviewed in detail by others; thus only a brief summary of data relevant to respiratory control will be presented here.

Premotoneurons in the medulla project unilaterally to respiratory motoneurons in the spinal cord. For the major inspiratory muscle, the diaphragm, the motoneurons are primarily at C3–C6. Most projections do not cross the midline, but some cross at the phrenic motor nucleus. However, these crossed phrenic pathways are normally silent.

There is little available evidence of recovery of function after injury to the spinal cord. However, in 1895, Porter (79) demonstrated that a hemidiaphragm paralyzed by cervical cord hemisection would recover in dogs if the contralateral phrenic nerve was cut. This effect, known as the crossed phrenic phenomenon, is not due to regeneration, but it is due to activation of silent synapses between phrenic motoneurons on the injured side and the bulbospinal projection on the intact side that crossed the midline. This phenomenon has been observed in several species (36, 37).

Numerous mechanisms have been proposed for the crossed phrenic phenomenon plasticity, including glial retraction and synaptogenesis in the phrenic nucleus (72), increased number of double synapses on phrenic motoneurons (38), removal of inhibition by contralateral afferents (37), and a 5-HT-dependent mechanism (35, 40, 41, 53, 100). Of these possibilities, the strongest support is for the postulate that 5-HT mediates the activation of the response; however, it may not be necessary to sustain the response. Noteworthy again is the central role of 5-HT in plasticity.

FUTURE STUDIES

There is overall a paucity of studies designed specifically for elucidating plasticity and its mechanisms following denervation or lesions in components of the ventilatory control system. A major need exists for studies over time following lesions in medullary respiratory nuclei. That there are currently insufficient data for conclusions whether indeed plasticity does occur after such lesions underscores the need for such studies.

Another major need is relative to the mechanism(s) of plasticity. Currently, there is strong support for 5-HT-mediated mechanisms at peripheral receptors and at phrenic motoneurons. An apparent key to both of these is the evidence suggesting that a signal from the CNS to a peripheral receptor or to diaphragm motoneurons is required for plasticity. Is there an even greater role for the CNS in plasticity? Although the regenerative capacities of the CNS are greatly limited compared with the peripheral nervous system (49), there is reason to believe that "reorganization" within the CNS underlies plasticity in other systems. For example, the cortical map of the body surface can be greatly altered by use and/or experience (46, 49). Dramatic demonstration of such changes is provided by data on monkeys in whom an upper limb was deafferented. Years later, the cortical areas that normally represent the upper limb were found to now represent the face, which is normally represented by an adjacent cortical area. Does some manner of reorganization contribute to plasticity of ventilatory control after sensory denervation? Certainly, the finding that plasticity after cervical dorsal rhyzotomy was experienced rather than time dependent is consistent with reorganization. Con-
ceivably then, hypercapnia after CBD may result in reorganization in the CNS to increased sensitivity of intracranial chemoreceptors to restore eucapnic CO₂ and CO₂ sensitivity to normal. In addition, the plasticity after respiratory muscle deafferentation and spinal cord injury may in part be due to reorganization within neural circuits of the brain.

The importance of studying plasticity and its mechanisms is that it is relevant to plasticity after disease-induced loss of function (67). It seems reasonable to assume that chronic whole animal studies to elucidate plasticity following lesions and appropriate subsequent cellular and molecular studies to elucidate the underlying mechanisms will enhance the possibility of better treatment and management of loss of function due to disease processes.

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REFERENCES


79. Porter WT. The path of the respiratory impulse from the bulb to the phrenic nuclei. J Physiol 17: 455–485, 1895.


