Preoptic Hypothalamic Warming Suppresses Laryngeal Dilator Activity During Sleep

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Abstract

Upper airway dilator activity during sleep appears to be diminished under conditions of enhanced sleep propensity such as following sleep deprivation, leading to worsening of obstructive sleep apnea. NREM sleep propensity originates in sleep-active neurons of the preoptic area (POA) of the hypothalamus and is facilitated by activation of POA warm-sensitive neurons (WSNs). We hypothesized that activation of WSNs by local POA warming would inhibit activity of the posterior cricoarytenoid (PCA) muscle, an airway dilator, during NREM sleep. In chronically-prepared unrestrained cats, the PCA exhibited inspiratory bursts in approximate synchrony with inspiratory diaphragmatic activity during waking, NREM and REM. Integrated inspiratory PCA activity (IA), peak activity (PA), and the lead time (LT) of the onset of inspiratory activity in PCA relative to diaphragm were significantly reduced in NREM sleep and further reduced during REM sleep compared to waking. Mild bilateral local POA warming (0.5-1.2 °C) significantly reduced IA, PA, and LT during NREM sleep, compared to a pre-warming NREM baseline. In some animals, effects of POA warming on PCA activity were found during waking or REM. Since POA WSN activity is increased during spontaneous NREM sleep and regulates sleep propensity, we hypothesize that this activation contributes to reduction of airway dilator activity in OSA patients.
Introduction:

Reduction of the upper airway dilator (UAD) muscle tone during sleep is a key pathophysiological element of human obstructive sleep apnea (OSA) (19). Reduction in UAD tone is thought to account for the emergence of airway occlusion during sleep, particularly if airway size is restricted (reviewed in 18). Some evidence suggests that processes coupled to sleep regulation modulate the severity of OSA, and, by implication, the regulation of UAD tone during sleep. For example, OSA is worsened during recovery sleep following sleep deprivation (35;39). Sleep deprivation increases sleep pressure as indicated by increased sleep propensity and by increased delta EEG activity within sleep, a measure of sleep depth (8). Sleep deprivation also decreased activation of the genioglossus muscle, an airway dilator, in response to increased CO₂ in normal subjects (25). This finding suggests that sleep pressure directly affects UAD responses rather than affecting only other elements of the apnea/hypopnea cycle such as arousal mechanisms. In cats, sleep deprivation increased the number of respiratory pauses during recovery REM sleep (44). Additional studies show that sleep pressure is elevated in OSA patients. Even after documented treatment of OSA with nasal continuous positive airway pressure, patients exhibited diminished arousal responses from sleep (20) and excessive daytime sleepiness (7;11;22;31;36). In comparison with controls, OSA patients may exhibit more rapid development of EEG delta activity during sleep after wake (35). A rapid increase in delta is also a marker of elevated sleep pressure. The increased sleep pressure in OSA patients may contribute to the reduction of UAD tone associated with sleep. However, the neural mechanisms underlying the connection between sleep pressure and UAD activity are uncertain. We assessed the hypothesis that hypothalamic neural mechanisms underlying sleep pressure could directly modulate UAD tone.

The preoptic hypothalamic area (POA) is an established sleep regulatory site (reviewed in 29). Electrical and chemical stimulation of the POA induces sleep. POA lesions suppress sleep. Neurons within the median POA (MnPN) and ventrolateral POA (VLPO), exhibited increased discharge during NREM sleep compared to wake as shown by both electrophysiological recordings (40;41)and increased expression of the immediate early gene, c-fos, a marker of cellular activation (13;37). These are identified as sleep-active neurons. After sleep-deprivation, sleep-active neurons in the VLPO exhibited increased sleep-related discharge compared to
baseline sleep (41). This increased discharge was correlated with increased delta EEG activity. VLPO lesions reduced delta activity within residual sleep (26). MnPN sleep-active neurons exhibit increased discharge prior to sleep after sustained waking and progressively decreased discharge across sustained sleep (40). This pattern mimics the build up of sleep drive during waking and its diminution with sustained sleep. These findings suggest that sleep drive is coded in the activity of POA sleep-active neurons.

