



Plasticity in Respiratory Motor Control Invited Review: Neuroplasticity in respiratory motor control

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Mitchell, Gordon S., and Stephen M. Johnson. Invited Review: Neuroplasticity in respiratory motor control. *J Appl Physiol* 94: 358–374, 2003; 10.1152/jappphysiol.00523.2002.—Although recent evidence demonstrates considerable neuroplasticity in the respiratory control system, a comprehensive conceptual framework is lacking. Our goals in this review are to define plasticity (and related neural properties) as it pertains to respiratory control and to discuss potential sites, mechanisms, and known categories of respiratory plasticity. Respiratory plasticity is defined as a persistent change in the neural control system based on prior experience. Plasticity may involve structural and/or functional alterations (most commonly both) and can arise from multiple cellular/synaptic mechanisms at different sites in the respiratory control system. Respiratory neuroplasticity is critically dependent on the establishment of necessary preconditions, the stimulus paradigm, the balance between opposing modulatory systems, age, gender, and genetics. Respiratory plasticity can be induced by hypoxia, hypercapnia, exercise, injury, stress, and pharmacological interventions or conditioning and occurs during development as well as in adults. Developmental plasticity is induced by experiences (e.g., altered respiratory gases) during sensitive developmental periods, thereby altering mature respiratory control. The same experience later in life has little or no effect. In adults, neuromodulation plays a prominent role in several forms of respiratory plasticity. For example, serotonergic modulation is thought to initiate and/or maintain respiratory plasticity following intermittent hypoxia, repeated hypercapnic exercise, spinal sensory denervation, spinal cord injury, and at least some conditioned reflexes. Considerable work is necessary before we fully appreciate the biological significance of respiratory plasticity, its underlying cellular/molecular and network mechanisms, and the potential to harness respiratory plasticity as a therapeutic tool.

respiratory control; neuromodulation; plasticity; serotonin; development

PLASTICITY IS A FUNDAMENTAL property of neural systems. Although the neural system subserving respiratory motor control has traditionally been regarded as fixed and immutable, compelling evidence has accumulated in recent years, demonstrating that the respiratory control system exhibits impressive plasticity, just as in other regions of the nervous system. Because of its relatively brief history, studies of plasticity in respira-

tory motor control have suffered from the lack of a coherent conceptual framework. The three goals of this review are to introduce workable definitions of plasticity and related neural properties as they pertain to respiratory control, discuss potential sites and mechanisms of plasticity in the respiratory control system, and categorize known examples of respiratory plasticity.

This review is not intended to be an exhaustive catalogue of all that is known concerning respiratory neuroplasticity. Instead, we will emphasize conceptual development and present possible mechanisms that occur in other regions of the nervous system if inad-

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quate reports are available in the respiratory neurobiology literature. In so doing, we hope that gaps in our knowledge will become apparent, thereby guiding future investigations.

Other reviews are available on selected aspects of respiratory plasticity [e.g., developmental plasticity (80, 133), respiratory “memories” (46), time-dependent mechanisms of the hypoxic ventilatory response (8, 21, 60, 117, 166, 197), serotonergic modulation and plasticity (157), plasticity in the exercise ventilatory response (157, 236), and activity-dependent synaptic plasticity (105, 193, 194)]. Comprehensive reviews focused on selected aspects of respiratory plasticity will appear as a part of this Highlighted Topics series in the *Journal of Applied Physiology*.

DEFINITIONS

Despite a growing appreciation of plasticity in the neural control of breathing, a common language has not been adopted. Thus the related concepts of modulation and plasticity are defined below to provide working definitions used throughout this review. Modulation and plasticity share common features, as well as distinctions; they are not mutually exclusive. Indeed, modulation (or metamodulation) may play a key role in the initiation and/or maintenance of plasticity. The concepts of modulation, metamodulation, plasticity, and metaplasticity as they pertain to respiratory motor control are represented in Fig. 1 and are defined below.

Modulation

Modulation (Fig. 1A) is a neurochemically induced alteration in synaptic strength or cellular properties, adjusting or even transforming neural network function (72, 113, 150). Modulation is typified by a relatively short time scale (e.g., within experimental trial) compared with plasticity and is reversed when the neuromodulator is no longer present. One notable example of modulation in respiratory motor control is serotonergic modulation of respiratory neurons (for reviews, see Refs. 19, 24, 157, 204).

Plasticity

Plasticity (Fig. 1B) is a persistent change in the neural control system (morphology and/or function) based on prior experience. Relevant experiences include neural activity, hypoxia, injury, disease, or aging. This simple, functional definition is similar to the working definition used by the Society for Neuroscience (218). Phrenic long-term facilitation (LTF) following intermittent hypoxia qualifies as an example of plasticity in respiratory motor control because it reflects an enhanced respiratory motor output that outlasts the stimulus (episodic hypoxia) (166).

Metamodulation

Metamodulation (Fig. 1C) describes a situation where neuromodulation is in itself subject to modulation (113). Although metamodulation may share mech-

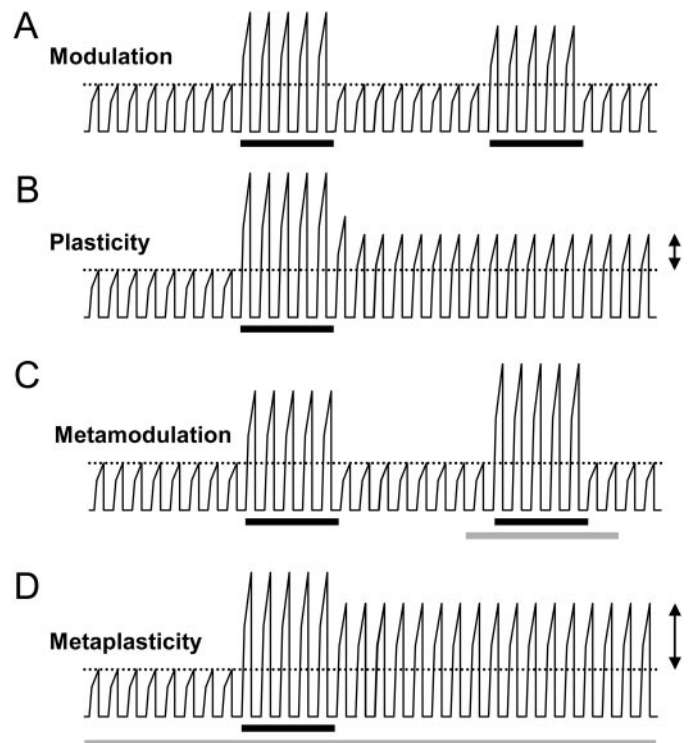


Fig. 1. Representations of modulation and plasticity in respiratory motor control. Tracings represent hypothetical integrated activity in respiratory nerves before, during, and after physiological or experimental perturbations (depicted as horizontal black and gray bars below the tracings). *A*: facilitatory modulation is illustrated as an enhanced respiratory motor output when the neuromodulator is active (black bars). When the neuromodulator is withdrawn, respiratory activity returns quickly to normal levels. *B*: plasticity is a persistent increase in respiratory motor output that outlasts the initiating stimulus (black bar). Thus plasticity is a change in future system behavior based on experience. *C*: metamodulation occurs when the response to a neuromodulator (black bar) is amplified in different experimental condition (gray bar). However, respiratory output still returns rapidly to normal levels when the primary neuromodulator is removed. *D*: metaplasticity is enhanced plasticity following the same initiating stimulus (black bar) due to a preconditioning or continuing stimulus (gray bar). Metaplasticity can occur, even if the preconditioning stimulus has no direct effect on respiratory behavior. Although this figure illustrates facilitatory processes, each process can also result in inhibition.

anisms with first-order modulation, it also involves mechanisms that are unique, for example controlling the elements involved in first-order modulation by phosphorylation (e.g., control of reuptake transport protein activity) or gene expression (e.g., receptor induction). Serotonergic metamodulation appears to underlie potentially important forms of plasticity in respiratory motor control (4, 120, 131).

