Brain circuitry mediating arousal from obstructive sleep apnea.

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Abstract

Obstructive sleep apnea (OSA) is a disorder of repetitive sleep disruption caused by reduced or blocked respiratory airflow. Although an anatomically compromised airway accounts for the major predisposition to OSA, a patient's arousal threshold and factors related to the central control of breathing (ventilatory control stability) are also important. Arousal from sleep (defined by EEG desynchronization) may be the only mechanism that allows airway re-opening following an obstructive event. However, in many cases arousal is unnecessary and even worsens the severity of OSA. Mechanisms for arousal are poorly understood. However, accumulating data are elucidating the relevant neural pathways and neurotransmitters. For example, serotonin is critically required, but its site of action is unknown. Important neural substrates for arousal have been recently identified in the parabrachial complex (PB), a visceral sensory nucleus in the rostral pons. Moreover, glutamatergic signaling from the PB contributes to arousal caused by hypercapnia, one of the arousal-promoting stimuli in OSA. A major current focus of OSA research is to find means to maintain airway patency during sleep, without sleep interruption.

Introduction: Importance of arousal in obstructive sleep apnea (OSA)

OSA is a disorder of sleep disruption caused by repetitive episodes of upper airway collapse. Sleep onset in OSA patients is associated with a drastic reduction (hypopnea) or even complete elimination (apnea) of airflow, followed by brief awakening with re-establishment of the airway. This cycle may repeat hundreds of times over the course of a single night. OSA severity is quantified by the apnea/hypopnea index (AHI), the number of events per hour that last at least 10 sec and cause blood oxygen desaturation. AHI values greater than 5 are considered to represent OSA, but patients with severe OSA may have an AHI of 30 or greater. Figure 1 shows a typical oscillatory breathing pattern in a person with severe OSA. Note that the breathing cycles between obstructed and unobstructed breaths and that each airway re-opening is associated with EEG arousal. OSA patients are unable to compensate for sleep-related increases in pharyngeal airway resistance without waking up. A portion of OSA morbidity is caused by detrimental effects of chronic intermittent hypoxia, however,

sleep fragmentation is responsible for many of the consequences of OSA including excessive daytime sleepiness and cognitive deficits [1].

A low arousal threshold can contribute to OSA pathogenesis

Several interacting traits contribute to OSA susceptibility with the most important of these being airway collapsibility [2,3]. The pharyngeal airway is vulnerable to collapse as this soft tissue structure can be narrowed by fat deposits and is dependent upon dilator muscle activity to retain patency. During wakefulness OSA patients can and do compensate for small airways. Most of this compensation takes the form of increased neuromuscular activity driving enhanced tone in upper airway dilator muscles such as the genioglossus (a tongue protruder) during wake [4]. However, for poorly understood reasons, the ongoing neuromuscular compensation often (but not always) fails during sleep causing OSA [5]. The extent to which the upper airway dilatory muscles can compensate is highly variable among individuals and strongly influences susceptibility to OSA.

Another trait that can influence OSA severity is the inherent stability of one's ventilatory control system. An OSA patient with unstable ventilatory control is prone to larger fluctuations in blood CO_2 as the airway obstructs and reopens. Note the difference between the two arrows on the PetCO2 trace during the last obstructed breath and the first unobstructed breath in Figure 1. Hypocapnia is thought to precipitate the next obstruction: most apneas occur during the decline of waxing and waning ventilatory efforts. A new paper by Xie and colleagues nicely demonstrates that administration of CO_2 to prevent hypocapnia following an apneic event is able to stabilize breathing in select OSA patients that exhibit not only collapsible airways, but also high CO_2 chemosensitivity [6].

