Chapter 17: Respiratory Physiology: Central Neural Control

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ABSTRACT
State-dependent changes in breathing are caused by nonrespiratory (tonic) inputs to the brainstem systems that control ventilation. In wakefulness, tonic excitatory inputs include those from the reticular formation, brainstem aminergic systems, and hypothalamic orexin-containing neurons. In non-rapid eye movement (NREM) sleep, decrements in these excitatory inputs can explain the features of breathing characteristic of this state. In patients with obstructive sleep apneas, these decrements facilitate upper airway obstructions because upper airway muscles fail to properly compensate for airway collapsing effects of the negative pressure generated by respiratory pump muscles. In rapid eye movement (REM) sleep, there are tonic excitatory inputs to the respiratory system that cause the irregularities and rapidity of breathing, as well as tonic and phasic inhibitory inputs that may cause periods of ineffective ventilation. The loss of excitation mediated by serotonin and norepinephrine contributes to the REM sleep-related hypotonia of motor neurons that innervate the genioglossus and possibly also other upper airway muscles.

The respiratory muscles are controlled by central neural systems that are influenced by feedback from chemical and mechanical sensors and by the sleep-waking state of the nervous system. This chapter deals with the mechanisms by which state of consciousness affects the respiratory system. We begin with non-rapid eye movement (NREM) sleep, a state in which the respiratory system seems to be in its most elemental configuration, and we then consider rapid eye movement (REM) sleep, in which there are both excitatory and inhibitory effects on the respiratory system. We will show that state-dependent effects are the result of either the presence or the absence of tonic inputs to the central respiratory controller.

RESPIRATORY ACTIVITY IN NON-RAPID EYE MOVEMENT SLEEP

Characteristics of Breathing in NREM Sleep
The frequency of breathing is lower and more regular in NREM sleep than in wakefulness [1,2]. Peak instantaneous airflow rate and the peak negative pressure developed against a narrowed airway decrease, whereas upper airway resistance increases. Tidal volume increases as the result of an increased duration of inspiration, but minute ventilation decreases and end-tidal carbon dioxide concentrations increase. Responses to carbon dioxide and low oxygen are intact (see Chapter 18). In humans, there may be periodic breathing, particularly at high altitude (see Chapter 20) [2].

Medullary Respiratory Neuronal Activity in NREM Sleep
There is a decrease in medullary respiratory neuronal activity in NREM sleep [3-6] (Fig. 17-1). The
neurons affected are those in the ventral and dorsal respiratory groups. Some cells are affected more than others. Quantitative analysis shows that the effect of sleep on a respiratory neuron is proportional to the amount of nonrespiratory (tonic) activity in the activity of that cell. That is, the drive to a cell may be rhythmic (i.e., respiratory related) or it may be nonrhythmic (i.e., tonic). Respiratory cells whose activity depends primarily on tonic inputs and only weakly on respiratory-modulated inputs are affected more by sleep than respiratory cells whose activity depends primarily on rhythmic, respiratory-related inputs. Some upper airway motor neurons are in the former category of cells, and their activity decreases accordingly. In contrast, neurons whose activity is primarily determined by rhythmic, respiratory inputs do not show dramatic changes in activity in NREM sleep compared to relaxed wakefulness (Fig. 17-2). This indicates that sleep affects primarily neurons that receive large amounts of nonrespiratory inputs. Consistent with this is the finding that iontophoresis of glutamate onto silent and sleep-sensitive respiratory neurons reveals their respiratory activity pattern during sleep [6] This indicates that respiratory-modulated inputs to these cells are not lost in sleep but become subthreshold because of a loss of state-dependent tonic excitatory inputs.

**Pontine, Mesencephalic, and Telencephalic Respiratory Neuronal Activities**

There are changes in the activities of pontine parabrachial respiratory-modulated neurons in NREM sleep. Increases and decreases are observed, but on average, decreases are minimal [7-10]. One study has found that respiratory activity in the pons is weak even in wakefulness and that with sleep there are few consistent changes [11]. The functional significance of these and other results showing state-related changes in the activity of respiratory cells in the amygdala, anterior cingulate gyrus, orbital frontal cortex, and mesencephalic central gray[12-14] is not known.

