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Current Opinion in Neurobiology

Brain circuitry mediating arousal from obstructive sleep apnea

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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.

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Current Opinion in Neurobiology 2013, **23**:774–779

This review comes from a themed issue on **Circadian rhythm and sleep**

Edited by **Clifford Saper** and **Amita Sehgal**

For a complete overview see the Issue and the Editorial

Available online 28th June 2013

0959-4388/$ – see front matter,

http://dx.doi.org/10.1016/j.conb.2013.06.001

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 s and cause blood oxygen desaturation. AHI values greater than five 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•].

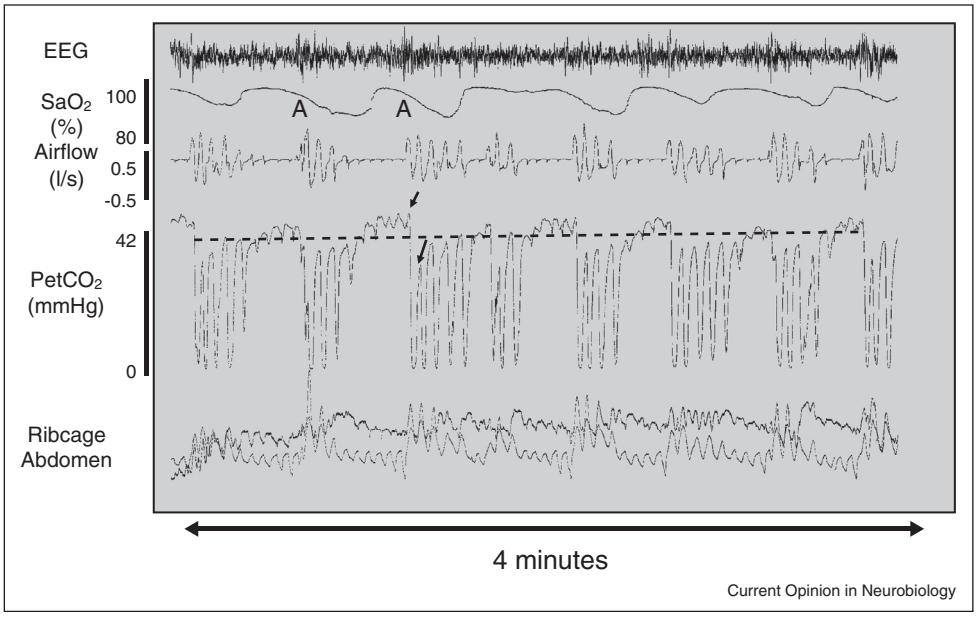
A low arousal threshold can contribute to OSA pathogenesis

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 $PetCO_2$ 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

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 (l/s), 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].

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 overbreathing 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 re-establish 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 probable 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