Finally, the arousal threshold is a key factor influencing OSA severity. In some cases, the increased respiratory efforts as CO_2 rises are sufficient to re-establish breathing without causing arousal. The less one is able to tolerate the increased CO_2 and mechanical stimuli that occur in flow-limited breathing without waking up, the more fragmented the individual's sleep will be. Moreover, the arousals themselves tend to perpetuate the cycle by worsening CO_2 fluctuations. Specifically, arousals contribute to over-breathing and subsequent CO_2 undershoot following an apnea, and these periods of reduced respiratory drive due to hypocapnia may contribute to the next episode of airway collapse [7,8]. Despite the widely held view that arousal is necessary for airway re-opening, evidence suggests that many obstructive events are resolved without arousal [8,9] and exploration of how this may happen is at the cutting edge of OSA research [10]. At least one study suggests that pharmacologically raising the arousal threshold can ameliorate OSA in select groups of patients [11]. Nonetheless for some patients arousal from sleep is the only process that provides sufficient muscle activation to open the airway and reestablish adequate airflow. Clearly arousal is both a blessing and a curse in the context of OSA: a vital survival response in some cases and a contributor to the disorder in others.

What triggers arousal in OSA?

The mechanisms by which airway obstruction causes arousal are uncertain although the available data implicate multiple contributing stimuli including hypercapnia, hypoxia and

the mechanical sensations associated with increased ventilatory effort [12]. During an obstructive apnea, airflow is reduced with a commensurate increase in blood CO_2 and varying degrees of hypoxia. The accumulating CO_2 and hypoxia drive increasing respiratory effort in turn producing progressively greater and greater negative airway pressures as well as proprioceptive feedback from contracting respiratory muscles. When these stimuli reach a critical threshold arousal occurs. Interestingly, arousal is associated with a particular level of respiratory effort (as assessed by mechanical metrics) in a given individual but not a consistent level of either blood CO_2 or O_2 [13,14]. These studies have been interpreted to emphasize the importance of mechanical stimuli in arousal. However, it is more likely given the complex and interdependent interactions between O_2 and CO_2 in the chemosensory system [15] and the fact that blood levels do not measure the level of either gas at the tissue levels where chemoreceptors reside, that respiratory effort may simply provide the most accurate and consistent readout of the total contribution of these two gases to simultaneously promote breathing and arousal. In the next sections I will describe the neural systems that control behavioral state and chemoreception as well as how they are linked together to elucidate arousal from OSA.

Arousal system

The arousal system can be defined as the neural substrates for maintenance of the waking state and consciousness. The concept of an ascending arousal system dates back to the experiments of Morruzi and Magoun demonstrating that brainstem lesions can cause coma whereas electrical stimulation can produce a wake-like pattern in the cortical EEG in experimental animals [16]. A wealth of neuroanatomical and physiological studies has subsequently identified a number of brain regions that may have been responsible for Morruzi and Magoun's observations. These areas a) have widespread forebrain projections with axons traversing the lesion and stimulation region and b) promote waking or wake-associated phenomena [17]. However systematic studies placing lesions in these cell groups have identified only two subcortical regions that are critically required for maintaining a behaviorally responsive state: the basal forebrain and the parabrachial/precoeruleus region [18]. It is likely that one or more of the structures in the arousal network mediates OSA arousal.

Sleep system

Although sleep is a state of overall decreased brain activity, several groups of neurons are actually more active during sleep and serve to stabilize this state or promote the transition from wake to sleep. The most well-known of these are located in the preoptic hypothalamus and include the ventrolateral preoptic nucleus (VLPO) and median preoptic nucleus (MnPO) [17,19]. An additional group, the parafacial zone, is located in the medulla [20], and there may be other as yet uncharacterized sleep-active groups. Sleep-active neurons in the VLPO are inhibitory and project to many of the arousal neurons [21]. The VLPO is in turn inhibited by components of the arousal system. This network is hypothesized to act as a flip-flop switch which prevents simultaneous activity in sleep and wake-promoting areas, thereby favoring rapid and complete transitions between behavioral states [17]. VLPO lesions cause significant increases in spontaneous wake time [22].

