

APSR RESPIRATORY UPDATES



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Sleep Disorders Associated With Alzheimer's Disease: A Perspective.

Authors: Brzecka A, et al.

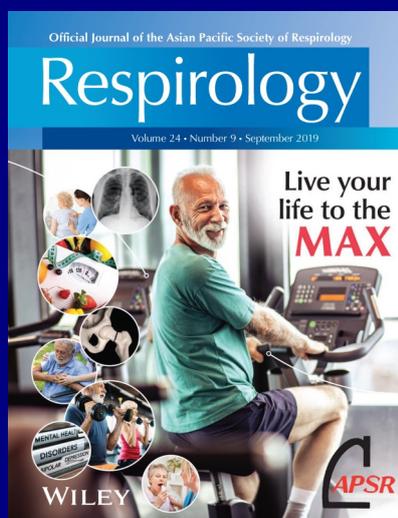
Reference: Front Neurosci. 2018; 12: 330.

URL: <https://doi.org/10.3389/fnins.2018.00330>

Comments: In this mini-review, the authors discuss the association between sleep disorders and Alzheimer's disease (AD).

Sleep disturbances, as well as sleep-wake rhythm disturbances, are typical symptoms of AD. Among sleep disorders occurring in patients with AD, the most frequent disorders are sleep breathing disorders and restless legs syndrome. Sleep abnormalities may increase the risk of AD development. There is accumulating evidence suggesting that disordered sleep contributes to cognitive decline and the development of AD pathology.

They hypothesize that the glymphatic system in the brain plays an important role in A β accumulation in AD patients. The glymphatic system in the brain acts like the lymphatic system in the other body organs. One of the glymphatic system functions is the removal of metabolites and neurotoxic compounds, including soluble A β from the CNS parenchyma. The diffusion-based MR technique called diffusion tensor image analysis shows the impairment of the glymphatic system in AD patients. In addition, slow wave sleep with periodic neuronal hyperpolarization and diminished neuronal firing in some brain regions can be associated with decreased A β production. Thus, they assert that altered sleep quality might contribute to the onset and progression of the AD both through impaired glymphatic clearance and disturbances in the A β production.



Don't miss our September issue of
Respirology on:

**“Rehabilitation in chronic respiratory
diseases”**

an invited review series co-edited by
Frits ME Franssen and Jennifer A. Alison

Obstructive Sleep Apnea Severity Affects Amyloid Burden in Cognitively Normal Elderly. A Longitudinal Study.

Authors: Sharma RA, et al.

Reference: Am J Respir Crit Care Med. 2018; 197(7):933-43.

URL: <https://doi.org/10.1164/rccm.201704-0704OC>

Comments: This is an interesting paper showing that obstructive sleep apnoea (OSA) is associated with markers of amyloid accumulation over the 2-year follow-up in a sample of cognitively normal elderly.

Recent evidence suggests that OSA may be a risk factor for developing mild cognitive impairment and Alzheimer's disease. The authors tested the hypothesis that there is an association between severity of OSA and longitudinal increase in amyloid burden in cognitively normal elderly. Data were derived from a 2-year prospective longitudinal study that sampled community-dwelling healthy cognitively normal elderly. Subjects received positron emission tomography (PET) scans and monitoring of OSA using a home sleep recording device.

They found that severity of OSA indices (AHIall and AHI4%) were associated with annual rate of change of cerebrospinal fluid amyloid β 42 using linear regression after adjusting for age, sex, body mass index, and apolipoprotein E4 status. OSA indices were not associated with increases in Alzheimer's disease vulnerable regions of interest on the PET scans, most likely because of the small sample size.

Effect of Supplemental Oxygen on Blood Pressure in Obstructive Sleep Apnea (SOX). A Randomized Continuous Positive Airway Pressure Withdrawal Trial.

Authors: Turnbull CD, et al.

Reference: Am J Respir Crit Care Med. 2019; 199(2): 211-9.

URL: <https://doi.org/10.1164/rccm.201802-0240OC>

Comments: This study indicates that intermittent hypoxia may be the dominant cause of daytime increases in blood pressure (BP) in Obstructive sleep apnoea (OSA).