POA temperature-sensitivity plays a central role in sleep control. The POA contains neurons with high sensitivity to local warming or cooling. Local warming of the POA area, which activates warm-sensitive neurons (WSNs), promotes sleep onset, increases subsequent sleep, and enhances EEG delta activity within sustained sleep (reviewed in 29). Ambient warming also increases subsequent sleep with delta activity in both humans (17) and rats (30), and increases sleep-related c-Fos expression in MnPN (13). Most POA WSNs are sleep-active neurons (1;4). These studies support a hypothesis that activation of WSNs contributes to the hypnogenic output of the POA and regulates sleep pressure.

We hypothesized that POA warm-sensitive neurons would regulate UAD muscle function during sleep. To test this hypothesis we examined the effects of POA warming on the inspiratory activity of a laryngeal dilator muscle, the posterior cricoarytenoid (PCA), during waking and sleep in the cat.

Methods:

Animals and Surgery. All experimental procedures were conducted in accordance with the National Research Council Guide for the Care and Use of Laboratory Animals. Six adult mongrel female cats weighing 2.5-3.9 kg were used in this study. Cats were obtained from an on-site breeding colony and were 6-18 months of age. Preoperatively each cat was given 5.5 mg/kg of Ketamine and 0.27 mg/kg Diazepam intramuscularly. The right femoral vein was catheterized for the administration of fluids and drugs. The animal was intubated with a No. 3 cuffed endotracheal tube attached to the anesthesia machine and administered Isoflurane (2.5-3%), balance O₂. The animals breathed spontaneously during surgery. Vital signs were checked and recorded every 10 minutes until completion of surgery. Sterile technique was used throughout.

With the animal in the supine position an abdominal incision below the right costal margin permitted exposure of the diaphragm for the implantation of 4 juxtaposed, gold-plated
barbed electrodes constructed from dental broaches (Fig. 1). Lead wires were tunneled subcutaneously to the back of the head. The abdominal incision was closed in layers.

A ventral midline incision in the neck from the hyoid bone to the sternum permitted exposure of the larynx and trachea. After partial rotation of the larynx on its long axis, taking care to preserve the recurrent laryngeal nerve, the PCA could be directly viewed. The PCA muscle was implanted with an array of gold-plated, broach-type electrodes (Fig. 1). Lead wires were tunneled subcutaneously to the back of the head. The neck incision was closed with nylon sutures.

Next, the cat was turned to the prone position and placed in a stereotaxic frame (KOPF 1430 model). A midline incision was made in the skin over the skull from the frontal bones to the lambdoid ridge. EEG and EOG electrodes consisted of small gold-plated stainless steel (SS) screws threaded into 1 mm holes bored into the skull over frontal cortex and in the orbital wall. EMG electrodes were Teflon-insulated wires with bared gold-plated 3 mm tips that were inserted into dorsal neck muscles with a needle. A pair of stainless steel water-perfused thermodes (O.D.=0.76 mm), with adjacent thermocouples, were stereotaxically implanted (AP 14.5, L 2.5, H –4.0) so as to bracket the medial POA (Fig. 1B). Thermocouple tips were centered 2.0 mm from the center of the thermode, about 1.6 mm from the thermocouple walls. All the electrode wires were soldered to separate pins of a connector which, along with the thermode-thermocouple assembly, were secured to the skull with sterile dental cement.

