Differential effects of clonidine on upper airway abductor and adductor muscle activity in awake goats

O’Halloran, K. D., J. K. Herman, and G. E. Bisgard. Differential effects of clonidine on upper airway abductor and adductor muscle activity in awake goats. J. Appl. Physiol. 87(2): 590–597, 1999.—The purpose of this study was to determine the extent to which $\alpha_2$-adrenoceptor ($\alpha_2$-AR) pathways affect the central motor output to upper airway muscles that regulate airflow. Electromyogram (EMG) measurements were made from posterior cricoarytenoid (PCA), cricothyroid (CT), thyroarytenoid (TA), and middle (MPC) and inferior (IPC) pharyngeal constrictor muscles in awake standing goats. Systemic administration of the $\alpha_2$-AR agonist clonidine induced a highly dysrhythmic pattern of ventilation in all animals that was characterized by alternating episodes of tachypnea and slow irregular breathing patterns, including prolonged and variable expiratory time intervals. Periods of apnea were commonly observed. Dysrhythmic ventilatory patterns induced by clonidine were associated with differential recruitment of upper airway muscles, $\alpha_2$-AR stimulation preferentially decreased the activity of the PCA, CT, and IPC muscles while increasing TA and MPC EMG activities. Clonidine-induced apneas were associated with continuous tonic activation of laryngeal (TA) and pharyngeal (MPC) adductors, leading to airway closure and arterial oxygen desaturation. Tonic activation of the TA and MPC muscles was interrupted only during the first inspiratory efforts after central apnea. Laryngeal abductor, diaphragm, and transversus abdominis EMG activities were completely silenced during apneic events. Ventilatory and EMG effects were reversed by selective $\alpha_2$-AR blockade with SKF-86466. The results demonstrate that $\alpha_2$-AR pathways are important modulators of central respiratory motor outputs to the upper airway muscles.

METHODS

Animals. Studies were conducted on 10 adult female or castrated male goats [58 ± 9 (SE) kg body wt] of mixed breed. The surgical and experimental protocols were approved by the Animal Care Committee of the University of Wisconsin-Madison.

Surgical preparation. With use of aseptic techniques, while under general anesthesia (induction with 15–20 mg/kg intravenous [iv] thiopental sodium and maintenance with 1% halothane-40% nitrous oxide-balance oxygen) each goat was prepared with a unilateral common carotid artery translocation to a subcutaneous position to facilitate the insertion of an arterial catheter at a later time. At this time, or during a second surgical procedure, EMG wire electrodes were inserted into the following laryngeal and pharyngeal abductor and adductor muscles: posterior cricoarytenoid (PCA; n = 8), cricothyroid (CT; n = 3), thyroarytenoid (TA; n = 5), middle pharyngeal constrictor (MPC; n = 7), and inferior pharyngeal constrictor (IPC; n = 6). All goats received intramuscular antibiotic (penicillin G) for 3 days postoperatively to control infection.

Bipolar, Teflon-insulated stainless steel EMG wire electrodes (model AS 637, Cooner Wire, Chatsworth, CA) were implanted unilaterally in each muscle. All EMG electrodes were sewn in place under direct visualization and fixed securely with a knot. A single lead sewn subcutaneously served as a common reference electrode. The larynx was exposed by a ventral midline incision in the neck. For the TA muscle, a small “C”-shaped opening was made on the lateral surface of the thyroid cartilage to allow direct access to the TA muscle as previously described (19). The cartilage was subsequently closed with a single suture. The PCA muscle was approached by lateral rotation of the larynx, and electrodes determined the extent to which $\alpha_2$-AR agonists in clinical medicine as anesthetics, analgesics, sedatives, and antihypertensive agents (36); however, relatively little is known about the role of $\alpha_2$-ARs in the control of breathing. Previous studies from our laboratory have demonstrated that systemic administration of $\alpha_2$-AR agonists, such as clonidine and guanabenz, causes profound breathing instabilities in awake and anesthetized goats (19–21). In awake goats, $\alpha_2$-AR agonists induce dysrhythmic ventilatory patterns that are characterized by alternating episodes of tachypnea and respiratory depression [prolonged and variable expiratory time (TE)], including prolonged apneas (19, 21).