**Figure 17-1.** The activity of a sleep-sensitive respiratory neuron, and the locations of it and others like it. AMB, Nucleus ambiguus; CN, cochlear nucleus; FTL, lateral tegmental field; IO, inferior olive; P, pyramidal tract; RB, restiform body; SOL, solitary tract; 5 SP, nucleus of the spinal tract of V; 5 ST, spinal tract of V; 7, facial nucleus; 12 N, hypoglossal nerve. (From Orem J, Montplaisir J, Dement W: Changes in the activity of respiratory neurones during sleep. Brain Res 1974;82:309-315.)
Figure 17-2. The activity of an inspiratory cell during wakefulness and non-rapid eye movement (NREM) sleep. Action potentials and respiration (downward deflection signals inspiration) during wakefulness (A-1) and during NREM sleep (A-2). B. Cycle-triggered histogram of the activity. The omega-squared statistic (with a value of 0.913) expresses the high relationship of the activity to breathing. C and D. Although the numbers of discharges per breath were equivalent in wakefulness (C-1) and NREM sleep (C-2), the frequency of discharge (plotted as slope in D) was slightly, but significantly, lower in NREM sleep. This effect seemed related to the duration of inspiration and was observed for breaths of different durations within wakefulness, as well as between wakefulness and NREM sleep. D/N, Drowsiness/NREM sleep; E, expiration; I, inspiration; n.s., not significant; W/D, wakefulness/drowsiness. (Data from Orem J, Osorio I, Brooks E, et al: Activity of respiratory neurons during NREM sleep. J Neurophysiol 1985;54:1144-1156.)

State-Dependent Excitatory Inputs to Respiratory System That Decrease during NREM Sleep

Recordings from medullary respiratory neurons show that tonic inputs to them decrease in NREM sleep. Although all sources of these inputs are not known, the following have been implicated by various studies: (1) the brainstem reticular formation, (2) the collection of higher structures that exert behavioral control on the respiratory system, (3) the aminergic brainstem nuclei, and (4) the hypothalamic orexin-containing neurons. These systems all excite the respiratory system and may collectively constitute the wakefulness stimulus for breathing. Another major excitatory drive to breathe originates in central neurons sensitive to pH/CO₂. Although breathing remains under chemical control during NREM sleep, the contribution of some of these neurons may vary with the sleep-wake cycle.

Reticular Formation

Stimulation of the reticular formation excites the respiratory system [15-24] Midbrain reticular stimulation causes a reduction in the duration of expiration and an increased rate of rise and amplitude of phrenic nerve activity. It also causes an increase in laryngeal abductor activity [23], converting it from patterns characteristic of NREM sleep to those of wakefulness, and, like wakefulness, reticular stimulation preferentially facilitates the activity of the muscles of the upper airway rather than the muscles of the diaphragm [23]. Respiratory activation declines slowly after the cessation of reticular stimulation. These results imply that, during the transition from wakefulness to NREM sleep, the muscles of the upper airway may lose their tonic excitatory inputs to a greater extent than the diaphragm. This could lead to occlusive collapse of the airway during sleep. Other studies indicate that the neural systems driving upper airway motor neurons are more sensitive than those of phrenic motor neurons to the depressive effects of ethanol, diazepam, pentobarbital, halothane, hypocapnia, chemical stimuli, and thermal depression of neuronal activity near the ventral medullary surface [25-30]. Similarly, the systems controlling the upper airway muscles are more sensitive than those of the diaphragm to the excitatory effects of protriptyline, strychnine, cyanide, and doxapram.
There is a preferential activation of upper airway muscles on arousal to wakefulness in response to occlusion [31]. In cats, tracheal occlusions instituted during NREM sleep cause progressive augmentation of both laryngeal abductor and diaphragmatic activity, but increases in laryngeal activity exceed the increases in diaphragmatic activity. The greatest augmentations between one breath and the next were seen when the first occluded breath occurred in sleep and the next in wakefulness. This increase in activity at the transition from sleep to wakefulness was greater for the laryngeal abductors than for the diaphragm. Similarly, the progressive response of the genioglossus muscle to occlusion, as well as the response to hypoxia and hypercapnia, is quantitatively greater than the diaphragmatic response [32,33]. Other studies confirm the powerful effect of arousal on upper airway dilating activity and demonstrate that airway-dilating responses to occlusions and negative pressure during sleep are weak compared to those in wakefulness. It has been suggested that the weaker response in sleep may contribute to pharyngeal collapse in patients with obstructive sleep apnea. According to this idea, occlusion is the result of failed compensation in sleep. The idea is supported by demonstrations of greater genioglossal muscle activity (compensatory activity) in wakefulness in patients with obstructive sleep apnea than in normal subjects [35].