At the end of the surgery all wound areas were cleaned and treated with an antibiotic cream. All cats awoke spontaneously at the end of the anesthesia. During the postoperative period they were placed in a warmed oxygenated chamber. Their vital signs and temperature were checked regularly. Antibiotic treatment (Cefazoline) and iv. fluids were given for 5 days.
Fig. 1. A. Schematic of construction of electrode assembly used for both diaphragm and PCA EMG recordings. Pieces of barbed dental broaches were soldered to insulated wires and embedded in dental acrylic in a desired configuration. Inter-electrode distance is therefore fixed. Lead wires were threaded subcutaneously to a head-mounted connector. Protruding barbs were gold-plated. The length and configuration of the barbs can be varied to suit the muscle of interest. B. Schematic view of location of bilaterally-implanted stainless steel concentric tube (inner tubes not shown) water-perfused thermodes and adjacent thermocouples within the lateral preoptic area of the hypothalamus. Warm water is pumped through an inner cannula and is “released” into the outer cannula at the tip. The walls of the outer cannula are thinned at the tip, to maximize heat exchange, and are sealed and gold-plated. ac: anterior commissure. oc: optic chiasm.
Data collection and analysis. Experiments started after the 12th postoperative day, when the cats were in stable condition. Cats were placed in a sound attenuated recording chamber (ambient temperature ~25°C) and connected to counter-weighted cables for recording the neurophysiologic variables and hypothalamic temperature. EEG, EOG, neck muscle EMG, diaphragm and PCA EMGs and their moving averages, and hypothalamic temperature were amplified (Grass Instruments), digitized (Cambridge Electronic Design), and displayed and recorded continuously. Thermodes were connected to a peristaltic pump via through silastic tubing through a Peltier device that was suspended about 12 cm above the animals’ heads. POA temperature could be rapidly elevated by 0.4-1.5°C by pumping water through this system. Physiological data were acquired first during spontaneous waking, NREM and REM states. Waking, NREM and REM were identified based on EEG and EMG patterns using standard criteria (43). Briefly, NREM was identified by occurrence of sustained periods with high amplitude spindles and slow waves. REM was identified by a low amplitude, mixed frequency EEG combined with very low neck muscle tone and occurrence of rapid eye movements. NREM samples were obtained from episodes with high amplitude EEG activity including delta activity and sleep spindles beginning 10-60 minutes after sustained sleep onset. These samples were obtained when EEG slow wave activity was maximal. REM samples were obtained from sustained REM periods lasting at least 3 minutes. REM samples did not contain episodes of very rapid breathing. For all comparisons, samples were obtained from contiguous sleep periods in which posture was unchanged. Two sleep cycles were examined in each cat. Subsequently, we determined responses to local POA warming by 0.5-1.5°C measured at the thermocouple tips. A minimum effective temperature in NREM was chosen for consistent use in each cat (average= 0.9°C). Warming periods lasted 75-90 sec during sustained waking, NREM, and REM episodes. We used tests in which states remained stable without postural change for at least 60 seconds before and during warming trials. Analyses were done on all breaths during continuous 60 sec samples (18-20 breaths, each). The raw and moving average of the EMG signals (CWE, time constant=50 msec) of the PCA and diaphragm were analyzed off-line with the Spike 2 program (Cambridge Electronic Design, U.K.). Analyzed parameters included integrated inspiratory activity (IA) and peak integrated amplitude (PA) for both PCA and diaphragm, and the inspiratory burst onset time difference between PCA and diaphragm or PCA lead time (LT). We also measured the total respiratory time (Ttot) and the inspiratory time (Ti).
To assure that effects of POA warming did not reflect progressive changes within sleep epochs, we measured PA during successive 60 samples within NREM without POA warming.

Fig. 2. Measurements of PCA and diaphragmatic EMG activity. Measurements, including peak and inspiratory PCA activity (PA and IA), were derived from the moving average signals (IDEMG and IPCA) as shown.

**Statistical analysis**  The means and variances of IA, PA and LT sample breaths recorded during baseline sleep and wake states were calculated, and % changes during sleep states compared to awake were determined. The effects of state on these parameters were assessed by analysis of variance (ANOVA) followed by multiple paired comparison tests (Holm-Sidak) in both individual cats and in pooled data. Effects of warming in each state were evaluated statistically using the Students t-test in both individual cats and pooled data. For all comparisons, a p < 0.05 was considered significant.

**Histology.** After completion of experiments, cats were deeply anesthetized and perfused transcardially with saline followed by 4% formaldehyde. Brains were removed, post-fixed in 15% and 30% sucrose in formaldehyde, and subsequently sectioned through the POA (40 µ) and stained with thionin. We confirmed that thermode tips were localized in the lateral POA or adjacent diagonal band within 0.75 mm of the target site (Fig 3).
Fig. 3. Photomicrograph showing track of bilateral thermodes, in this case about 0.75 mm anterior to the POA.

**Results:**

In 4 of 6 cats, both the PCA and diaphragm EMG recordings exhibited inspiratory bursts that were stable for several weeks (Fig. 4). These four cats were used for all analyses. The ANOVAs showed an overall effect of state on measures of PCA activity as well as PCA-diaphragm lead time in each cat. Post-hoc tests showed significant decreases in individual cats in both NREM and REM compared to waking (Table 1) as well as in pooled data. As shown in Fig. 5, in NREM compared to waking, a decrease was found in integrated inspiratory activity (IA, -19%), peak integrated activity (PA, -31%), and lead time (LT -21%). PA decreased significantly in each cat, and IA decreased significantly in 2 of 4 cats.