$\alpha_2$-ADRENOCEPTOR (2-AR) agonists are widely used in veterinary medicine. Furthermore, clonidine causes apnea in fetal lambs (6), and hypoxia-induced fetal apnea is blocked by $\alpha_2$-AR blockade (7). Dysrhythmic breathing induced by clonidine in awake goats is accompanied by differential recruitment of respiratory “pump” muscles (19). Prolonged TE intervals and central apneas induced by $\alpha_2$-AR agonists in the goat are associated with expiratory laryngeal motoneuronal activation (19, 20), suggesting active glottal closure. These findings are entirely consistent with observations of laryngeal closure during mechanically induced or spontaneous central apneas in animals (18, 24, 25, 34) and human subjects (22, 26, 37). We hypothesized that differential recruitment of upper airway muscles important in the control of upper airway patency may be involved in the development of airway obstruction associated with clonidine administration (19, 20). The extent to which $\alpha_2$-AR pathways affect the central motor output to upper airway muscles that regulate airflow is unclear. Therefore, we examined the effects of clonidine on electromyogram (EMG) activities of upper airway abductor (dilator) and adductor (constrictor) muscles in awake adult goats.

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were inserted via a small incision in the IPC over the posterior margin of the thyroid cartilage. The MPC and IPC muscles were identified by gently lifting and rotating the larynx, and electrodes were inserted under direct visualization in the main body of each muscle with care taken to avoid electrode placement in underlying neighboring muscles or damage to the nerve supply in this region. Electrodes were also placed in the main body of the CT muscle. In addition, in some animals, EMG electrodes were placed in one inspiratory pump muscle, the costal diaphragm (Dia), and, in one expiratory pump muscle, the transversus abdominis (Abd) by using established techniques (42). The EMG leads were sutured to nearby fascia to relieve any strain on the electrodes, and all leads were tunneled subcutaneously and exteriorized through the skin at common exit sites in the neck and chest to facilitate access for recording on the day of the experiment. When not in use, the leads were protected in elastic bandage wraps that were changed regularly.

After surgical procedures, during a minimum 2-wk recovery period, each goat was trained to stand quietly in a stanchion while wearing a tight-fitting face mask. One day before the study, an arterial catheter was inserted into the elevated carotid artery for anaerobic collection of blood samples for blood-gas analysis and for arterial blood pressure measurement. A catheter was also placed in an external jugular vein for intravenous drug administration. All catheters were flushed with heparinized saline and closed until the day of the experiment.

Measurements. EMG signals were amplified (model BMA 831, CWE, Arlington, PA, or model 1700, A-M Systems, Everett, WA), filtered (band pass 0.01–10.0 kHz), and recorded on FM tape (with inspired tidal volume) by using a modified videocassette recorder (models 3000A and 5001, Vetter Digital, Rebersburg, PA) for off-line analysis. Individual signals were visualized on an oscilloscope (model 5111, Tektronix, Beaverton, OR) and fed to an audiomonitor (model AM 7, Grass, Quincy, MA). The taped EMG signals were replayed through an analog-to-digital converter and processed by using the WINDAQ data-acquisition system (DATAQ Instruments, Akron, OH).

Ventilatory data were collected while the goats were wearing a tight-fitting face mask equipped with a low-resistance, one-way breathing valve (model 2700, Hans Rudolph, Kansas City, MO). Inspired gases were delivered to the goat via flexible tubing (3-cm ID). Expired gases were collected in a spirometer (120 liters) from which steady-state expired minute ventilation could be measured during the experiment. Inspired airflow was measured by using a pneumotachometer (model T-2, Fleisch, Zurich, Switzerland) that was electronically integrated to give inspired tidal volume. An O2 analyzer (model S-3A, Applied Electrochemistry, Sunnyvale, CA) was used to measure O2 concentration in the inspired gases. Inspired and expired CO2 levels were measured from a port in the face mask by using a CO2 analyzer (PM-20R, Cavitron Anarad PM-20R, Paramus, NJ).

A six-channel polygraph recorder (model 5/6H, Gilson, Middleton, WI) was used to record end-tidal CO2, systemic arterial blood pressure, inspired flow, inspired tidal volume, and minute ventilation. The analog signal outputs were digitized and stored on a personal computer for later analysis. Arterial blood samples were analyzed for arterial pH, Pco2 and PO2 (pHb, PaO2, and PaO2, respectively) by using a blood-gas analyzer (model ABL 500, Radiometer, Copenhagen, Denmark). A thermistor probe in the rectum was used for measurement of body temperature for blood-gas temperature correction.