Metaplasticity

Metaplasticity (Fig. 1D) is a change in the capacity to express plasticity based on prior experience (i.e., “plastic plasticity,” Ref. 29). Metaplasticity is a higher-order form of plasticity that has only recently been described in other neural systems (1, 2, 29, 116). Metaplasticity exists in respiratory motor control since, for example, phrenic LTF is enhanced

following chronic intermittent hypoxia (131) or cervical dorsal rhizotomy (120). In these examples, the experience (chronic intermittent hypoxia or sensory denervation) alters another form of plasticity (LTF).

Such inclusive, functional definitions make distinctions between these processes somewhat arbitrary. If modulation continues beyond the duration of an experimental perturbation, it becomes a form of plasticity. Similarly, an experience may directly influence behavior (plasticity) and modify the system capacity to exhibit plasticity in response to a subsequent perturbation (metaplasticity).

SIGNIFICANCE OF PLASTICITY IN RESPIRATORY MOTOR CONTROL

The fundamental significance of breathing is obvious: it is necessary for life. Breathing must be rigorously controlled in accordance with ever-changing life circumstances. For example, the (seemingly) simple act of walking increases metabolic oxygen consumption and carbon dioxide production by two- to fivefold relative to quiet, resting conditions. Breathing must be rapidly adjusted in accordance with these changing metabolic demands; otherwise, arterial blood-gas levels will be severely disrupted, thereby limiting physical activity. Other common short-term perturbations accommodated by the respiratory control system include changes in arousal state, vocalization, postural changes, airway protective reflexes, the beginning of a respiratory infection, and changing environmental conditions (e.g., ascent to altitude). On longer time scales, the normal development of lung and chest wall mechanics, a gain or loss of weight, chronic altitude exposure, and pregnancy all require substantial changes in respiratory motor output if adequate ventilation is to be maintained. Plasticity is beneficial in adapting respiratory motor control to longer lasting or frequent perturbations (167, 193).

By studying respiratory plasticity, we may gain insights into mechanisms that guide normal development of the respiratory control system and that enable flexibility throughout life when confronted with changing circumstances. Furthermore, an understanding of respiratory plasticity may yield insights into pathological states, thereby providing the rationale for therapeutic intervention in cases of respiratory insufficiency (chronic lung disease, sudden infant death syndrome, sleep-disordered breathing, congenital alveolar hypoventilation syndrome, and neuromuscular injury). Insights derived from studies on respiratory plasticity may also provide unique models, relevant to other neural systems.

POTENTIAL SITES OF RESPIRATORY NEUROPLASTICITY

Long-term functional and morphological changes in cellular and synaptic properties that underlie respiratory plasticity may be distributed throughout the respiratory control system. Fortunately, our understand-

ing of the locations and functions of the main components of the mammalian respiratory control system has advanced considerably in the past few decades (49, 200, 203, 206). Furthermore, respiratory motor output is well characterized and can be readily quantified, even under *in vitro* conditions. To frame our discussion, fundamental processes that underlie respiratory control (49) are illustrated in Fig. 2.

Rhythm Generation

Rhythm generation arises in medullary neurons that initiate rhythmic inspiratory and expiratory activity. Several studies suggest that the pre-Bötzinger complex, a discrete group of propriobulbar neurons in the ventrolateral medulla, plays a critical role in respiratory rhythm generation (201, 203, 217), although this hypothesis is not without controversy (223–225). In awake, unrestrained adult rats, pre-Bötzinger neurons are necessary for normal breathing rhythm (81).

Pattern Formation

Pattern formation establishes the detailed spatio-temporal motor output to respiratory muscles, coordinating their activation to produce a breath with appropriate characteristics for the prevailing conditions (49, 50). Pattern-forming neurons include premotoneurons and motoneurons in the brain stem or spinal cord, with complex activation patterns arising from the interactions of their intrinsic properties with synaptic inputs.

Neuromodulatory Neurons

Neuromodulatory neurons project to and release neuroactive substances (e.g., monoamines, peptides,

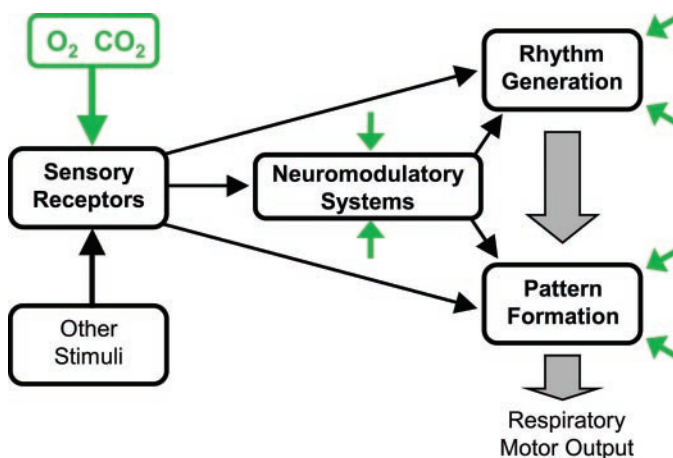


Fig. 2. Potential sites of plasticity in respiratory motor control. Respiratory rhythm is generated by neurons in the ventral medulla (rhythm generation) and transmitted to brain stem and spinal cord neurons that shape the detailed spatiotemporal pattern of respiratory motor output (pattern formation). Rhythm generation and pattern formation are continually influenced by sensory receptors (i.e., chemoreceptors and mechanoreceptors) and neuromodulatory systems (e.g., monoamines). Other inputs also influence the respiratory control system such as inputs from the cortex or the direct effects of oxygen, carbon dioxide, and pH on respiratory neurons (green arrows). Plasticity may occur in one or multiple sites, and it is often initiated by sensory or neuromodulatory influences.

trophic proteins and so forth) that alter the synaptic and cellular properties of other respiratory-related neurons. Neuromodulators may promote plasticity in their targets by enabling (i.e., necessary preconditions) or initiating the cellular/synaptic events that lead to plasticity. On the other hand, the capacity for neuromodulation may be altered, representing a novel and potentially important form of plasticity (plasticity via metamodulation; Ref. 113). Neuromodulatory systems that appear to play key roles in certain forms of adult respiratory plasticity include the serotonergic, noradrenergic, and dopaminergic systems.

