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UPPER AIRWAY MOTOR CONTROL

Although the upper airway of children with obstructive sleep apnea (OSA) is more collapsible than in control subjects, most children with OSA experience prolonged periods of stable breathing at night. Both anatomic factors and the ability to mount a robust neuromuscular compensatory response to loading are important to the pathogenesis of OSA, with the latter particularly relevant to the ability to restore adequate airflow and sustain stable breathing. Accordingly, Katz and colleagues (1) determined the neuromuscular compensatory pharyngeal dilator muscle responses to airway collapsing pressures by recording genioglossus muscle activity in normal, healthy, sleeping children. The subjects (age range, 9.1–16.4 yr; mean, 11.9 yr; body mass index in the 70th percentile) were placed on +3 cm H_2O of continuous positive airway pressure (CPAP), and mask pressure was then varied during sleep to a minimum of −22 cm H_2O, with pressures applied for five consecutive breaths and returned to baseline for 30 seconds between interventions. There was wide intersubject variability in the magnitude of the genioglossus muscle responses to airway collapsing pressures in sleep. Importantly, the prominent increases in genioglossus activity in some subjects were associated with increased airflow during loading, increased respiratory rate, and decreased airflow resistance, and in some cases, recovery of normal ventilation without evidence of electrocortical arousal. The authors speculate that this robust pharyngeal dilator muscle response to loading may account for the periods of stable breathing during sleep in some children with OSA, and that the severity of sleep apnea for a given child is influenced by the balance between intrinsic anatomic factors (airway size and stiffness), neuromuscular compensatory responses to loading, and arousal threshold.

The concept of a tonic drive activating respiratory muscles in wakefulness, but not sleep, has been an important and enduring notion in respiratory medicine, not least because it is the root mechanism to understand the effects of sleep on breathing and pathogenesis of sleep-related breathing disorders such as OSA. However, a neurotransmitter substrate that mediates activation of respiratory muscle across sleep–wake states had not been identified. Chan and colleagues (2) determined the role of endogenous α_1-adrenergic receptor mechanisms at the hypoglossal motor nucleus in modulating genioglossus muscle activity in rats. The rats were implanted with electrodes to record genioglossus and diaphragm activities across sleep–wake states. Microdialysis probes in the hypoglossal motor nucleus were used to perfuse artificial cerebrospinal fluid (control) and terazosin (α_1-receptor antagonist). The results showed that an endogenous α_1-receptor–mediated excitatory drive contributes significantly to the level of genioglossus muscle activity in wakefulness and non–rapid eye movement (non-REM) sleep, with this effect withdrawn in REM sleep. This finding is significant because since the first clinical description of OSA more than 35 years ago, this is the first identification of a neural drive contributing to the sleep-state–dependent activity of a muscle that is central to this disorder. It is also relevant that, using this same model, endogenous serotonin inputs play a relatively minor role in modulating genioglossus activity across natural sleep–wake states (3, 4). Furthermore, the role of endogenous serotonin in the control of genioglossus activity may even have been overemphasized in previous studies in reduced (anesthetized, decerebrate, or *in vitro*) preparations because of deafferentation and vagotomy (3, 4).

Previous studies modulating pharyngeal muscle activity with pharmacologic approaches have all targeted membrane receptors on pharyngeal motoneurons. Whether modulation of intracellular pathways can increase pharyngeal muscle activity across sleep–wake states, however, had not been investigated but is relevant to pharmacologic treatments of OSA as it may allow for sustained pharyngeal motoneuron activation in sleep despite changes in extracellular neurotransmitters. Using rats instrumented for manipulation of the hypoglossal motor nucleus while recording genioglossus and diaphragm muscle activities, Aoki and coworkers (5) showed that modulation of the cyclic adenosine-3′-5′-monophosphate (cAMP)–protein kinase A pathway at the hypoglossal motor nucleus increased genioglossus muscle activity in wakefulness and non-REM sleep but not in REM sleep. This result emphasizes the consistent finding that REM sleep recruits powerful neural mechanisms that can overcome excitatory motor responses and powerfully suppress genioglossus activity (2). The study also demonstrated a new mechanism in respiratory motor control by which cyclic guanosine-3′-5′-monophosphate (cGMP) at the hypoglossal motor nucleus abolished the normally potent excitatory responses to locally applied serotonin and α_1-receptor agonists, whereas ionotropic responses to non-*N*-methyl-D-aspartate (non-NMDA) glutamate receptor agonists were preserved. This study suggests that targeting intracellular mechanisms may open up potential new pharmacological strategies that increase pharyngeal muscle activity in sleep relevant to OSA. The consideration of such strategies, however, has to be tempered by possible interactions between intracellular pathways—for example, modulation by cGMP of the otherwise strong excitatory responses to applied serotonin and α_1-receptor agonists.

UPPER AIRWAY ANATOMY

Development and validation of techniques to quantitatively image the upper airway are important to investigate the pathophysiology

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of OSA, and to evaluate potential treatments. Armstrong and colleagues (6) used an endoscopic technique to image upper airway size and shape in real time using optical coherence tomography. The optical probe is placed inside a transparent catheter (3.0 mm outside diameter), which is inserted through the nares; subsequent movement of the probe does not stimulate or irritate the airway mucosa because the probe is inside the catheter. Rotation of the probe tip at 1.25 Hz provides a 360° view of the upper airway, with motorized movement of the probe allowing images to be obtained from the nasopharynx to the laryngopharynx. The mean differences in upper airway dimensions between measurements obtained with this method and computed tomography were small (0.7 and 0.4 mm for anteroposterior and lateral diameters, respectively, with limits of agreement of −3.5 to 4.8 mm and −6.8 to 7.6 mm). The correlation coefficient for measurements of airway cross-sectional area using optical coherence versus computed tomography was 0.89. Measurements of airway compliance with application of CPAP, and images of the sites of upper airway closure in a sleeping patient with OSA, were also obtained. The authors conclude that this application of optical coherence tomography can provide quantitative measurements of upper airway size and shape with minimal invasiveness and few of the disadvantages of other imaging techniques, while also allowing study over prolonged periods of time, such as during wakefulness and sleep.