Fiber-optic endoscopy. To further characterize the suspected changes in airway caliber induced by α2-AR stimulation (see RESULTS), fiber-optic endoscopy of the upper airway was performed in one additional goat. Several weeks before the study the animal was surgically prepared with a chronic tracheostomy below the larynx at the level of the eighth tracheal ring. On the day of the study, a flexible pediatric fiber-optic endoscope (model BF-4510, Olympus) attached to a video camera (models CLV-10 and OTV-F2, Olympus) was passed transnasally after local anesthesia and lubrication (2% lidocaine jelly) of one nasal passage. The tip of the scope was positioned at the caudal end of the soft palate. The scope was marked at the point of entry through a face mask worn by the goat and was secured in position with adhesive tape and silicone rubber foam. One hour was allowed for complete recovery from local anesthesia before any data were collected. Recordings began once a stable breathing pattern was established and respiratory movements of the glottis appeared to be reproducible. The fiber-optic image of the upper airway was recorded on videocassette recorder together with a time code. Ventilatory data were digitized and stored together with the time code on a personal computer for off-line analysis.

Protocol. The animals remained standing throughout the entire experimental period. After the goat assumed a comfortable standing position, the animal was loosely restrained with the head and neck in a normal resting position. Only ventilatory and EMG data collected in this position were included in the analyses in an attempt to minimize changes in EMG activity that were related to postural changes. After the face mask was placed on the goat, 30 min were allowed for baseline control measurements with the goat breathing room air. Once a stable ventilatory baseline was established and several arterial blood-gas samples were taken, the α2-AR agonist clonidine was administered by bolus injection via the jugular catheter. Clonidine was administered in cumulative doses (0.5–2.0 µg/kg; 5–11 µg/kg final cumulative dose) every 5–10 min to achieve maximal ventilatory effects without eliciting excessive sedation (21). At the end of the experiment, the selective α2-AR antagonist SKF-86466 was administered (50–100 µg/kg iv), and ventilatory, EMG, and blood-gas data were collected. EMG activities recorded during swallowing and fiber-optic endoscopy breaths were eliminated. The protocol was completed in all animals. The CT muscle was chosen only in later experiments. There were no technical difficulties associated with the EMG recordings.

Drugs. All drugs were prepared on the day of each experiment. Doses of all drugs were calculated on the basis of salt weight. Clonidine HCl and SKF-86466 were dissolved in sterile saline (0.9% NaCl) to obtain stock solutions (1.0 mg/ml), which were further diluted in NaCl for intravenous administration. Clonidine HCl was obtained from Sigma Chemical (St. Louis, MO), and SKF-86466 was obtained from SmithKline Beecham (King of Prussia, PA).

Data and statistical analysis. The data were digitized off line at 250 Hz. The EMG signals were full-wave rectified and moving time averaged (100-ms time constant) to quantify the mean electrical activity for each muscle in arbitrary units. Phasic activity was derived by dividing the area under the moving average trace by EMG burst duration during a phasic discharge. Tonic activity was defined as the mean electrical activity recorded between phasic bursts and included any noise in the system. In addition, EMG timing parameters were calculated and assessed relative to the respiratory cycle. Phasic MPC, TA, and IPC activities began in the latter part of inspiration, and this preactivation was quantified as the time from the onset of phasic activity to the end of inspiration. Phasic activity was usually discernible in the PCA and CT
EMG beginning just before inspiration. This preactivation was quantified as the time from the onset of phasic activity to the beginning of inspiratory flow. The total burst duration during inspiration and expiration was also calculated for each muscle under each condition. Ventilatory and EMG data were averaged from 5–10 "10-breath bins" during control conditions (preclonidine), during dysrhythmic breathing patterns induced by clonidine, and after administration of the selective α₂-adrenergic antagonist SKF-86466. All data were initially averaged for each animal. All values are presented as means ± SE. Data are expressed either as absolute or arbitrary values or as percentage of control data. Statistical analysis was evaluated by means of Student’s paired t-test. Statistical significance was taken at P < 0.05.