Sensory Neurons

Sensory neurons in the lungs, muscles, blood vessels, and central nervous system send important chemosensory (oxygen, carbon dioxide, pH) and mechanosensory information to brain stem respiratory neurons. Thus sensory receptors provide negative feedback, adjusting breathing to meet changing conditions. Less widely appreciated functions of sensory receptors in respiratory control include their effects on neuromodulatory systems (101, 157), on cortical areas associated with arousal and respiratory sensation (13, 99), and their actions as guides to respiratory plasticity (166, 167, 193).

Plasticity may arise from changes in the central neuroanatomic sites associated with respiratory control or from changes in peripheral sensory receptors. For example, chronic, sustained hypoxia elicits plasticity in the carotid body chemoreceptors (21), with delayed effects on the central neural integration of carotid chemoafferent neurons that become more prominent as the duration of hypoxia is extended (45, 197). Chronic intermittent hypoxia elicits plasticity via central neural mechanisms (131) with additional effects at the carotid body chemoreceptors (198). In each example of respiratory plasticity, it is essential to evaluate changes in both peripheral and central neural sites, as well as the possibility that multiple central sites are involved.

POTENTIAL MECHANISMS OF RESPIRATORY PLASTICITY

Detailed cellular or synaptic mechanisms are not yet known in any model of respiratory plasticity. Because basic mechanisms known to operate in other regions of the nervous system most likely contribute to respiratory neuroplasticity, they will be outlined briefly in this review (see Figs. 3 and 4). Cellular and/or synaptic mechanisms of plasticity may operate alone or in concert, in parallel, or in sequence to establish plasticity in respiratory control.

Changes in Synaptic Strength

Changes in synaptic strength are shown in Fig. 3A. *Activity-dependent synaptic plasticity.* Activity-dependent synaptic plasticity is a change in the efficacy of synaptic transmission due to previous activity at that synapse. In many regions of the central nervous sys-

tem, high-frequency activity enhances synaptic transmission for hours to days, a phenomenon known as long-term potentiation (LTP) (8, 48, 115, 145). In contrast, low-frequency activity may decrease synaptic strength for minutes to hours, an effect known as long-term depression (LTD) (42, 114). Shorter forms of potentiation and depression are also observed after synaptic activation (53, 144, 251). The specific manifestations of activity-dependent synaptic plasticity often depend on the recent history of synaptic activation (i.e., metaplasticity; Refs. 1 and 2) or the presence of neuromodulators (69, 111, 159). Thus synaptic activity within the respiratory control system may induce activity-dependent synaptic plasticity, although the ex-

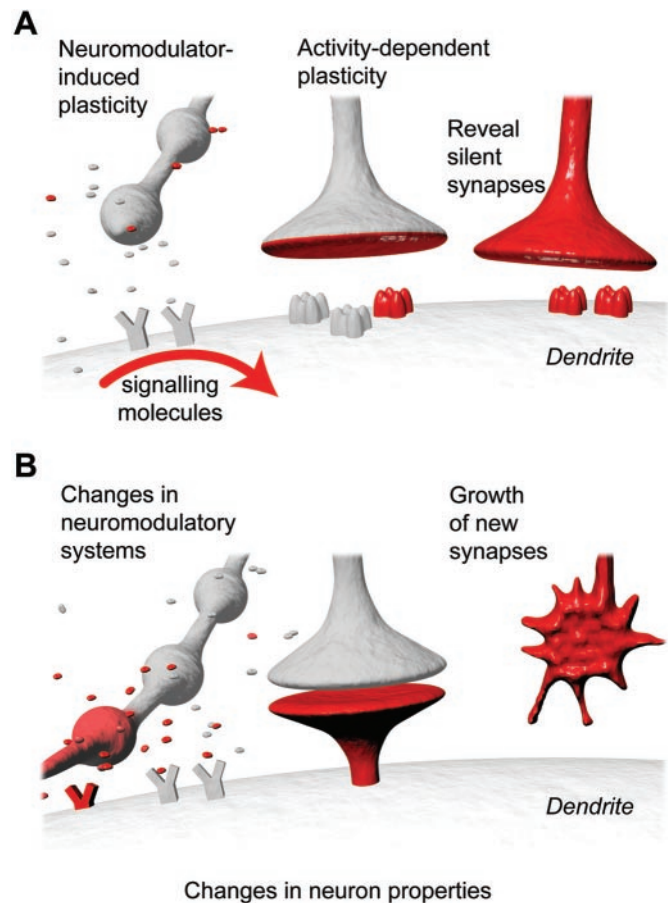


Fig. 3. Potential cellular and/or synaptic mechanisms of respiratory plasticity. In each panel, plasticity is specified by the red color. *A:* synaptic plasticity may be initiated by neuromodulators (neuromodulator-induced plasticity), which activate intracellular signaling molecules (red), secondarily altering the strength of other (glutamatergic or GABAergic) synaptic inputs. Activity-dependent plasticity may arise from coincident pre- and postsynaptic activity, thereby altering presynaptic transmitter release or postsynaptic receptor function in a manner similar to hippocampal long-term potentiation and long-term depression. Silent synapses (anatomically present but functionally ineffective) may be revealed by neuromodulator or activity-dependent mechanisms. *B:* morphological changes may underlie functional respiratory plasticity. The structure/function of neuromodulatory systems may change, increasing or decreasing the capacity for neuromodulation. Neuron properties may change, such as size and shape of the dendrites or somata, and the density of dendritic spines. Finally, new synapses may be formed or pruned.

tent and direction of such plasticity may be critically dependent on the synapse and prevailing conditions.

Neuromodulator-induced synaptic plasticity. A classical model of synaptic plasticity is facilitation of the sensorimotor synapse in *Aplysia* (30, 109, 154, 155, 227). In this model system, serotonin release onto the presynaptic terminal initiates intracellular cascades, increasing synaptic strength in multiple time domains. Serotonin-dependent plasticity is also important in respiratory motor control (Ref. 166; see *Serotonin-Dependent Respiratory Plasticity* below), although the detailed cellular and/or synaptic mechanisms may differ. Other neurochemicals such as norepinephrine (8, 117) or trophic factors such as brain-derived neurotrophic factor (BDNF) may initiate or regulate synaptic plasticity (124, 147, 191, 214, 231).

Silent synapses revealed. In some neural systems, nonfunctional synaptic pathways exist. These existing but ineffective synaptic pathways can be enhanced by experimental manipulations or injury (48, 71, 128, 129, 190, 247). In respiratory motor control, ineffective crossed spinal synaptic pathways to phrenic motoneurons are revealed by serotonin receptor activation (130, 248), spinal injury (74, 86, 181), and spinal sensory denervation (63). Plasticity in silent synaptic pathways may be a specialized case of activity-dependent or neuromodulator-induced synaptic enhancement; however, pending further investigation, this must be regarded as a separate category of synaptic plasticity.