Since sleep-active GABAergic/galaninergic neurons in the VLPO presumably inhibit several arousal centers, including the PB, acute interruption of this activity would be expected to promote awakening. Therefore one possible mechanism for arousal would be acute withdrawal of the sleep-promoting influence of the VLPO. However, it is not known whether acute withdrawal of VLPO activity might be a wake-promoting influence during arousal from OSA. Evidence investigating this possibility, for example by acutely inhibiting the VLPO neurons optogenetically, would be welcome.

Chemoreceptor system

Blood levels of CO_2 and O_2 reflect the adequacy of ventilation and dictate ventilatory drive by acting on two sets of chemoreceptors located respectively in the periphery and in the brain. Peripheral chemoreceptors in the carotid body project centrally via the carotid sinus branch of the glossopharyngeal nerve and terminate in the nucleus of the solitary tract (NTS). Chemosensory neurons in the carotid body are more sensitive to a falling O_2 than a rising CO_2, but their sensitivity to CO_2 rises as O_2 falls, as occurs during apnea. Given that blood from the heart arrives at the carotid artery before the brain, the peripheral chemoreceptors respond to a change in blood gases with a shorter latency than central chemoreceptors [23]. Several types of central neurons are sensitive to changes in blood CO_2, because the bicarbonate buffering in cerebrospinal fluid couples CO_2 levels to changes in local pH.

Early experiments in cats demonstrated that the rostral medullary surface just lateral to the pyramidal tract is especially important in CO_2 chemoreception. Subsequent work demonstrated two sets of neurons in this area that are responsive to CO_2 (and pH) and play an important role in respiratory chemosensitivity. The retrotrapezoid nucleus (RTN) [24,25] which is adjacent to the facial nucleus at the ponto-medullary junction, is both intrinsically CO_2 sensitive as well as also receiving signals from peripheral chemoreceptors via the NTS. A potential role of the RTN in arousal is indicated by experiments showing that optogenetic stimulation of the RTN not only increases ventilatory rate and volume, but also enhances the probability of transition from sleep to wake [26]. The RTN projects heavily to medullary respiratory control areas, but has a major ascending projection to the PB, which may contribute to arousal [27]. A second population of serotonin-containing CO_2 sensitive neurons is found just caudal to the RTN in the area lateral to the pyramidal tract. Mice lacking serotonin neurons or with acutely inhibited serotonin neurons demonstrate very poor sensitivity to arousal from inspired CO_2 [28-31]. These findings initially led to the hypothesis that serotoninergic neurons might carry the hypercapnic signal needed for arousal. However, the CO_2 responsiveness of mice lacking serotonin neurons was restored by treating the mice with a serotonin 5HT2a receptor agonist [32]. Hence, serotonin is not required to carry the hypercapnic signal, but probably sensitizes the remaining brain circuitry to hypercapnia. Perhaps serotonin acts to increase the gain of the CO_2 arousal pathway by modulating neuronal response properties as it does in the facial motor nucleus [33].

Role of the parabrachial complex in OSA arousal

The parabrachial complex is an attractive candidate for mediating OSA arousal. As a key component of both the central respiratory [34] and arousal [18] networks, the PB is well positioned to access relevant data to determine whether respiratory difficulty warrants arousal. The PB receives intense inputs from both the NTS and the RTN that overlap in the external lateral, lateral crescent and Kolliker-Fuse subnuclei [27,35]. Via the NTS and the trigeminal system, the PB receives mechanosensory information from the airways. Via the NTS and the RTN the PB receives both peripheral and central chemoreceptor inputs. This connectivity suggests that the PB is appropriately positioned to translate visceral sensory stimuli to arousal [36]. To test the hypothesis that the neurons in the PB mediate hypercapnic arousal, Kaur and colleagues [36] developed a mouse model in which mice are periodically exposed to brief increases in CO_2 ramping from near zero to 10% over 30 seconds. When applied during NREM sleep, this stimulus is sufficient to cause a brief (often less than 5 sec) awakening on almost all trials. To test the role of glutamatergic PB neurons in hypercapnic arousal, they used mice that were genetically engineered so that the vesicular glutamate transporter (vGluT2) could be eliminated focally in the brain by injections of a viral vector containing the gene for cre-recombinase. When they deleted expression of vGluT2 in the from the external lateral (PBel) and lateral crescent (PBlc) subnuclei, the mice showed substantial deficits in hypercapnic arousal. Upon exposure to hypercapnia mice took on average about 3 times as long as normal to awaken, and in almost 30% of trials they failed to wake up at all during the CO_2 presentation. Interestingly, the portion of the PB, which was most important for hypercapnic arousal overlaps with the zone of afferent input from the NTS and the RTN, consistent with the hypothesis that the external lateral PB is a relay for arousal signals to the forebrain.