RESULTS

Ventilation and EMG activity during quiet breathing (preclonidine). Mean expired minute ventilation was 10.4 ± 1.2 l/min with a respiratory frequency of 20.1 ± 2.4 breaths/min and a tidal volume of 0.54 ± 0.05 liter. Arterial blood-gas and acid-base variables were normal (pH = 7.40 ± 0.01; PaCO₂ = 38.8 ± 0.5 Torr; PaO₂ = 90.2 ± 1.6 Torr). Phasic expiratory MPC activity was observed in all animals. Phasic activation began in late inspiration and persisted throughout expiration with a steady, an augmenting, or a biphasic pattern of discharge (Figs. 1–4). Similar recruitment patterns were
observed in the IPC except that tonic activation was also present throughout the respiratory cycle (Figs. 2A and 3). Phasic activity in early expiration was observed in the TA muscle in two out of five goats (Fig. 1B). Intermittent or no respiratory-related activity was observed in the other animals (Figs. 1A, 3, and 4). Phasic PCA and CT activation began just before inspiration with considerable tonic activation present during expiration (Figs. 2B, 3, and 4). The Dia and Abd were phasically active during inspiration and end expiration, respectively.

Effects of clonidine on breathing. Clonidine (0.5–11.0 µg/kg) induced a highly dysrhythmic pattern of breathing in all animals that was characterized by alternating episodes of tachypnea and slow irregular breathing patterns, including prolonged and variable TE intervals. Periods of apnea were commonly observed. We have previously documented the ventilatory and cardiovascular effects of clonidine in awake standing goats (19, 21), and the results of the present study were qualitatively and quantitatively similar to our previous observations. Ventilatory disturbances induced by α2-AR stimulation with clonidine were reflected in the blood-gas variables. Five minutes before SKF-86466 administration, \( \text{PaO}_2 \) was 78.1 ± 2.3 Torr and \( \text{PaCO}_2 \) was 45.7 ± 1.3 Torr. Clonidine caused a significant reduction in arterial blood pressure and slowed heart rate. Mean arterial blood pressure decreased from 115 ± 4 to 98 ± 8 Torr (P < 0.05), and heart rate decreased from 74 ± 4 to 54 ± 2 beats/min (P < 0.05).

Effects of clonidine on upper airway EMG activity. Dysrhythmic ventilatory patterns induced by clonidine were accompanied by significant increases in laryngeal and pharyngeal adductor EMG activities. Phasic expiratory MPC activity increased to 929 ± 414% (P < 0.05) of control during the slow arrhythmic breathing patterns observed in this study (Fig. 5). Similarly, TA EMG activity increased (263 ± 90% of control) or were recruited during prolonged and irregular TE intervals (Fig. 5). Tonic activation (recruitment) of the laryngeal and pharyngeal adductors persisted throughout the duration of prolonged TE intervals. These changes were accompanied by significant reductions in tonic (expiratory) activity of the laryngeal abductor muscles (Figs. 2B, 3, and 4). Tonic PCA and CT activities decreased to 29 ± 12 and 44 ± 6% of control activities, respectively, during clonidine-induced hypo-

Fig. 3. Representative recordings of IPC, cricothyroid (CT), MPC, TA, and Dia EMG activities and \( V_T \) in an awake goat. After clonidine administration (9 µg/kg cumulative dose), the animal exhibits a tachypneic breathing pattern before entering a spontaneous central apnea. Phasic and tonic IPC activities are substantially attenuated after clonidine. Note tonic activation of MPC and TA activities (pharyngeal and laryngeal adductors) and complete suppression of CT activity (laryngeal abductor) during apneic event. Time bars represent 5 s.

Fig. 4. Representative recordings of MPC, PCA, and TA EMG activities and \( V_T \) in an awake goat. A: control conditions before clonidine administration. B: dysrhythmic breathing episodes induced by clonidine (2 µg/kg cumulative dose) are associated with reciprocal modulation of upper airway abductor and adductor muscle activities. Clonidine administration increases MPC and TA activities and abolishes tonic PCA activity. C: note continuous tonic activation of MPC and TA EMG activities that persist for duration of a clonidine-induced apnea. PCA activity is completely suppressed during entire apneic event. Break in record equals 20 s. Time bars represent 5 s.
ventilation (Fig. 6). Phasic inspiratory PCA (71 ± 12% of control) and CT (94 ± 13% of control) activities were reduced, but these changes were not statistically significant (Fig. 6). PCA burst duration was significantly reduced, decreasing from 88 ± 2% of inspiratory duration before clonidine to 82 ± 3% (P < 0.01) after drug treatment. A substantial reduction in IPC activity was also observed (Figs. 2A and 3). Phasic and tonic IPC EMG activities decreased significantly to 11 ± 5 and 8 ± 3% of control activities, respectively (Fig. 6). In addition, Dia activity was significantly increased (126 ± 7% of control) during slow, dysrhythmic breathing episodes induced by clonidine.