Changes in Neuromodulatory Systems

Changes in neuromodulatory systems are shown in Fig. 3B. Breathing is under the influence of multiple excitatory and inhibitory neuromodulatory systems, each active under different physiological circumstances and each with the potential to exhibit plasticity. Altered concentrations of neuromodulators near their targets may result from changes in the activity of neuromodulatory neurons, the number and size of neuromodulatory terminals, reuptake of neuromodulator once released, or synthesis and degradation. The function of any neuromodulatory system also depends on the density and type of receptors on their pre- and postsynaptic targets, as well as their intracellular signaling mechanisms. An altered capacity for neuromodulation resulting from changes in any of these factors is both a form of plasticity and a form of meta-modulation. Notable examples of plasticity via meta-modulation include serotonin-dependent plasticity in the social status of crayfish (244), altered serotonin transport protein function (174), altered serotonin degradation (25, 28), and alterations in serotonin-dependent respiratory plasticity following chronic spinal sensory denervation (63, 106, 120).

Changes in Neuron Properties

Changes in neuron properties are illustrated in Fig. 3B. Neurons can alter their functional characteristics by morphological plasticity, changing the size and shape of their somata and dendrites or dendritic spine

characteristics (33, 91, 180, 222). Electrophysiologically, neurons can alter their membrane potential, input resistance, capacitance, and action potential threshold (and so forth) by changing the expression or distribution of membrane channels or postsynaptic receptors (84, 110, 139, 250).

Growth of New Synapses

Growth of new synapses is illustrated in Fig. 3B. The strength of excitatory and inhibitory synapses may be increased by the formation of new synaptic connections between existing neurons, especially during the early stages of development. Increased synaptic connectivity may result from the arrival of new growth cones or to sprouting of existing nerve terminals (33, 43, 55, 120, 136, 146). The growth of new synapses may be triggered by synaptic activation, by deafferentation, and/or by increased expression of neurotrophic factors. Synaptic pruning may also be an important mechanism of plasticity during development or after therapeutic tissue transplants, such as the implantation of stem cells (188, 230).

Modulatory Balance

Modulatory balance is illustrated in Fig. 4. Another example of changes in modulatory systems is the circumstance where opposing modulatory systems exist in a balance (Fig. 4A). By shifting the balance of facili-

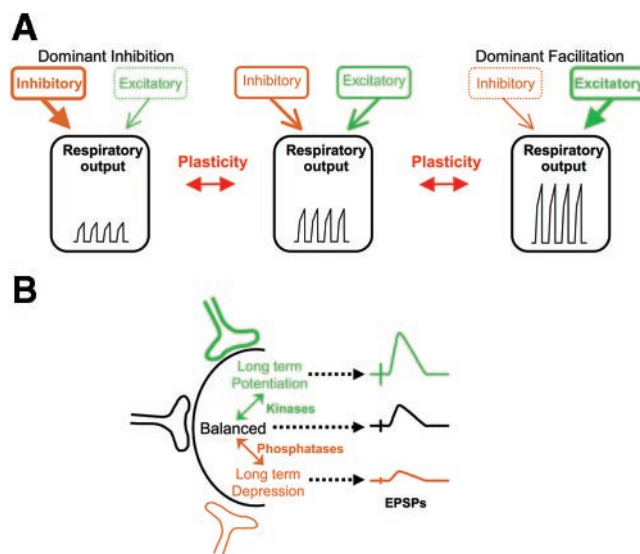


Fig. 4. Plasticity via changes in network or synaptic balance. **A:** modulatory balance results from the off-setting influences of facilitatory and inhibitory neuromodulatory systems, resulting in normal respiratory motor output. This balance can be disrupted by strengthening the influence of one modulatory system or weakening the other. Respiratory plasticity may result from changes in this balance, reflecting a net inhibition or facilitation. On the other hand, modulatory influences may be regulated in parallel, maintaining a balance at a different level. In this way, facilitatory plasticity may be used to offset maladaptive inhibitory mechanisms. **B:** synaptic balance may be represented by offsetting influences from postsynaptic kinases (facilitatory) and phosphatases (inhibitory) on synaptic strength. The net activation of phosphatases and kinases will thus determine the overall synaptic strength.

tatory and inhibitory modulatory systems, the overall neural network may be shifted to net facilitation or net inhibition. Shifts in modulatory balance have been suggested as a possible explanation for differential responses of the respiratory control system to episodic hypoxia vs. hypercapnia, invoking an imbalance between the opposing influences of the serotonergic and noradrenergic modulatory systems (8, 117).

By analogy, changes in synaptic strength may arise from a balance between the facilitatory influences of pre- and postsynaptic kinases and phosphatases (Fig. 4B). For example, the difference between LTD and LTP in hippocampal synapses is postulated to arise from a predominant action of phosphatases at low stimulation frequencies and of kinases at higher stimulation frequencies, the degree of depression or potentiation arising from the net phosphorylation state (98, 219, 234).

Changes in Neural Network Dynamics

In addition to changes in cellular and/or synaptic properties, it is important to consider emergent properties that arise in the neural network subserving ventilatory control. Emergent properties may represent novel mechanisms of plasticity, not easily detected at the cellular and/or synaptic level. For example, after a stimulus that elicits plasticity (e.g., carotid chemoafferent neuron activation), brain stem respiratory neurons exhibit greater synchronization (vs. changes in mean firing rate) (171–173). Although the significance of greater synchronization is not clear, synchronized synaptic inputs may trigger a greater postsynaptic response than the same number of synaptic potentials presented in a constant temporal pattern (186).

FACTORS THAT INITIATE AND MAINTAIN PLASTICITY

Factors that initiate and maintain plasticity are illustrated in Fig. 5. In many models of neuroplasticity, factors that initiate plasticity are often distinct from the factors that maintain it. Maintenance often results

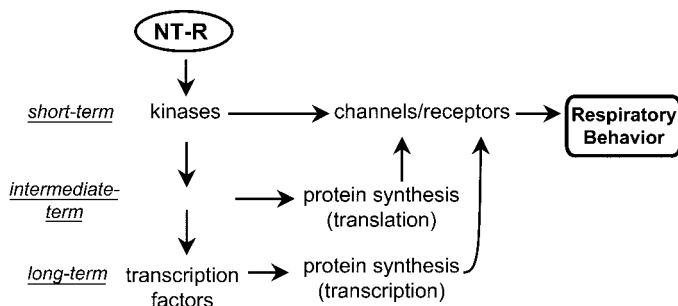


Fig. 5. Hypothetical basis of cellular/molecular mechanisms that give rise to different time domains of respiratory plasticity. Many forms of plasticity are initiated when selected kinases are activated by neurotransmitter or neuromodulator receptors (NT-R). Short-term plasticity may arise from the direct, covalent modification (phosphorylation) of pre- and/or postsynaptic channels and receptors. Intermediate-term plasticity often requires new protein synthesis, most likely via increased translation of existing mRNA. Long-term plasticity is more likely to be associated with transcription-dependent protein synthesis. Time-dependent changes in synaptic strength alter respiratory behavior.