OSA is associated with diurnal systemic hypertension. Either overnight intermittent hypoxia, or the recurrent arousals that occur in OSA, could cause the daytime increases in BP. To establish the role of intermittent hypoxia in the increased morning BP in patients with OSA, they conducted randomized, double-blinded, crossover trial assessing the effects of overnight supplemental oxygen versus air (sham) on morning BP, after continuous positive airway pressure (CPAP) withdrawal in patients with moderate to severe OSA. The primary outcome was the change in home morning BP after CPAP withdrawal for 14 nights, oxygen versus air. Secondary outcomes included oxygen desaturation index (ODI), apnoea-hypopnea index (AHI), subjective sleepiness (Epworth Sleepiness Scale score), and objective sleepiness (Oxford Sleep Re-

sistance Test). Supplemental oxygen virtually abolished the BP rise after CPAP withdrawal and, compared with air, significantly reduced the rise in mean systolic BP (-6.6mmHg; P = 0.008), mean diastolic BP (-4.6 mm Hg; P = 0.006), and median ODI (-23.8/h; P < 0.001) after CPAP withdrawal. There was no significant difference, oxygen versus air, in AHI, subjective sleepiness, or objective sleepiness. These data indicate that intermittent hypoxia is an independent contributor, irrespective of recurrent arousals, to the increased morning BP.

Intermittent Hypoxia and Cancer: Undesirable Bed Partners?

Authors: Almendros I, et al.

Reference: Respir Physiol Neurobiol. 2018; 256:79-86.

URL: <https://doi.org/10.1016/j.resp.2017.08.008>

Comments: The aberrant circulation is often observed in solid tumours, which results in recurrent intra-tumoral episodic hypoxia. This intermittent hypoxia (IH) within the tumour tissue has been associated with an accelerated tumour progression, metastasis and resistance to therapies. More recently, the role of IH in cancer has also been studied in conjunction with obstructive sleep apnoea (OSA), since IH is a hallmark characteristic of this condition. This mini-review article summarizes all the available evidence to date linking intermittent hypoxia (IH) effects on several types of cancer.

Circulating Exosomes in Obstructive Sleep Apnea as Phenotypic Biomarkers and Mechanistic Messengers of End-Organ Morbidity.

Authors: Khalyfa A, et al.

Reference: Respir Physiol Neurobiol. 2018; 256: 143-56.

URL: <https://doi.org/10.1016/j.resp.2017.06.004>

Comments: This article summarizes recent findings, focusing on exosomal miRNAs in both adult and children which mediate intercellular communication relevant to obstructive sleep apnoea (OSA) and endothelial dysfunction, and their potential value as diagnostic and prognostic biomarkers. Exosomes (30–100 nm) are one of circulating extracellular vesicles derived from multi-vesicular bodies or from the plasma membrane and play important roles in mediating cell-cell communication via cargo that includes lipids, proteins, mRNAs, miRNAs and DNA. The authors have recently identified a unique cluster of exosomal miRNAs in both humans and rodents exposed to intermittent hypoxia as well as in patients with OSA with divergent morbid phenotypes.

Portable Sleep Monitoring for Diagnosing Sleep Apnea in Hospitalized Patients With Heart Failure.

Authors: Aurora RN, et al.

Reference: Chest. 2018; 154(1): 91-8.

URL: <https://doi.org/10.1016/j.chest.2018.04.008>

Comments: Sleep apnoea is an underdiagnosed condition in patients with heart failure. Currently, clinical guidelines do not recommend the use of unattended portable monitors in the diagnosis of sleep apnoea in adult patients. However in this study, the authors show that portable sleep monitoring can accurately diagnose sleep apnoea in hospitalized patients with heart failure and may promote early initiation of treatment.