During tachypneic breathing, MPC activity was not significantly different from control activity; however, burst duration was significantly reduced, decreasing from 93 ± 2% of TE before clonidine to 80 ± 4% of TE after drug treatment (P < 0.05). TA EMG activity was abolished or was not recruited during tachypnea. Phasic and tonic PCA and CT activities were not significantly different from control. However, IPC activity was significantly attenuated during clonidine-induced tachypnea (Fig. 3).

Clonidine-induced apneas. Apneas of variable duration were observed in all animals. Continuous tonic activation (recruitment) of MPC and TA EMG activities at a level equal to or greater than that observed in the preceding breaths was observed during each central apnea regardless of the duration of the apnea (Figs. 1–4). Tonic activation of the laryngeal and pharyngeal adductor muscles was interrupted only during the first inspiratory effort after a clonidine-induced apnea. On occasion, however, laryngeal and pharyngeal closure persisted at the end of a central apnea despite inspiratory efforts leading to obstructive or “mixed” apneas. Laryngeal abductor EMG activities (PCA and CT) were completely abolished during central apneic events (Figs. 2B, 3, and 4). Phasic inspiratory bursts in the PCA and CT muscles (and Dia) were observed with the first inspiratory efforts after a central apnea. With the
resumption of breathing, MPC and TA EMG activities were converted from continuous to expiratory patterns. Similar to Dia activity, Abd EMG activity was silenced throughout the central apnea duration.

Fiber-optic endoscopy. Endoscopic visualization of the laryngeal and pharyngeal airway in one additional goat demonstrated that clonidine results in a graded narrowing of the upper airway during expiration before the onset of respiratory instabilities induced by \( \alpha_2 \)-AR stimulation. As the cumulative dose of clonidine was increased (2 \( \mu \)g/kg increments; 6 \( \mu \)g/kg total) the larynx and pharynx progressively narrowed during expiration. After 4 \( \mu \)g/kg clonidine, the glottis was completely closed throughout expiration and progressive narrowing of the hypopharynx was observed with incremental doses of the \( \alpha_2 \)-AR agonist. During prolonged T\( \varepsilon \) intervals, there was obvious pharyngeal and laryngeal occlusion, with airway reopening occurring only during brief inspiratory efforts. Pharyngeal and laryngeal closure was consistently observed across several clonidine-induced central apneas. Control (predonidine) conditions were reestablished after systemic administration of SKF-86466 (100 \( \mu \)g/kg).

Effects of SKF-86466 on breathing and upper airway EMG activity. Five to ten minutes after SKF-86466 administration, respiratory and cardiovascular variables had returned to preclonidine control values. Mean expired minute ventilation was 12.1 \pm 1.5 l/min with a respiratory frequency of 21.0 \pm 2.2 breaths/min and a tidal volume of 0.61 \pm 0.07 liter. Arterial blood-gas and acid-base variables were restored to normal (\( \text{pH}_a \) = 7.42 \pm 0.01; \( \text{Pa}_2 \text{CO}_2 \) = 40.1 \pm 0.7 Torr; \( \text{Pa}_2 \text{O}_2 \) = 92.5 \pm 2.0 Torr). Similarly, mean arterial blood pressure (119 \pm 7 Torr) and heart rate (74 \pm 8 beats/min) were not significantly different from control. With the possible exception of MPC activity (Fig. 5), the differential effects of clonidine on upper airway abductor and adductor muscles were reversed by \( \alpha_2 \)-AR blockade (Figs. 5 and 6).