**Behavioral Control**

Behavioral control of breathing may be reflexive, as occurs in sneezing, coughing, vomiting, and eructation, or voluntary, as during speaking, breath holding, and playing a wind instrument. These behavioral acts require the integration of nonrespiratory inputs into circuits of the respiratory oscillator. Behavioral respiratory acts generally occur only in wakefulness. For example, mechanical and chemical stimulation of the larynx [36] and bronchopulmonary stimulation [37] cause coughing in wakefulness but not in sleep [38]. It is not known why these responses can occur in wakefulness but not sleep, but it may be that the readiness of behavioral control in wakefulness constitutes a stimulus for the respiratory system. The potential for behavioral controllers to affect breathing directly is clear in REM sleep, when they may act in association with dreams (see "Increased Respiratory Neuronal Activity in REM Sleep: Endogenous Excitatory Drives," later). In contrast, in NREM sleep, effects on breathing may be the result of the absence of behavioral control. This may be relevant to obstructive sleep apnea if what is lost in sleep is a wakefulness-dependent behavioral compensation for a high upper airway resistance.

The list of structures that can contribute to behavioral control of brainstem and spinal respiratory neurons includes structures from all levels of the neuraxis. The controls exerted by telencephalic structures, amygdala, and the central gray may occur in relation to emotional and volitional acts [39-41]. Many of these higher structures, such as the central nucleus of the amygdala, the anterior cingulate gyrus, the orbital frontal cortex, and the central gray, contain cells that have state-dependent respiratory activity [12-14]. Stimulation or inactivation of limbic [13,14], subcortical [42] and cerebellar [43] structures can influence the respiratory system. The site of behavioral control within the respiratory neuraxis varies depending on the behavioral act. It may be exerted directly on respiratory motor neurons, thus bypassing the central respiratory generator, or on medullary premotor and higher-order central respiratory neurons.

**Aminergic Systems**

Serotonin (5-hydroxytryptamine [5-HT])-containing and norepinephrine-containing neurons of the brainstem are an important source of sleep-related changes in breathing. Their activity decreases during sleep and they have extensive axonal projections to respiratory regions. Both central respiratory neurons and respiratory motor neurons have receptors for 5-HT and norepinephrine.
The activity of the neurons belonging to these two aminergic systems is highest during active wakefulness, declines during NREM sleep, and is minimal or absent during REM sleep [44-46]. Serotonin has excitatory effects on motor neurons, including those innervating the upper airway and respiratory pump muscles [47-51]. Antagonists of the excitatory effects of 5-HT reduce the spontaneous activity of XII motor neurons, thus showing the presence of an endogenous serotonergic excitatory drive [52,53]. Data from pharmacologic models of REM sleep (see "The Atonia of REM Sleep and the Carbachol Models," later) reveal that the suppression of XII motor neuron activity produced during the carbachol-induced REM sleep-like state is associated with silencing of medullary serotonergic cells and decrements in extracellular levels of 5-HT in the XII nucleus region [54,55] (Fig. 17-3). Likewise, norepinephrine levels are reduced in the XII motor nucleus region during the motor atonia elicited by electrical stimulation of the pontine REM sleep-triggering region [56].

Figure 17-3. Extracellular level of 5-hydroxytryptamine (5-HT) is reduced in the region of the hypoglossal (XII) motor nucleus during the rapid eye movement (REM) sleep-like atonia produced by pontine injection of carbachol. A, 5-HT level in microdialysis samples collected in successive 20-minute intervals from the XII nucleus in a decerebrate, paralyzed, and artificially ventilated cat. At the end of collection of sample 14, carbachol was injected into the pons and produced a suppression of (fictive) postural and respiratory activity. One hour and three samples later, pontine microinjection of atropine was made to terminate the atonia. The level of 5-HT decreased in association with the onset of the atonia and then increased when the atonia was terminated. The inset shows the location of the dialysis probe in this experiment. NTS, Nucleus tractus solitarius; XII, hypoglossal motor nucleus. B, Moving averages of the activities recorded from the XII nerve (Hypo) and a cervical nerve branch innervating dorsal neck muscles (C4) at the times of transition into and out of the carbachol-induced atonia. The bars attached to the marker arrows in A indicate the position of the records in B relative to the changes in 5-HT level shown in A. (Modified from Kubin L, Reignier C, Tojima H, et al: Changes in serotonin level in the hypoglossal nucleus region during the carbachol-induced atonia. Brain Res 1994;645:291-302, with permission.)