from a cascade of cellular and/or synaptic mechanisms operating in different time domains (Fig. 5). Common factors initiating plasticity include neuronal activity (with associated calcium influx), neuromodulators, injury, hypoxia/ischemia, and unique associations between coincident or temporally associated neural activity (e.g., during associative learning). Increased intracellular calcium activates calcium-dependent kinases or phosphatases, thereby triggering a signaling cascade resulting in short-term and long-term plasticity (110, 250). In short time domains, activated kinases may covalently modify existing proteins (i.e., phosphorylation), giving rise to enhanced synaptic transmission. However, more robust stimuli may trigger new protein synthesis (or delay protein breakdown), leading to longer lasting plasticity. New protein synthesis may arise from increased translation of existing mRNA (intermediate-term plasticity) or increased transcriptional activity (long-term plasticity) (110). New proteins may include kinases, neurotrophic factors, scaffolding proteins, transcription factors, and structural proteins such as adhesion molecules.

CONSIDERATIONS

Respiratory Motor Output Is Spontaneous and Interpretable

One of the greatest difficulties in studying plasticity in other parts of the nervous system (e.g., the hippocampus) is interpreting the physiological significance of the plasticity (31, 109, 156, 212). For example, in hippocampal slices, the significance of a long-term increase or decrease in synaptic strength is difficult to interpret because learning and memory cannot be measured. Conversely, in intact animals, there is debate as to whether changes in behavior can be attributed to learning and memory. In contrast, respiration is a spontaneous, endogenous rhythmic motor behavior that can be described in considerable quantitative detail. Thus, following an experimental protocol designed to induce plasticity, long-term changes in the amplitude or timing of respiratory motor output can be measured, and the physiological relevance of these changes can be interpreted in the context of breathing.

Necessary Preconditions Must Be Satisfied

Certain forms of plasticity would not be optimal in the normal, day-to-day operation of the respiratory control system. For example, it is not desirable for a sigh or deep breath to initiate activity-dependent plasticity in the bulbospinal synapse onto phrenic motoneurons. If this synapse were to undergo LTP after a sigh, the persistent increase in respiratory motor output would cause persistent hyperventilation, disrupting blood-gas homeostasis. On the other hand, plasticity may be critical to maintain function in the face of injury or the onset of lung disease. The key to maintaining the capacity for plasticity, while preventing inappropriate expressions of plasticity, may be through the regulation of factors that play a permissive role in

plasticity (i.e., necessary preconditions). For example, although there is little evidence for potentiation of synapses on spinal respiratory motoneurons under normal conditions, spinal injury strengthens existing but ineffective synaptic pathways to phrenic motoneurons (63, 65, 74, 181, 248). Thus spinal injury may establish necessary preconditions for functional synaptic enhancement.

Necessary preconditions might include adequate levels of neurotrophic factors, neuromodulators, neurotransmitters, or intracellular signaling molecules. Several neurochemicals are necessary for the expression of activity-dependent LTP in the mammalian hippocampus, including BDNF. BDNF is ordinarily expressed at high levels in the hippocampus, where LTP can be evoked with relatively little difficulty. LTP is difficult to evoke in BDNF knockout mice, unless hippocampal BDNF protein levels are replenished experimentally (123, 187). In contrast, BDNF concentrations are relatively low in the mammalian spinal cord (75, 106), and activity-dependent LTP is difficult to evoke (105, 158). An upregulation of spinal BDNF (104) might improve the ability to express spinal synaptic plasticity. As another example, protein kinase A (PKA) is necessary for BDNF-induced potentiation at the neuromuscular synapse; however, PKA is not sufficient to initiate the plasticity when acting alone (26).

The Stimulus Paradigm Is a Key Determinant of Plasticity

In many models of neuroplasticity, the specific stimulus paradigm is critical (97, 155, 170). Important variables include the duration, intensity, pattern, and history of stimulation. The duration and intensity of stimulation often determine the duration and direction (potentiation vs. depression) of the resulting plasticity (36, 168). Important forms of synaptic plasticity are elicited preferentially by intermittent vs. sustained stimuli. For example, in *Aplysia*, serotonin-dependent LTF (154, 155) and sustained PKA activation (227) are elicited by episodic serotonin exposures but not by serotonin exposures of equal total duration when applied in a "massed" or continuous pattern. Hippocampal LTP is most effectively induced by repeated tetanization (97). Similarly, the stability of mitogen-activated protein kinase activation (a key molecule in several forms of plasticity) is increased when stimuli are presented in an episodic pattern, an effect necessary for dendritic plasticity in cultured hippocampal neurons (243).

The basis of this profound pattern sensitivity is not clear, yet it may result from unique cellular properties elicited by cytosolic calcium oscillations. Some calcium-sensitive kinases become autophosphorylated after a series of rapid calcium spikes and, therefore, do not deactivate as rapidly between oscillations (199). Calcium oscillations reduce the effective threshold for transcription factor activation and thus gene expression (27, 44, 52, 160). For example, BDNF, a neurotrophic factor implicated in many forms of neural plastic-

ity, exhibits pattern-sensitive, activity-dependent synthesis (166), and release (11, 125), at least in some types of neurons.

The observation that episodic but not sustained hypoxia elicits serotonin-dependent phrenic LTF (9) may not represent a ubiquitous characteristic of the respiratory control system. To the contrary, continuous, but not intermittent hypoxia elicits CREB phosphorylation in carotid body glomus cells (241). The specific pattern of stimulation necessary to evoke plasticity in any neural structure is likely to depend on the details of cell signaling pathways available in those neurons.

The history of stimulation can also be a critical determinant of plasticity. For example, brief synaptic activation in the hippocampal CA1 region at low frequencies that cause neither LTP nor LTD alters future responses to stimulation: protocols that ordinarily cause LTP now elicit LTD (1, 2). Thus metaplasticity is a potentially confounding influence of relevance to the design and interpretation in any study of plasticity. One example of metaplasticity in respiratory control is the progressive decrease in posthypoxia frequency decline with successive hypoxic exposures in anesthetized rats (4).

Facilitatory and Inhibitory Balance

Several facilitatory and inhibitory modulatory processes influence breathing (19, 24, 157). Some of these apparently opposing processes act in a similar time frame, establishing a balance that offsets inappropriate influences on respiratory motor output. Indeed, the major biological role of facilitatory plasticity (e.g., LTF after episodic hypoxia) may be to offset inhibitory mechanisms, thereby preserving adequate ventilation. Before conclusions are made that specific forms of respiratory plasticity do not occur in a specific model or experimental circumstance, full consideration should be given to the possibility that the mechanism has been invoked but is not detectable in ventilation due to a concurrent offsetting mechanism (8, 117).