Table I. Effects of sleep states on PCA function:
Holm-Sidak pairwise multiple comparisons.

<table>
<thead>
<tr>
<th>Cat</th>
<th>NREM vs W</th>
<th>REM vs W</th>
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<tbody>
<tr>
<td></td>
<td>IA PA LT</td>
<td>IA PA LT</td>
</tr>
<tr>
<td>1</td>
<td>**** **** ****</td>
<td>**** **** ****</td>
</tr>
<tr>
<td>2</td>
<td>* **** ns</td>
<td>**** **** ****</td>
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<tr>
<td>3</td>
<td>ns **** **</td>
<td>**** **** ****</td>
</tr>
<tr>
<td>4</td>
<td>ns **** **</td>
<td>*** **** ****</td>
</tr>
</tbody>
</table>

* p < .05, ** p < .025, *** p < .01, **** p < .001, ns: not significant
Significant decreases were also observed in REM sleep compared to waking (IA, -63%, PA, -66%). These differences were significant in each cat as well as in pooled data (Table 1). REM sleep PA was also significantly reduced compared to NREM sleep in 3 of 4 cats. The onset of PCA inspiratory activity preceded the onset of diaphragmatic activity (PCA lead time), averaging 0.55 sec in waking. PCA lead time decreased significantly compared to waking in NREM (22%,) and REM (40%, Fig. 4). Compared to quiet waking, breath by breath integrated diaphragmatic inspiratory activity exhibited only minimal and non-significant decreases, 5.5 percent in NREM and 4.5% in REM sleep.

Fig. 4. Polygraphic recordings from quite waking, NREM and REM sleep. Recordings included cortical EEG, EOG, nuchal diaphragmatic and PCA EMGs, and moving averages of diaphragmatic EMGs. Inspiratory PCA activity was maintained in REM sleep, but was reduced in amplitude and exhibited variability in relationship to phasic events.
Fig. 5. Changes in PCA EMG parameters during NREM and REM sleep compared to waking. Inspiratory activity, peak activity and the PCA vs diaphragm lead time were significantly reduced in both NREM and REM compared to waking.

Effects of POA Warming

Local warming of the POA within NREM sleep further decreased the PCA inspiratory activity from the NREM baseline (Fig. 6). As shown in Fig. 7, significant decreases in response to POA warming were seen in IA (-9%) and PA (-25%). This effect was consistent and statistically significant in both pooled data and in each of the four cats, with the exception of IA in one cat (Table II). In analyses of successive NREM epochs without POA warming or postural change, PA did not exhibit significant changes (Table II). In 3 of 4 cats, POA warming also decreased PCA activity in REM. In pooled data during REM sleep, PA decreased 14% during warming (p<0001), but other parameters were not changed significantly. During waking, POA warming decreased both PCA parameters and LT significantly in 2 of 4 cats. T/Ttot was significantly reduced during warming during both NREM and REM but was increased during waking (Table III). Total integrated diaphragmatic activity was not significantly changed during POA warming in any state. In addition, during the warming trials, the respiratory rate did not change significantly (data not shown).
Fig. 6. Polygraphic example of POA warming trial during NREM sleep. A horizontal line is provided to assist visualization of the warming effect. During warming, PCA integrated activity was mildly, but consistently reduced. Expanded samples (A, B and C) are shown below.
Fig. 7. Effects of mild POA warming on parameters of PCA activity in NREM sleep, expressed as a percent of baseline (and S.E.). Significant reductions were seen in integrated inspiratory activity, peak activity, and the PCA-diaphragm lead time. Pooled data from 4 cats.

Table II. POA Warming-induced reductions in PCA activity: Significance in individual subjects.

<table>
<thead>
<tr>
<th>Cat</th>
<th>Waking</th>
<th>NREM</th>
<th>REM</th>
<th>Control</th>
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<tbody>
<tr>
<td></td>
<td>IA</td>
<td>PA</td>
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<td>IA</td>
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<tr>
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<td>ns</td>
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<tr>
<td>4</td>
<td>****</td>
<td>****</td>
<td>***</td>
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</tbody>
</table>

* p < .05, ** p < .025, *** p < .01, **** p < .001, ns: not significant
### Table III.