Like 5-HT, norepinephrine is predominantly excitatory to motor neurons, whereas its effect on medullary respiratory neurons is inhibitory [51,57-60]. The excitatory effects of 5-HT and norepinephrine on respiratory motor neurons may represent an important neurochemical substrate of the wakefulness stimulus. The magnitude of the excitatory effect of 5-HT on different groups of upper airway motor neurons varies [61], and the same is likely to be the case for norepinephrine. These differences may contribute to major differences in the magnitude of the suppressant effect of sleep among different upper airway muscles [62,63].
The activity of locus coeruleus neurons, which are often regarded as typical of norepinephrine-containing brainstem neurons, is more variable than that of the serotonergic neurons, with phasic bursts occurring in response to various peripheral stimuli, especially those perceived as novel or stressful [64]. Thus, in addition to its tonic effects related to the sleep-related decrements in noradrenergic cell activity, norepinephrine may have phasic effects on breathing during wakefulness, especially during states with emotional or sensory activation.

**Hypothalamic Orexin-Containing Neurons**

The hypothalamus exerts control over the respiratory system in relation to temperature regulation, metabolism, and motor activation. These original findings were recently refined by the discovery of a unique group of hypothalamic neurons containing excitatory peptides, orexins (also known as hypocretins) [65]. These cells, located exclusively in the perifornical region of the posterior hypothalamus, have widespread axonal projections that target all known wakefulness-related neuronal groups (serotonergic, noradrenergic, histaminergic, and cholinergic), as well as motor neurons and sympathetic preganglionic neurons [66-71]. The activity of orexin neurons and orexin release are maximal during wakefulness, especially in relation to motor activation [72-75]. Thus, orexins have the potential to enhance the respiratory output in a manner consistent with the concept of the wakefulness stimulus for breathing by their direct actions on motor neurons and indirectly by stimulation of the activity of brainstem aminergic neurons.

**Central pH/CO₂-Sensitive Sites**

The level of O₂, CO₂, and acidity of the cerebrospinal fluid and blood are the major determinants of the drive to breathe. The chemical control of breathing is maintained during sleep [76-78]. However, end-tidal CO₂ increases in NREM sleep, and, in REM sleep, as in wakefulness, there are periods during which respiratory effort varies independently of the chemical drive.

The ventral medullary surface has three chemosensitive zones. The use of topical anesthetic agents or cold blockade of these zones eliminates respiratory responses to changes in the pH of the cerebrospinal fluid and reduces respiratory effort, but other regions of the medullary reticular formation also contain cells sensitive to extracellular pH and CO₂ [79,80]. In vitro studies reveal that cells located near the ventral medullary surface, cells in the nucleus of the solitary tract, and serotonergic and noradrenergic brainstem neurons have pH/CO₂ sensitivity [81-84]. Also, ventral medullary cells, which may be involved in the generation of respiratory rhythm in the in vitro neonatal rat brainstem, are excited by a decrease in pH [85]. The connectivity with central respiratory neurons and excitability changes with the sleep-wake cycle, if any, remain to be determined for most known putative central chemosensors. Although the activity of aminergic cells is reduced during sleep, it is not known whether selective silencing of these neurons attenuates central respiratory chemosensitivity.

**RESPIRATORY ACTIVITY IN RAPID EYE MOVEMENT SLEEP**

**Characteristics of Breathing in REM Sleep**

In REM sleep, the frequency of breathing increases, tidal volumes decrease, and minute ventilation decreases [1,2]. In the cat, end-tidal CO₂ decreases, signifying hyperventilation, which is associated with a decrease in the rate of metabolism. In humans, however, metabolic rate increases in REM sleep, presumably because of a large increase in cerebral metabolism. The average peak inspiratory airflow rates are about 15% less than in NREM sleep or wakefulness. Ventilatory responses to
chemical stimuli and other respiratory reflexes are impaired during phasic REM activity [2], and laryngeal and diaphragmatic responses to occlusions are inconsistent and variable [31]. In cats [86] and adolescent humans [87], but not in rats [88] atonia of the intercostal muscles reduces or eliminates costal breathing in REM sleep. Many upper airway respiratory muscles are also atonic or hypotonic [23,62]. There is a decrease in postinspiratory diaphragmatic activity in REM sleep [89]. Both central apneas and hyperpneas occur as the extremes of very irregular breathing in REM sleep. The variable breathing pattern of REM sleep does not depend on variations in chemoreceptor [90], vagal [91-93], or thoracic [93,94] afferent activity.