DISCUSSION

The main findings of the present study are as follows. 1) Dysrhythmic breathing resulting from systemic administration of clonidine is associated with differential recruitment of upper airway muscles in awake goats. Specifically, \( \alpha_2 \)-AR stimulation preferentially decreases the activity of upper airway abductor muscles while increasing the activity of upper airway adductor muscles further demonstrating that \( \alpha_2 \)-AR pathways are important in the control of central respiratory output. 2) Prolonged T\( \varepsilon \) intervals and apneas induced by clonidine are associated with continuous expiratory laryngeal and pharyngeal motoneuronal activation, leading to airway closure in awake goats. Our results in awake goats indicate that, during quiet breathing, the pharyngeal constrictor muscles exhibit phasic expiratory activity, consistent with previous EMG studies in anesthetized (40) and decerebrate (28) cats and unanesthetized dogs (23) and with neural recordings of branches innervating the pharyngeal constrictor muscles in anesthetized cats (39). However, we have observed considerable differences in the EMG responses of the MPC and IPC muscles to respiratory-related stimuli, suggesting that these muscles may have different mechanical effects on pharyngeal airway caliber in the goat (unpublished observations). The response of the MPC to respiratory-related stimuli was similar to that of the TA (a laryngeal adductor), suggesting that the MPC may help brake expiratory airflow, thus helping to control expiratory timing and lung volume. In contrast, respiratory-related activity of the IPC was similar to that of the laryngeal and pharyngeal dilator muscles, suggesting that the IPC may function to stabilize or dilate the pharyngeal airway thereby promoting pharyngeal patency (unpublished observations). Similarity in the responses of the pharyngeal constrictor muscles with other known adductor muscles to respiratory-related stimuli has been described elsewhere (26–28). Although the extent to which the pharyngeal constrictor muscles affect resistance to airflow in the upper airway remains unclear we have broadly referred to the MPC and IPC as pharyngeal adductor and abductor muscles, respectively, in this report on the basis of our preliminary observations.

The present study clearly shows differential effects of clonidine on laryngeal and pharyngeal abductor and adductor muscles during characteristic dysrhythmic breathing episodes associated with \( \alpha_2 \)-AR stimulation in the goat. The attenuation or loss of abductor EMG activities and increase or recruitment of adductor EMG activities occurred during ventilatory instabilities before substantial prolongation in T\( \varepsilon \) intervals and well in advance of apneic events. On occasion these changes were observed before the disruption of respiratory rhythm, suggesting a direct effect of clonidine on upper airway motoneurons independent of rhythm-generating mechanisms. The latter is supported by the recent observation that clonidine directly hyperpolarizes hypoglossal motoneurons in the rat (32). In preliminary studies (unpublished observations), we tested the hypothesis that \( \alpha_2 \)-AR stimulation results in differential activation of cranial motoneurons compared with spinal motoneuronal activity. Nine chloralose-anesthetized, vagotomized, paralyzed, mechanically ventilated goats were studied. Phrenic and hypoglossal nerves were isolated and prepared for neural recordings. However, phasic inspiratory hypoglossal activity was observed in only three animals. In each of these experiments, clonidine administration (up to 5 \( \mu \)g/kg iv) abolished hypoglossal activity, further demonstrating that \( \alpha_2 \)-ARs are inhibitory to hypoglossal motoneurons and this is consistent with a potential contribution of these receptors in the development of upper airway obstruction.

EMG has been used extensively in animal and human studies of upper airway function. Changes in the electrical activity of a muscle may be a poor indicator of the likely mechanical consequences of recruitment of a given muscle. However, our upper airway EMG data in awake goats suggest that dysrhythmic breathing and apneas induced by clonidine are accompanied by active laryngeal and pharyngeal closure. This was further supported by endoscopic examination in one goat.
Active glottal closure, as indicated by tonic activation of the TA muscle, has been demonstrated during provoked central apneas in awake lambs (25, 34) and sleeping adult humans (26), and these observations are consistent with continuous TA activity seen during spontaneous central apneas in fetal and postnatal lambs (18, 24) and during central apneas in sleeping humans with the sleep apnea syndrome (22). Fiber-optic endoscopy confirmed laryngeal closure in hypocapnic-induced apneas in humans (26) and lambs (25) and during spontaneous apneas in preterm infants (37). Corroborating evidence comes from other studies in anesthetized or decerebrate cats showing continuous expiratory activity of laryngeal motoneurons during hypocapnic-induced apnea (8, 9).

Tonic activation of the MPC during clonidine-induced apnea is consistent with tonic pharyngeal constrictor muscle activation during passively induced hypocapnia in anesthetized (40) and decerebrate (28) cats. Complete pharyngeal occlusion occurs during spontaneous central apneas and during hypocapnic-induced apneas in patients with the central sleep apnea syndrome (5). Furthermore, progressive pharyngeal narrowing was observed endoscopically during hypocapnic central apneas in normal subjects (5). Taken together, the results suggest that central apneas are an active process during which specific brain stem centers drive tonic laryngeal and pharyngeal adductor activity. Furthermore, the data suggest that closure of the upper airway is common to all forms of apnea. Interestingly, our observations in awake goats demonstrate that laryngeal and pharyngeal closure can occur in the absence of central hypocapnia, and this is consistent with recent observations showing prolonged active glottic closure during barbiturate-induced respiratory arrest in awake lambs (34).