Because there is some evidence of genetic risk factors for sleep apnea, Schwab and coworkers (7) hypothesized that anatomic risk factors for OSA would demonstrate family aggregation. The authors performed volumetric (three-dimensional) magnetic resonance imaging of the upper airway in 55 probands with OSA and their siblings of the same sex, and 55 neighborhood control subjects and their siblings also of the same sex, all matched for age and ethnicity. The volumes of the lateral pharyngeal walls, tongue, and total upper airway soft tissue all showed significant levels of heritability. The degree of heritability was assessed as the percentage of total variance around the mean of the phenotype measure that was explained by systematic variance between families. Heritability was between 36 and 38% for these measures of upper airway soft tissue and was highly statistically significant (each $p \leq 0.001$) after adjusting for sex, ethnicity, age, visceral neck fat, and craniofacial dimensions (lateral and anteroposterior head measurements). Because Schwab and colleagues have previously demonstrated that increased volumes of these soft tissue structures pose significantly increased risk for OSA (8), the finding that these same anatomic risk factors also show family aggregation and heritability is an important observation. Analysis also showed that, in individuals without significant sleep apnea, increased upper airway soft tissue volume was associated with having a family member who had OSA. This latter result was taken to suggest that the increased volume of upper airway soft tissue structures likely precedes the onset of the clinical disorder rather than being a consequence of OSA (i.e., as may occur with remodeling due to tissue trauma, edema, or inflammation), a finding that is also relevant to the natural history of OSA.

Obesity is associated with upper airway narrowing in humans and is a known risk factor for OSA. Because the Zucker rat is an established model of obesity, Brennick and colleagues (9) measured upper airway size in anesthetized and spontaneously breathing obese Zucker rats and lean littermate control rats using respiratory-gated magnetic resonance imaging. Noninvasive tissue tagging was also performed to provide an index of pharyngeal wall tissue strain. Obese Zucker rats had narrower upper airways compared with lean littermates, and showed smaller increases in airway size during inspiration. Despite these differences in airway size during breathing, lean and obese rats showed similar values of pharyngeal wall tissue strain. The authors suggest that obesity imposes a mechanical load on the upper airway that prevents a normal airway opening response to a given change in pharyngeal wall tissue strain in the obese rats. Overall, therefore, this study provides support for the concept that obesity, a major predictor of OSA, compromises upper airway size and function.

NEUROMODULATION AND ADVANCES IN THE CONTROL OF BREATHING

Respiratory depression can occur in a variety of clinical circumstances, such as after pharmacological manipulation (e.g., opiate administration). Respiratory depression can also vary as a function of age (e.g., apnea of prematurity, and central and obstructive apneas in adults). Ampakines constitute a group of molecules that modulate the class of non-NMDA receptors that are activated by α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA). Non-NMDA receptors are importantly involved in the central nervous system modulation of respiratory drive and transmission. Accordingly, Ren and colleagues (10) investigated whether the ampakine CX546 would increase the amplitude and frequency of respiratory motor activity across various stages of development in rats (fetal, perinatal, neonatal, juvenile, and adult), and whether this drug could also reverse μ-opioid– and barbiturate-induced respiratory depression. The authors used an array of complementary experimental preparations, which included *in vitro* models from perinatal and neonatal rats, and *in vivo* responses in intact neonates and adults. The former preparations allowed the effects of CX546 on components of the brainstem respiratory network to be determined, whereas the latter allowed investigation of the effects of systemically applied CX546 on overall lung ventilation as estimated by whole body plethysmography. CX546 reversed respiratory depression induced by low external K^+ concentration and application of μ-opioid receptor agonists *in vitro*, and also reversed both opioid- and barbiturate-induced respiratory depression *in vivo*. Importantly, this reversal of respiratory depression after CX546 in the presence of opiates occurred without any effect on analgesia, as assessed by the pedal withdrawal reflex in response to thermal stress (i.e., the clinically desirable analgesic actions of the opiate drugs were unaffected). Interestingly, application of CX546 by itself had no effect on baseline respiratory activity in animals older than Postnatal Day 0. This latter result also suggested that, from this age, the stimulating effects of CX546 on breathing were confined to situations in which respiratory activity was first suppressed. The authors conclude that ampakines may provide a novel method of counteracting respiratory depression in rodents, which may also prove useful in humans after appropriate further testing.

Seminal *in vitro* studies have identified a small region of the ventral lateral medulla termed the "pre–Bötzinger complex" as critical for the generation of basic respiratory rhythm in mammals (11). However, recent studies now implicate a second key site located in the parafacial respiratory group that overlaps the retrotrapezoid nucleus (12). Two articles discuss the evidence for which is the primary site of respiratory rhythm generation in mammals (13, 14), a significant topic given the fundamental importance of the genesis of breathing, and which provoked debate in the field (15). Specific interventions can also exploit the different pharmacological properties of pre–Bötzinger complex and parafacial respiratory group neurons to determine effects on their respiratory motor outputs. Although μ-opioid receptor agonists inhibit pre–Bötzinger complex neurons and slow respiratory rate, there is no effect on rhythmic activity of preinspiratory neurons of the parafacial respiratory group, with this