Changes in Mechanics or Gas Exchange Must Not Be Confused for Neuroplasticity

Experiences may alter respiratory mechanics or gas exchange, thereby altering ventilation but obscuring the underlying change in (neural) respiratory motor output. For example, neonatal hypoxia causes persistent changes in respiratory mechanics, diminishing future hypoxic ventilatory responses (182–184), but without changing integrated neural responses to hypoxia as assessed in the phrenic neurogram (17). Thus, although neonatal hypoxia elicits developmental plasticity, it may not reflect neuroplasticity. Similarly, developmental hyperoxia alters pulmonary gas exchange during hypoxia (132). Thus the same inspired oxygen fraction cannot be used to test future hypoxic ventilatory responses because differential effects on arterial oxygen levels elicit hypoxic ventilatory responses that are not comparable. Only with comparable arterial oxygen levels (by adjusting the inspired oxygen frac-

tion in treated rats) can the underlying neuroplasticity be assessed (132, 135). Any study on respiratory neuroplasticity must consider the confounding influences of changes in respiratory mechanics and gas exchange.

Genotype Can Influence Plasticity

Genotype can influence hippocampal synaptic plasticity (148, 153). Substantial anatomic differences in important neuromodulatory systems have also been reported between rat substrains (37). Evidence is also accumulating that genotype can influence respiratory plasticity. For example, experiments on Sprague-Dawley rats from different colonies (60, 61) revealed that phrenic and hypoglossal LTF after intermittent hypoxia differ substantially between rat substrains. Mutations in selected genes can also influence respiratory plasticity (112, 121, 122). Any study of respiratory neuroplasticity must consider potential genetic influences.

Age and Gender Influence Plasticity

Age and gender can exert powerful influences on hippocampal synaptic plasticity (38, 56, 88, 140). Age affects a number of ventilatory control mechanisms (58, 59), including the magnitudes of phrenic and hypoglossal LTF after intermittent hypoxia. Specifically, LTF decreases from young adult to middle-aged male rats (245). In contrast, LTF actually increases with age in female rats and is dependent on the stage of the estrus cycle (246). Thus age and gender can be important influences on respiratory plasticity.

Respiratory Gases Influence Plasticity

Hypercapnia and hypocapnia have detrimental effects on memory, cognition, and motor tasks in humans and other animals (73, 149, 161, 213). Adverse effects of hypercapnia are reflected as impaired hippocampal LTP (96, 100, 238). On the other hand, synaptic activation in the hippocampus induces transient alkalization of the extracellular fluid, indirectly enhancing *N*-methyl-D-aspartate (NMDA) receptor-mediated synaptic transmission and LTP (78, 79, 235).

Hypoxia and ischemia also impair brain function in humans and other animals (35, 93, 239). Interactions between hypoxia, synaptic transmission, and synaptic plasticity in the hippocampus are complex and poorly understood. For example, 1) hypoxia induces a form of LTP distinct from activity-dependent LTP (41, 94, 141), 2) decreased oxygen tension impairs activity-dependent LTP (95), and yet 3) pretreatment with moderate hypoxia enhances hippocampal LTP (210).

In a closed-loop homeostatic control system with chemoreceptor feedback, changes in the level of arterial PCO_2 are also important considerations in studies of respiratory plasticity. For example, an increase in respiratory drive will decrease arterial PCO_2 , thereby attenuating and obscuring the overall ventilatory response. Thus a small ventilatory facilitation of 20–30% may actually reflect a 70–100% increase in respiratory drive. Similarly, a decrease in arterial PCO_2 during

ventilatory stimulation may cause ventilatory depression during the poststimulation period. Such a depression may reflect persistent hypocapnic inhibition vs. neuroplasticity per se.

At the very least, the effects of altered oxygen or carbon dioxide levels on synaptic plasticity suggest that one must pay careful attention to gas levels when performing *in vivo* or *in vitro* experiments on any form of plasticity. Indeed, appropriate levels of oxygen, carbon dioxide, and pH may represent necessary preconditions for the expression of plasticity. Conversely, certain forms of respiratory plasticity may result directly from altered oxygen or carbon dioxide levels acting on respiratory neurons.

MODELS OF RESPIRATORY PLASTICITY

Known categories of respiratory plasticity will be mentioned, although the discussion will be brief. Several of these categories are the topics of other reviews in this series or were topics of previous reviews in the *Journal of Applied Physiology* (80, 166, 178, 198).

Hypoxia-Induced Respiratory Plasticity (Adult)

Hypoxia-induced respiratory plasticity is the most thoroughly studied and best understood form of respiratory plasticity. The hypoxic ventilatory response is characterized by discreet, time-dependent mechanisms that depend on the severity, duration, and pattern of hypoxic exposure. Recent reviews have characterized these time domains of the hypoxic ventilatory response (21, 166, 197, 198). In brief, continuous hypoxia is characterized by an acute response, followed immediately by short-term potentiation and then short-term depression (46, 197). In the subsequent minutes to days of hypoxic exposure, ventilatory activity exhibits hypoxic ventilatory decline, followed by ventilatory acclimatization to chronic hypoxia. Ventilatory acclimatization appears to be dominated by initial, peripheral chemoreceptor sensitization (21), followed by progressively increasing contributions from the central neural integration of carotid chemoafferent neurons (45, 220). Thus the ventilatory response to continuous hypoxia is characterized by several unique forms of respiratory plasticity.

After a single hypoxic episode, a short-term depression of phrenic motor output is observed in anesthetized rats (39, 89), an effect now referred to as posthypoxia frequency decline (39, 197). Posthypoxia frequency decline is abolished by pontine lesions in the vicinity of the A5 region and is modulated by α_2 -adrenergic (Ref. 4, but see Ref. 40) and serotonin receptor activation (119). Posthypoxia frequency decline in rats is subject to a degree of metaplasticity, since prior exposures diminish its expression after subsequent hypoxic exposures (4).

When hypoxia is experienced in an intermittent or episodic pattern, unique forms of plasticity are revealed (9, 166, 198). In normoxic intervals between successive hypoxic episodes, a progressive windup of respiratory activity is often observed, reflecting the

development of LTF (162, 197). After 3–10 hypoxic episodes, LTF is expressed as a persistent elevation of respiratory motor output, lasting many minutes to hours. Phrenic LTF is a central neural mechanism (162, 166) elicited by intermittent but not continuous hypoxia (9). LTF requires spinal serotonin receptor activation and spinal protein synthesis (10), enhancing synaptic inputs to phrenic motoneurons (64). Network (6, 117) and cellular/synaptic (8, 166) models of LTF have been proposed. However, the persistent increase in brain stem neurons following intermittent activation of carotid chemoafferent neurons (171–173) suggests that multiple sites may be involved in this complex form of respiratory neuroplasticity.

If intermittent hypoxia continues, different mechanisms of plasticity are evoked. For example, chronic intermittent hypoxia augments the short-term hypoxic ventilatory response, eliminates posthypoxia frequency decline, and amplifies LTF in rats (131). These effects can be accounted for by enhanced central neural integration of chemoafferent inputs (131), particularly in the spinal cord (65). However, additional carotid body plasticity may contribute to these effects (198).