In the present study, clonidine administration had differential effects on EMG activities of the pharyngeal constrictor muscles, decreasing IPC activity (similar to laryngeal abductor responses) while increasing MPC activity (similar to laryngeal adductor responses). This observation is further suggestive of opposing mechanical actions of these muscles in the goat. A substantial decrease or loss of IPC activity (and tonic laryngeal abductor activities) was consistently observed after clonidine administration and likely contributed to the upper airway closure that we observed in one goat. During pronounced ventilatory disturbances the IPC exhibited phasic inspiratory bursts in four of six goats. Inspiratory activity has been observed in motor outputs supplying the pharyngeal constrictor muscles in decerebrate cats (15) and in anesthetized and decerebrate rats (13). Furthermore, phasic inspiratory pharyngeal constrictor EMG activity has been reported in unanesthetized dogs (23) and rats (41) and has been observed on occasion in humans (27). Interestingly, it is reported that the superior pharyngeal constrictor muscle exhibits inspiratory bursts coincident with activation of upper airway-dilating muscles during airway reopening after spontaneous apneas in patients with obstructive sleep apnea (27).

The underlying mechanisms responsible for the clonidine-induced reciprocal modulation of upper airway abductor and adductor muscle activities are not clear from the present study. α2-ARs are found extensively in brain stem sites responsible for cardiorespiratory control (17, 30, 35, 43). These sites include pontine and medullary locations associated with catecholamine-synthesizing cells and sites of respiratory integration (11, 12, 33). Motoneurons supplying laryngeal and pharyngeal abductor and adductor muscles are found within the nucleus ambiguous where they are somatotopically distributed (38). Anatomic studies have clearly demonstrated the presence of α2-ARs in this area of the medulla (35, 43). There are several plausible explanations for the attenuation of tonic (expiratory) upper airway abductor EMG activity by clonidine. However, given that α2-AR agonists have been shown to hyperpolarize or attenuate the activity of central respiratory-related neurons (1, 2, 10, 14), a direct inhibitory effect of clonidine on nucleus ambiguous motoneurons is consistent with our observations and is supported by the observation that clonidine directly hyperpolarizes hypoglossal motoneurons in the rat (32).

The mechanism(s) resulting in continuous tonic activation of respiratory TA and MPC EMG activities during clonidine-induced apneas is unclear. A direct depolarization of these neurons by α2-AR agonists is unlikely but cannot be excluded. We favor the possibility of an α2-AR-mediated withdrawal of an inhibitory input that unmasks a tonic excitation i.e., disinhibition of expiratory-related activity. A major function of central α2-ARs involves the regulation of neurotransmitter release, usually norepinephrine (NE), through feedback interactions with presynaptic autoreceptors (3). Stimulation of α2-autoreceptors by NE or α2-AR agonists (e.g., clonidine) causes a reduction of NE turnover and release from presynaptic terminals (31). NE has been shown to hyperpolarize neurons at pontine and medullary respiratory-related sites (2, 10, 14, 16). It has also been reported that NE is inhibitory to neurons of the nucleus ambiguus (4). Thus α2-AR agonists such as clonidine acting at presynaptic terminals could reduce the release of NE, thereby removing an inhibitory noradrenergic input and allowing tonic excitatory inputs to depolarize expiratory-related neurons. Further studies are needed to determine the precise mechanisms by which α2-AR stimulation influences central respiratory drive to the upper airway muscles. In conclusion, our findings in awake goats demonstrate that α2-AR pathways are important modulators of central respiratory motor outputs to upper airway muscles that regulate airflow.

We thank G. Johnson and J. Pizarro for excellent technical assistance. This work was supported by National Heart, Lung, and Blood Institute Grants HL-53969 and HL-07654. Address for reprint requests and other correspondence: K. D. O’Halloran, Dept. of Comparative Biosciences, School of Veterinary Medicine, Univ. of Wisconsin, 2015 Linden Dr. West, Madison, WI 53706-1102 (E-mail: keh0n@svm.vetmed.wisc.edu). Received 2 October 1998; accepted in final form 1 April 1999.
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