Obstructive episodes are the longest, and blood oxygen desaturations most severe, during REM sleep in patients with obstructive sleep apnea. Similarly, oxygen desaturations are generally most severe during REM sleep in patients with lung disease.

**Increased Respiratory Neuronal Activity in REM Sleep: Endogenous Excitatory Drives**

Many results support the existence of excitatory drives to the respiratory system in REM sleep and indicate that these drives are of central origin. The first description of REM sleep noted the rapid breathing in that state, which has been confirmed many times since then [1,2]. In addition, with few exceptions, cells throughout the nervous system are more active in REM sleep than in NREM sleep. This generalized activation in REM sleep also includes parts of the respiratory system. Medullary respiratory neurons activated in REM sleep include augmenting and late inspiratory cells [95] (Fig. 17-4) and some augmenting expiratory cells, which are active even during the very short expirations that occur during periods of irregular and rapid breathing [96]. Like medullary respiratory neurons, many, but not all, pontine parabrachial respiratory neurons show prominent increases in activity during REM sleep [8]. Similar changes occur in non-respiratory-modulated cells in this region [8,10].

*Figure 17-4. Increased and advanced activity of a late inspiratory neuron in rapid eye movement (REM) sleep. A. The cell discharges during the last part of inspiration in wakefulness and non-rapid eye movement (NREM) sleep but is active throughout inspiration during REM sleep. Traces from top to bottom for each section are the action potentials, intratracheal pressure (inspiration is signaled by an upward deflection), and the electroencephalogram. B. Cycle-triggered histograms constructed from 50 breaths in wakefulness/NREM sleep (W-NREM) and REM sleep. E, expiration. (Modified from Orem J: The activity of late respiratory cells during the behavioral inhibition of inspiration. Brain Res 1988;458:224-230.)*
The excitation of respiratory neurons in REM sleep is apparently the result of endogenous processes. Excitation of respiratory neurons and respiratory pump muscles occurs during REM sleep even when mechanical variables (e.g., airway resistance, chest wall compliance) are removed or held constant by mechanical ventilation [97] (Fig. 17-5). This indicates that the excitatory drive has an internal source—an idea supported also by reported positive relationships between activity of some respiratory neurons and phasic REM sleep activity [98] and between the rate of breathing in REM sleep and the activity of REM sleep-specific neurons [99]. Little is known about the characteristics or sources of this endogenous excitatory drive. During apnea caused by mechanical hyperventilation, the drive is seen as the emergence of activity in respiratory muscles and neurons out of the background apnea (see Fig. 17-5). It has been suggested that the drive may account for the rapid and irregular breathing in this state [97]. The function of the drive is not known, but it may be that it produces the first respiratory movements in utero.

There has been the long-standing idea that the endogenous drive during REM sleep is related to behavioral mechanisms that are activated during the dream. Evidence of this comes from studies in which the dreamer is aroused and the pattern of breathing is related to the reported content of the dream. Just as eye movements have been related to a recalled dream involving visual scanning, the pattern of breathing might be appropriate to the content of the dream. One study found that the probability of a dream report and the vividness, emotional content, and amount of physical activity in the dream were higher when breathing rates were high and variable. They found also that specific respiratory content was twice as likely when the subject was awakened following apnea as compared to following other respiratory patterns [100]. Other authors found that highly variable rates of breathing were associated with reports of the sleeper having little active participation in the dream and of there being little physical aggression in it. However, large-amplitude breaths were associated with the sleeper having intense active participation in the dream, and variability in amplitude was associated with dreams containing a high degree of physical aggression [101]. These results support the idea that breathing patterns may parallel the content of the dream.