Exercise-Induced Respiratory Plasticity (Adult)

Although the exercise ventilatory response is the largest ventilatory response in our day-to-day lives, our understanding of the primary drive to breathe during exercise has advanced little in more than 50 years (82). On the other hand, we have recently gained an appreciation that at least some degree of plasticity can be observed in the exercise ventilatory response. The exercise ventilatory response is enhanced by small increments of respiratory dead space (i.e., hypercapnia) during mild to moderate exercise in goats and humans (163, 192). This effect, known as short-term modulation, requires the activation of serotonin receptors (5) located in the spinal cord (164). If the animal experiences hypercapnic exercise during one trial only, subsequent exercise ventilatory responses revert to normal (i.e., this is modulation). However, after repeated hypercapnic exercise, a form of respiratory plasticity is observed as a persistent augmentation of subsequent exercise ventilatory responses, an effect originally referred to as long-term modulation (152, 157, 164). Long-term modulation in goats is serotonin-dependent because it is blocked by pretreatment with *para*-chlorophenylalanine, a serotonin depletor (103), and may represent a consolidation of the mechanisms that underlie short-term modulation. In humans, long-term modulation (if it exists), is more subtle. Whereas some report long-term modulation during the onset of exercise in humans, no steady-state response is observed (90, 202, 237). Other investigators have been unable to find long-term modulation in humans (169), although a less rigorous training protocol was used in this study. The biological significance of short- and long-term modulation of the exercise ventilatory response remains unclear.

Another example of exercise-induced respiratory plasticity is observed after chronic sensory denervation of the thoracic spinal cord (157, 167). After thoracic dorsal rhizotomy from T₂ through T₁₂, goats initially exhibit severe ventilatory failure during even mild exercise when wearing a respiratory mask, a mask easily tolerated prior to surgery (167). In subsequent exercise trials, functional recovery is observed, suggesting that plasticity compensates for the loss of spinal sensory feedback (167). Although the mechanism of functional recovery is not clear, it is associated with increased spinal serotonergic innervation and serotonin concentration (165), suggesting a mechanism similar to long-term modulation induced by repeated hypercapnic exercise (152).

Injury-Induced Respiratory Plasticity

Spinal cord injury. The mammalian spinal cord has ineffective (“silent”) synaptic pathways that cross the spinal midline to innervate contralateral phrenic motoneurons (76, 77, 130). This crossed phrenic pathway can be revealed in phrenic motor output below a spinal hemisection. By cutting the phrenic nerve contralateral to hemisection, descending respiratory drive is increased, thereby recruiting the formerly ineffective crossed phrenic pathway and restoring at least some diaphragmatic activity (77, 83). With time, the crossed spinal pathway increases in strength, allowing progressively greater recruitment of the formerly paralyzed hemidiaphragm (74, 175). This form of time-dependent plasticity following chronic spinal hemisection has been called the “crossed phrenic phenomenon” and is one of the longest known examples of plasticity in respiratory motor control (83, 196). Spontaneous enhancement of crossed spinal pathways to phrenic motoneurons is serotonin dependent (85, 86, 228). Similarly, depression of respiratory motor output in the phrenic nerve contralateral to hemisection requires serotonergic neurons (74). The crossed phrenic pathway can be enhanced pharmacologically (130, 176, 248), by pretreatment with chronic cervical sensory denervation (63) or by chronic intermittent hypoxia following (but not prior to) chronic hemisection (65). Respiratory plasticity elicited by spinal injury will be the topic of a specialized review in this series (75a).

Spinal sensory denervation. Chronic thoracic dorsal rhizotomy causes severe ventilatory failure during exercise in goats, followed by progressive functional recovery (157, 164, 167). This form of plasticity is associated with increased spinal serotonin terminal density and concentration, including effects in functionally related regions of the spinal cord not directly affected by the surgery (165). Changes in spinal dopamine and norepinephrine concentrations are also observed within the surgically affected area (165), although the functional significance of these changes is unknown. In subsequent studies on rats, bilateral cervical dorsal rhizotomy increased serotonin terminal density in the phrenic motor nucleus and increased serotonin-dependent LTF following intermittent hypoxia in both

phrenic (120) and hypoglossal motor output (3). In association, cervical dorsal rhizotomy increased ventral spinal BDNF and neurotrophin-3 concentrations (106) and crossed spinal synaptic pathways to phrenic motoneurons (63). Thus spinal sensory denervation elicits functional, morphological, and neurochemical plasticity in respiratory motor control.

Chemosensory denervation. Chemosensory nerve transection can elicit compensatory plasticity. For example, carotid denervation upregulates the impact of the aortic body chemoreceptors on ventilatory control via a serotonin-dependent mechanism (54, 137, 216). Carotid denervation also influences central neural chemoreflex pathways (142, 143, 208, 209). Plasticity elicited by neural injury or sensory denervation is considered in another review (53a, 54).

Serotonin-Dependent Respiratory Plasticity

Serotonin is a key element in several forms of respiratory plasticity, particularly in adults (157). Specifically, serotonin plays a key role in respiratory plasticity elicited by intermittent hypoxia (131, 166), hypercapnic exercise (103), spinal sensory denervation (120), chemoafferent denervation (216), spinal cord injury (74, 85, 86), and long-lasting enhancement of respiratory frequency (107).

Developmental Plasticity

The ventilatory control system exhibits developmental plasticity, whereby experiences in sensitive stages of development alter adult ventilatory responses. The same experiences have little or no impact when they occur later in life, indicating that the plasticity is unique to development. Such developmental plasticity may be essential in guiding normal development of the ventilatory control system. When these essential experiences are altered, unique, potentially pathological forms of plasticity may emerge.

Developmental hypoxia. Hypoxia during the neonatal period affects adult ventilatory control, altering resting breathing patterns (182) and attenuating the hypoxic ventilatory response (184). Furthermore, prenatal hypoxia (189) and postnatal hypoxia (108) impair chemoafferent pathways in rats, an effect that is sexually dimorphic (108). Brief associations of hypoxia with auditory or tactile stimulation during the first month of life have a lasting impact on ventilatory patterns during sleep in adult rats (232, 233). Thus early life experiences with hypoxia elicit developmental plasticity.

Developmental hyperoxia. Hyperoxia during the neonatal period also affects adult ventilatory control, suppressing the normal development of arterial chemoreceptors (132, 133). For example, rats raised in enriched oxygen mixtures for the first postnatal month have impaired hypoxic ventilatory responses for the duration of life (62). The functional impairment is not due to alterations in pulmonary mechanics or gas exchange (135) or changes in the central integration of carotid chemoafferent inputs (62, 134). Rather, carotid chemo-

receptor development is impaired because the carotid bodies are hypoplastic (47, 66), the number of chemoafferent neurons in the carotid sinus nerve is reduced (47), and carotid sinus nerve afferent responses to cyanide, asphyxia, and hypoxia are reduced (20, 62, 133). The sensitive developmental period for these changes is within the first 2 postnatal wk (15). Hyperoxia for the first postnatal week and month elicit similar functional impairment (15). However, whereas rats exposed to 1 wk of hyperoxia exhibit slow spontaneous functional recovery (16), rats exposed to 1 mo of hyperoxia do not (62). Functional recovery can be evoked in adults by chronic intermittent or chronic sustained hypoxia, although the mechanisms underlying functional recovery appear to differ (66). The biological or clinical significance of hyperoxia-induced developmental plasticity is unclear since the required oxygen exposures are prolonged. Nonetheless, developmental hyperoxia provides an intriguing model to study developmental plasticity in ventilatory control and may have some clinical relevance for hyperoxia experienced in a neonatal intensive care unit.