<table>
<thead>
<tr>
<th></th>
<th>Baseline $T_i/T_{Total}$ (mean ± SEM)</th>
<th>Warming $T_i/T_{Total}$ (mean ± SEM)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wake</td>
<td>$0.40 \pm 0.009$</td>
<td>$0.47 \pm 0.008$</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>NREM</td>
<td>$0.47 \pm 0.009$</td>
<td>$0.43 \pm 0.009$</td>
<td>0.0024</td>
</tr>
<tr>
<td>REM</td>
<td>$0.51 \pm 0.009$</td>
<td>$0.44 \pm 0.011$</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

### Discussion:

The PCA was shown in previous studies to exhibit inspiratory bursts in approximate synchrony with diaphragmatic activity, with variable expiratory activity. We found that the inspiratory bursts were maintained throughout the sleep-wake cycle. Our observations in the unrestrained cat of reductions in PCA activity during NREM and further reductions in REM sleep are in substantial agreement with previous work of Orem and Lydic (34) in the head-restrained cats with tracheal fistulas. We found somewhat greater reductions compared to a waking baseline in integrated inspiratory activity in REM sleep (63% vs. 27% reduction), but reductions in NREM sleep were comparable (19% vs. 17%). We also found significant reductions in peak inspiratory activity and in the PCA inspiratory onset lead time vs. diaphragm onset in both NREM and REM sleep, compared to waking. The present study showed that the decrease during REM in the cat occurs in unrestrained as well as head-restrained cats, and is not crucially dependent on head position (16). However, head position could also affect PCA activity. Humans subjects also exhibited decreased peak PCA activity in both stages 1-2 and 3-4 of NREM sleep (38% and 44% reductions, respectively) (24). In humans, REM sleep was reported to be associated with high variability in PCA activity. In the cat, moderate tonic PCA expiratory activity was maintained in NREM sleep, but lost in REM. In humans, expiratory activity is lost in NREM sleep (24). There are additional species differences in the changes in PCA activity during REM. In contrast to the reduction in PCA activity seen in cats and rats (27;28;34;38), dogs (16) and lambs (21) were found to exhibit no change, or variable, or increased PCA discharge during REM. All studies must overcome the technical difficulties in
obtaining isolated recordings from this small fragile muscle in close proximity to other laryngeal muscles. Our results were obtained only from recordings that were stable for weeks.

Our study confirmed our primary hypothesis that PCA activity could be inhibited within waking and sleep by mild POA warming. During NREM small but consistent inhibitory effects were observed in integrated (-9%) and peak activity (-25%). The PCA lead time was also reduced by POA warming (-35%). In 2 of 4 cats, POA warming also significantly decreased PCA activity in waking and REM. In addition, POA warming decreased the PCA vs diaphragm lead time, most consistently in NREM (-35%). As it is likely that the activation of airway dilator muscles before onset of diaphragmatic inspiratory activity reduces airway resistance, it seems reasonable to hypothesize that a reduction in lead time could contribute to a potential for airway obstruction.

The effects of POA warming were most consistent among individual cats in NREM sleep. The response to POA warming depends on the sensitivity of the warm-sensitive neurons which is increased in NREM (2). Increased neuronal response to warming in NREM probably accounts for the consistent responses during this state. Only 2 or 4 cats exhibited responses to POA warming in waking and REM. We do not have a definitive explanation for differences among cats in responses to POA warming in waking and REM. The anatomical distributions of sleep-active and warm-sensitive neurons in POA are not uniform (29), so slight variations in the position of thermodes within the POA could be important. The mild POA warming applied in this study did not significantly change respiratory rate or total integrated diaphragmatic activity in any state, but the duration of the inspiratory phase of breathing measured with the diaphragmatic EMG was changed differentially, depending on state. During waking POA warming increased Ti/Tot, but during both NREM and REM, Ti/Tot was reduced. This suggests a differential effect of added thermal drive during waking vs. sleep. The reduction of Ti/Tot during sleep and in response to POA warming suggests that the duration of the inspiratory phase could also be reduced under conditions of increased activation of warm-sensitive neurons.

We studied responses to mild POA warming ranging from 0.7-1.2 °C measured 2.0 mm from the center of the thermode tip. The response reported here is distinct from thermoregulatory heat loss responses such as panting typically elicited by stronger POA warming of 2.0°C or more (33).