Parabrachial-to-forebrain pathways that may mediate OSA arousal

The PBel and PBlc have very different output patterns[36]. PBlc primarily projects to the respiratory areas of the medulla, and is likely to be involved in the increased ventilatory efforts during hypercapnia. By contrast the PBel mainly projects to rostral targets, including the basal forebrain [37-39], lateral hypothalamus [40], midline thalamus [41], and the infralimbic cortex [40,42], as well as providing particularly strong projections to the extended amygdala including the bed nucleus of the stria terminalis and the central nucleus of the amygdala [37,40,43]. The PB-amygdala pathway has been associated with autonomic responses, ingestive behavior, conditioned taste aversion [44], and pain [45], but it has not previously been associated with arousal. However, the amygdala may affect the arousal system via projections to the locus coeruleus, infralimbic cortex, tuberomamillary nucleus, or lateral hypothalamus. Furthermore, the amygdala itself has been implicated in promotion of vigilance [46]. Areas of the PB that are adjacent to the PBel also project to the VLPO, but deleting glutamate transmission from these neurons is not likely to have impaired CO_2 arousal from sleep, because this would have decreased, not increased sleep propensity [47]. Further work will be necessary to uncover the specific PB pathway that contributes to hypercapnic arousal.

Summary

In summary, despite its ostensible simplicity, OSA is a highly complex disorder with marked inter-individual variability in pathophysiology. The reciprocal interactions between ventilation and behavioral state is thought to contribute to a vicious cycle of arousal and over-breathing, falling back to sleep with under-breathing and airway closure, arousal and over-breathing, etc. An especially low arousal threshold can contribute to OSA in an individual who otherwise would not have it. OSA arousal is mostly likely mediated by PB neurons that receive a convergence of asphyxia-related sensations and project to the arousal system. Finally, a complete understanding of hypercapnic arousal must include elucidation of the role of serotonin, which may modulate responses at any or all of the synapses relaying hypercapnia detection to targets that cause arousal. Through further insights into the pathogenesis of OSA arousal, new therapeutic approaches are likely to emerge.