Developmental hypercapnia. Developmental hypercapnia causes long-lasting attenuation in the acute hypercapnic ventilatory response (205, 242), particularly in females (14). Hypercapnia-induced developmental plasticity may play a role in the reduced hypercapnic ventilatory responses commonly observed in fossorial birds and mammals (22, 23, 57, 242).

Other examples. Other examples of developmental plasticity include altered adult chemoreflexes caused by maternal separation stress (118) and prenatal nicotine exposures (12, 51, 70, 87, 207). In the pond snail *Lymnaea stagnalis*, preventing lung ventilation from hatching through adulthood alters mechanisms of ventilatory control in adults (92). Developmental plasticity in ventilatory control will be discussed in other reviews in this series (34a, 53a).

Activity-Dependent Respiratory Plasticity

Brief carotid sinus nerve stimulation in anesthetized cats increases phrenic nerve activity during stimulation and causes a persistent amplitude increase lasting seconds to minutes poststimulation (i.e., short-term potentiation; formerly "afterdischarge") (46, 240). Short-term potentiation is observed after hypoxia (197) or other respiratory stimuli (46, 102) and can be observed in multiple respiratory nerves (102). High-frequency electrical stimulation of the lateral funiculus at C₁-C₂ in anesthetized rats elicits increased phrenic discharge for several minutes poststimulation (158), possibly by NMDA-dependent mechanisms (105, 158).

High-frequency stimulation in the tractus solitarius elicits LTD in synaptic inputs to neurons within the nucleus of the solitary tract, an area of importance to cardiorespiratory integration (194, 195, 249). However, the synaptic pathways studied were not identified as respiratory inputs. LTD is also elicited by low-frequency (1–10 Hz) synaptic activation of descending pathways to expiratory-related spinal motoneurons in

in vitro turtle brain stem/spinal cord preparations (105, 106). The physiological role of synaptic LTD in the nucleus tractus solitarii or spinal cord is not known.

To date, there are no clear examples of activity-dependent LTP in any respiratory-related synaptic pathway. Instead, there seems to be a bias toward controlling synaptic strength via neuromodulator-induced synaptic plasticity (105, 166). Because bursts of high-frequency, glutamatergic synaptic activity are commonly found in the respiratory control system, activity-dependent LTP is inappropriate under normal circumstances. However, this does not rule out an ability to express LTP in certain conditions, such as following spinal injury.

Hypercapnia-Induced Respiratory Plasticity (Adult)

Unlike hypoxia, hypercapnia is more often associated with long-lasting depression (vs. facilitation) of respiratory motor output. During hypercapnia, respiratory activity initially increases and then decreases progressively as the hypercapnia is sustained (177). Once the hypercapnia has ended, both sustained and intermittent hypercapnia elicit long-term phrenic depression in anesthetized rats (minutes to hours; Refs. 7 and 8). Hypercapnia-induced phrenic depression requires α_2 -adrenergic receptor activation (7, 117).

Conditioning

The classical model of response conditioning was established by Pavlov in his famous experiments on dogs, associating a conditioned (irrelevant stimuli such as a tone) with relevant unconditioned stimuli (e.g., food). The most widely studied example of a conditioned respiratory reflex is the gill withdrawal reflex in *Aplysia*. Kandel, Carew, and others (110) did pioneering work on this respiratory defense reflex, establishing a model that has led to profound advances in our understanding of synaptic plasticity in general, eventually leading to the recent award of a Nobel Prize shared by Dr. Kandel. In the gill withdrawal reflex, habituation, sensitization, and associative forms of plasticity could be studied, first in the intact mollusk and then in in vitro preparations where episodic serotonin is used to initiate plasticity in the sensory motor synapse (110). Another serotonin-dependent form of associative learning in *Aplysia* is the sensitization of gill movement in response to decreased pH after repeated, paired associations of low pH and an aversive stimulus (126).

Operant conditioning is a form of associative learning where an external stimulus is associated with a behavioral response (34); the external stimulus is presented only if and when an animal performs a particular behavior. In the fresh water snail, *Lymnaea stagnalis*, operant conditioning of aerial respiratory behavior has been demonstrated (138, 229). When hypoxic, the animal rises to the air-water interface and acquires oxygen from air via its pneumostome. Poking the pneumostome during each attempted breath closes

the pneumostome and reduces future attempts at aerial respiration (138). Operant conditioning of aerial respiration in *Lymnaea* reduces the spontaneous activity of at least two interneurons within the respiratory network, presumably decreasing the activation of the neurons that initiate breathing attempts (221).

In one of the earliest experiments concerning conditioning of respiratory behavior in mammals, hyperventilation-induced apnea was produced in adult sheep for which the unconditioned stimulus was an electric shock (32). After thousands of training trials, environmental cues related to the test apparatus became conditioned stimuli, triggering further apneic events. Adult ventilatory patterns during sleep can be conditioned by neonatal experiences with tactile or auditory stimuli paired with hypoxia (226, 232, 233). In adult rats and cats, associations between a tone (conditioned stimulus) and hypercapnia (179) or ammonia vapors (185) (unconditioned stimuli) elicit conditioned ventilatory inhibition. Recent reviews have considered the evidence for classical conditioning of respiratory behaviors (67, 68, 127). Although the significance of respiratory conditioning is unclear, it may be of relevance to anxiety hyperventilation disorders.

CLOSING REMARKS

We have only recently begun to make progress in understanding the manifestations, mechanisms, and biological significance of neuroplasticity in respiratory control. Specific areas to emphasize in future research include a continued effort to identify new models of respiratory plasticity, with a focus on the specific conditions or experimental manipulations that trigger plasticity. Such "descriptive" studies are still critical in understanding the breadth of respiratory plasticity but must be followed by detailed investigations of underlying mechanisms. At the cellular/synaptic level, an important concern is to identify specific factors that regulate the expression of plasticity (i.e., the necessary preconditions). It is also important to understand the biological significance of respiratory plasticity in everyday life (e.g., weight gain, pregnancy), in individuals compensating for the pathophysiology of disease and injury, and in individuals with maladaptive plasticity triggered by abnormal developmental cues. With gains in understanding each of these levels, it may become possible to harness plasticity as a therapeutic tool in the treatment of respiratory pathophysiology, such as lung disease, sleep-disordered breathing, sudden infant death syndrome, and respiratory insufficiency following central nervous system injury.

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