Other literature is less convincing. Hauri and Van de Castle [102] examined heart rate, the galvanic skin response, and breathing in relation to dream emotionality, physical activity in the dream, and dream intensity. Respiration rate was related to emotionality and to dream intensity, but these authors found that there was no significant relationship between physical activity in the dream and the rate of breathing.
Others have argued that the irregular pattern of breathing in REM sleep is a byproduct of endogenous REM-sleep processes and does not have its origin in the content of the dream. According to this theory, there are REM-sleep processes that depend on the pons and that affect the entire nervous system. In support of this idea, discharge rates of medullary respiratory neurons in REM sleep are related positively to the frequency of ponto-geniculo-occipital (PGO) waves [98], and the discharge rates of REM-specific cells are positively correlated with the rate of breathing [99]. Furthermore, brief inhibitions of diaphragmatic activity (lasting in the order of 80 msec) are associated with PGO waves [103]. These results support the idea that REM-specific processes affect central respiratory drive, but they do not refute the idea that they cause also the dream that then affects the respiratory system.

The endogenous drive may be clinically important. At times, it may be so intense that it causes a breathing pattern that can be characterized as respiratory fibrillation. Patients with lung disease desaturate in REM sleep and, in particular, during periods with intense rapid eye movements.

The Atonia of REM Sleep and the Carbachol Models

Intercostal and some accessory respiratory muscles innervated by spinal and cranial motor neurons are atonic or hypotonic in REM sleep. Patients with narrow and collapsible upper airways may experience upper airway obstructions, and those with lung disease may become hypoxemic because of the atonia. The loss of intercostal and accessory (scaleni and sternocleidomastoid) muscle activity may lead to severe oxygen desaturation in a patient whose diaphragm is compromised or ineffective. State-specific inhibitory actions and disfacilitation (i.e., withdrawal of excitatory inputs) contribute to the atonia. We review here the latter mechanism and the work in the carbachol models that led to its understanding.

Microinjections of agonists that stimulate muscarinic cholinergic receptors (e.g., carbachol, bethanechol) into the dorsal pontine reticular formation are used in experimental animals to induce a REM sleep-like state (see George et al. [104], Baghdoyan et al. [105] and Vanni-Mercier et al. [106]). Individual phenomena of REM sleep, such as postural atonia, hippocampal theta rhythm, and PGO waves, can be elicited this way from wide areas of the pons and midbrain [106-110] but the site at which carbachol produces a state that best corresponds to natural REM sleep is discrete and localized in the dorsomedial pontine tegmentum [106,110-113]. Increases in acetylcholine release occur during natural REM sleep in this region [114].

The ability to trigger a REM sleep-like state by pontine injections of muscarinic cholinergic receptor agonists has been used to study the mechanisms of respiratory changes characteristic of REM sleep in chronically instrumented cats [9,10,115,116], decerebrate cats [117-119], decerebrate rats [109] and urethane-anesthetized rats [110,113,120]. Following pontine carbachol injections, medullary serotonergic cells are silenced [55] as they are in natural REM sleep, and so are noradrenergic neurons of the locus coeruleus and the A5 group [113,121] the latter being particularly important for cardiorespiratory regulation (Fig. 17-6). Also as in REM sleep, pharyngeal motor neurons are profoundly suppressed, whereas phrenic and laryngeal motor neurons are relatively unaffected [117-119], and the activity of medullary inspiratory neurons is minimally suppressed or even increased [120,122]. One notable difference is that the respiratory rate is reduced and regular in carbachol models, whereas it may be greatly accelerated during natural REM sleep.
Noradrenergic cells of the pontine A5 group are silenced during the rapid eye movement (REM) sleep-like episodes elicited by pontine microinjections of carbachol in urethane-anesthetized, paralyzed and artificially ventilated rats. Silencing of these cells, which play an important role in cardiorespiratory regulation, shows that a withdrawal of noradrenergic influences may contribute to respiratory changes characteristic of REM sleep. The REM sleep-like episode is marked by a simultaneous appearance of the hippocampal theta rhythm (top trace, with 5-second insets showing portions of the trace at an expanded time scale) and a profound suppression of hypoglossal nerve activity (bottom trace, showing the moving average of the signal). The cell stops firing and then resumes activity just prior to the reappearance of hypoglossal nerve activity. (From Fenik V, Marchenko V, Janssen P, et al: A5 cells are silenced when REM sleep-like signs are elicited by pontine carbachol. J Appl Physiol 2002;93:1448-1456.)