Acknowledgements

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Highlights

1. Arousal threshold is an important trait that determines obstructive sleep apnea severity.

2. Several respiratory stimuli associated with airway obstruction promote arousal.

3. Normal hypercapnia-evoked arousal requires intact glutamatergic signaling from the parabrachial nucleus.
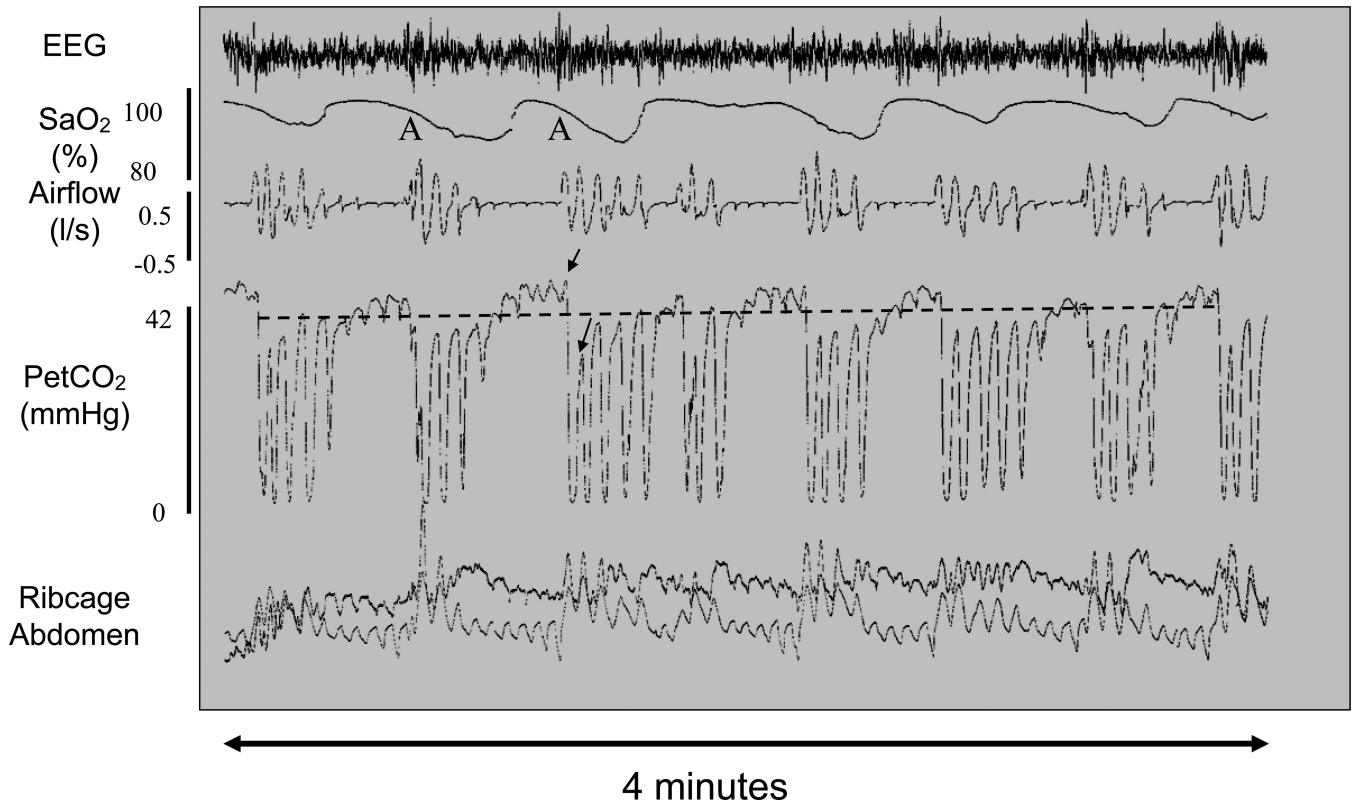
Figure 1.
Typical OSA breathing pattern with recurrent obstructive events. This polysomnogram from a patient with obstructive sleep apnea shows multiple cycles over a four minute period of airway collapse accompanied by hypercapnia and hypoxia and terminating with arousal (A) and airway restoration. Traces show (from top to bottom) EEG, arterial oxygen saturation (SaO_2), airflow (liters/sec), end tidal partial pressure of CO_2 ($PetCO_2$), ribcage and abdominal movements. Obstructive apneas are characterized by reduced or absent airflow despite attempts to breathe as shown by rib cage and abdominal movements. Hypoxia is measured by a pulse oximeter. The level of CO_2 in exhaled air at the end of an expiratory cycle approximates the partial pressure of CO_2 in arterial blood, whereas the signal drops towards zero during inspiration. In this example airflow was reduced but not completely abolished during the obstructions. The dotted line overlying the trace indicates average end tidal CO_2. Note the rise in CO_2 during the airway obstruction and the large breaths that accompany arousal at apnea termination and that drive the CO_2 below baseline. The two arrows on the trace indicate the $PetCO_2$ during the last obstructed breath and the first unobstructed breath. The magnitude of the $PetCO_2$ undershoot is thought to contribute to the likelihood of another obstructive event occurring when the individual falls back to sleep. Adapted from [6].