We showed previously that most POA WSNs exhibit strongly increased neuronal activity prior to and during spontaneous NREM sleep (1;3). Increased WSN in NREM was equivalent to
that seen in response to POA warming during waking. As noted above, the amplitude of warm-sensitivity, i.e., the magnitude of the response of POA WSNs to a specific warming stimulus, also increased during NREM sleep (2). In our studies, POA neuronal warm-sensitivity was also maintained in REM sleep. Activation of WSNs during waking induces heat loss, body cooling, and reduced metabolic rate, processes which also occur during spontaneous NREM sleep (29). WSN activation in NREM may account for the thermoregulatory and metabolic changes associated with this state.

Since we found that the activation of WSNs is sufficient to suppress PCA inspiratory discharge, and this activation occurs in spontaneous NREM and REM sleep, we can hypothesize that WSN activation could account some part of the suppression of PCA activity that occurs in NREM and REM sleep. It is worth noting that many OSA patients exhibit intense nocturnal sweating, a heat loss process (15). Sweating suggests that POA WSNs are strongly activated in these patients. Hypoxia also induces active down-regulation of body temperature, probably as an element of a coordinated protective lowering of metabolic rate (32). Thus, hypoxia associated with OSA could further increase activation of WSNs, and contribute to the inhibition of airway dilator muscles.

Recent studies suggest possible pathways that could mediate the POA output from WSNs. Using the c-Fos and GABAergic marker immunostaining techniques, we showed that segregated subgroups of sleep-active neurons localized in the VLPO and MnPN are GABAergic (14) and that the numbers of sleep-active neurons are increased by ambient warming (13). Most GABAergic neurons in these sites express c-Fos during rebound sleep after sleep deprivation (12). Sleep deprivation increased sleep-related activity of VLPO neurons (41). The posterior hypothalamus (PH) is a potent cardiorespiratory excitatory region (reviewed in 47) which sends projections to pontine and medullary respiratory centers (5;45). Sites within pontine and medullary reticular regions which generate either inhibition or excitation of PCA have been identified (34). Cardiorespiratory facilitation by the PH was shown to be regulated by inhibitory GABergic input (46). POA GABAergic neurons send projections to the PH. We showed that local POA warming inhibits PH arousal-related neuronal activity (23). Thus, activation of POA sleep-active GABAergic WSNs would be expected to inhibit PH-induced cardiorespiratory activation by suppressing excitatory influences from PH on medullary respiratory centers.

Our study may have relevance to OSA. Although in humans the critical level of airway obstruction is the pharyngeal airway rather than the larynx (18;42), pharyngeal dilator muscles
and the PCA exhibit similar sleep-related activity changes, timing with respect to the respiratory cycle, and reflex control (18).

Two related hypotheses can be considered. The baseline reduction in measures of PCA activity as well as PCA lead time in spontaneous REM sleep are likely related to the general loss of muscle tone in this state (9) and may account for the initial emergence of OSA in REM sleep in the natural history of the disease seen in many patients. OSA may begin as REM-related airway obstruction and REM fragmentation, perhaps accompanied by NREM snoring. This initial sleep fragmentation would result in increased sleep drive, leading to increased activation of hypnogenic POA WSNs, and subsequent worsening of NREM as well as REM OSA, through the mechanism shown in this report. The severity of OSA is modulated by sleep drive and OSA patients exhibit signs of enhanced sleep drive, even after CPAP treatment (see introduction). This hypothesis implies that OSA is worsened through a positive feedback loop, in which sleep fragmentation on one night worsens OSA on the next. A second hypothesis stems from the observation that many OSA patients began snoring and gaining weight as young adults (15). Weight gain in humans is best predicted by low resting metabolic rate (6). Metabolic rate is thought to be controlled primarily by POA neurons (10), including WSNs. WSN activation reduces energy expenditure. We can speculate that some potential OSA patients have pre-existing elevated output of POA WSNs both awake and asleep, as an element of a phenotypic (and genotypic) propensity for energy conservation. Tonic activation of WSNs would lead to weight gain and, via effects on airway dilator muscles described here, early onset of snoring. Later in life this propensity could be additive with emerging effects of further weight gain, changing airway size and compliance, and aging, leading to full-blown OSA.
Reference List


10. **Dallman, M., S. Akana, A. Strack, E. Hanson, and R. Sebastian.** The neural network that regulates energy balance is responsive to glucocorticoids and insulin and also regulates HPA axis responsivity at a site proximal to CRF neurons. *Ann NY Acad Sci* 771: 730-742, 1995.