To explain the absence of irregularities in the respiratory rate, Kimura et al. [117] proposed that they may be caused, at least in part, by rapidly changing levels of endogenous acetylcholine that are likely to occur during natural REM sleep but cannot be adequately mimicked by pontine carbachol microinjections. This, however, does not explain the large respiratory rate accelerations observed at times during natural REM sleep. Such respiratory rate increases must be mediated by pathways and mechanisms other than those activated by carbachol injections into the dorsal pontine tegmentum, whereas cholinergic stimulation within the dorsal pontine reticular formation appears to activate those pathways that act to reduce the respiratory rate.

Carbachol models helped elucidate the mechanisms of REM sleep-related upper airway hypotonia. In the decerebrate cat model, the atonia of XII motor neurons is not caused by inhibitory amino acids such as glycine or gamma-aminobutyric acid (GABA) [123]. Instead, a loss of serotonergic excitatory influences that impinge on motor neurons makes a major, albeit only partial, contribution to the observed decrements in their activity [54,55,124]. Thus, although inhibitory synaptic events occur in XII motor neurons in carbachol models of REM sleep [125], their contribution to the suppression of motor activity appears to be small.

A major role of the withdrawal of aminergic excitation in the suppression of XII motoneuronal activity during REM sleep is further supported by studies in the urethane-anesthetized rat carbachol model. In this model, a combined antagonism of noradrenergic, serotonergic, GABAergic, and glycinergeric receptors located in the XII nucleus region (by prazosin, methysergide, bicuculline, and strychnine, respectively) reversibly abolished the carbachol-induced, REM sleep-like decrements of XII motoneuronal activity [126]. It was then determined that neither the GABA_A receptor antagonist, bicuculline, nor the glycinergeric receptor antagonist, strychnine, was required to achieve this effect, whereas the combined antagonism of serotonergic and noradrenergic receptors was both necessary.
and sufficient to abolish the REM sleep-like depression of XII nerve activity [127]. These results suggest that the suppression of XII motoneuronal activity during REM sleep is primarily caused by a simultaneous withdrawal of serotonergic and noradrenergic excitation.

The results from the carbachol models are supported by recordings from upper airway muscles innervated by XII motor neurons in chronically instrumented, behaving animals. For example, antagonism of serotonergic excitatory effects during wakefulness reduced the activity of geniohyoid and sternohyoid muscles in the English bulldog, which is a natural model of obstructive sleep apnea [53], and perfusion of the XII nucleus with 5-HT attenuated the suppression of genioglossal muscle activity during sleep in rats [128]. The applicability of these findings to the behavior of other upper airway motor neurons during natural REM sleep remains to be determined.

Animal studies have suggested that obstructive sleep apnea could be alleviated by increasing aminergic excitation of upper airway motor neurons during sleep. However, most clinical trials based on this hypothesis yielded weak results or proved ineffective. One reason for such an unsatisfactory outcome may be that most trials have not been designed to target appropriate combinations of aminergic receptors. The main receptors mediating the excitatory effects of 5-HT and norepinephrine in upper airway motor neurons have now been identified as type 5-HT<sub>2A</sub> and alpha<sub>1B</sub>-adrenergic receptors, respectively [129-132]. Interestingly, in one study in the English bulldog, the results of a systemic treatment that had a partial preference towards 5-HT<sub>2</sub> receptors were more promising than in other trials [133].

Nevertheless, the prospects for pharmacotherapy for obstructive sleep apnea are complicated by the fact that the same excitatory aminergic receptors that mediate wakefulness-related excitatory effects in upper airway motor neurons are also present in many other brain regions and subserve many other functions, including sleep. Thus, targeting selected combinations of receptors may be insufficient, and a successful therapeutic intervention may require new methods of selective drug delivery to the desired sites of their action.

**Clinical Pearl**
There is a wakefulness stimulus for breathing that, when lost in NREM sleep, allows occlusive collapse of the extrathoracic airway in patients with obstructive sleep apnea. This stimulus may involve multiple systems within the brain, including those that are serotonergic and noradrenergic. In REM sleep, there are both excitatory and suppressant influences on the respiratory system. Excitatory influences may cause rapid, irregular breathing and hypoventilation that, in patients with lung disease, leads to oxygen desaturation. Suppressant influences cause atonia of intercostal and accessory respiratory muscles, which in patients with lung disease or compromised upper airways can lead to hypoxemia and upper airway obstructions. In the carbachol model of REM sleep, suppression of the activity of hypoglossal motor neurons results primarily from the withdrawal of excitation mediated by serotonin and norepinephrine.

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