They examined whether portable sleep monitoring with respiratory polygraphy can accurately diagnose sleep apnoea in patients hospitalized with decompensated heart failure. Hospitalized patients with decompensated heart failure underwent concurrent respiratory polygraphy and polysomnography. Both recordings were scored for obstructive and central disordered breathing events in a blinded fashion, using standard criteria, and the apnoea-hypopnea index (AHI) was determined. Analyses of the central and obstructive AHI values showed strong concordance between the two methods, with correlation coefficients of 0.98 (95% CI, 0.96-0.99) and 0.91 (95% CI, 0.84-0.95), respectively. Complete agreement in the classification of sleep apnoea severity between the two methods was seen in 89% of the sample. These results indicate that portable sleep monitoring may be used to diagnose sleep apnoea in hospitalized patients with heart failure.

The Ageing Neuromuscular System and Sarcopenia: a Mitochondrial Perspective.

Authors: Rygiel KA, et al.

Reference: J Physiol. 2016; 594(16): 4499-512.

URL: <https://doi.org/10.1113/JP271212>

Comments: Sarcopenia is an ageing process characterized by the loss of muscle mass and function. Recent intensive investigations have revealed underlying cellular and molecular mechanisms, and sarcopenia has been recognized as a disease entity with the awarding of an ICD-10 code. This article provides an overview of the cellular mechanisms whereby mitochondria may promote maladaptive changes within motor neurons, the neuromuscular junction and muscle fibres. Lifelong physical activity, which promotes mitochondrial health across tissues, is emerging as an effective countermeasure for sarcopenia.

Release of ATP by pre-Bötzinger Complex Astrocytes Contributes to the Hypoxic Ventilatory Response via a Ca²⁺ -Dependent P2Y₁ Receptor Mechanism.

Authors: Rajani V, et al.

Reference: J Physiol. 2018; 596(15): 3245-69.

URL: <https://doi.org/10.1113/JP274727>

Comments: For most of the past century, “the neuron doctrine” has been the widely accepted concept, where the nervous system is composed of discrete cells, the neurons, supported by glial cells. However, there is an emerging view, in which brain function actually arises from the coordinated activity of a network comprising both neurons and glia cells. In this paper, the authors show that ATP released from astrocytes mitigates the central hypoxic ventilatory depression.

The hypoxic ventilatory response is biphasic, comprising an initial increase in ventilation followed by a secondary depression. The authors found that, during hypoxia, astrocytes in the pre-Bötzinger complex (preBötC), a critical site of inspiratory rhythm generation, release a gliotransmitter that acts via P2Y₁ purinergic receptors to stimulate ventilation and reduce the secondary depression. Clinically, this astrocytic function is relevant to conditions in which hypoxia and respiratory depression are implicated, including apnoea of prematurity, sleep disordered breathing and congestive heart failure.

D-serine Released by Astrocytes in Brainstem Regulates Breathing Response to CO₂ Levels.

Authors: Beltrán-Castillo S, et al.

Reference: Nat Commun. 2017; 8(1): 838.

URL: <https://doi.org/10.1038/s41467-017-00960-3>

Comments: This paper also shows that the coordinated activity of a network comprising both neurons and glia cells plays an important role for the maintenance of CO₂ homeostasis. Central chemoreception is essential to maintain CO₂ and pH homeostasis. CO₂ is sensed by neurons and astrocytes in the brainstem, which stimulates ventilation. NMDA receptor (NMDAR) antagonism reduces the CO₂-induced hyperventilation by unknown mechanisms. Here the authors show that astrocytes in the mouse caudal medullary brainstem can synthesize, store, and release D-serine, an agonist for the glycine-binding site of the NMDAR, in response to elevated CO₂ levels.

The authors show that systemic and raphe nucleus D-serine administration to awake, unrestrained mice increases the respiratory frequency. Application of D-serine to brainstem slices also increases respiratory frequency, which is prevented by NMDAR blockade. Inhibition of D-serine synthesis, enzymatic degradation of D-serine, or an impairment of astrocytic functions decreases the basal respiratory frequency and the CO₂-induced respiratory response in vivo

and in vitro. These findings suggest that astrocytic release of D-serine may account for the NMDAR-mediated hypercapnic ventilatory response.

Piezo2 Senses Airway Stretch and Mediates Lung Inflation-Induced Apnoea.

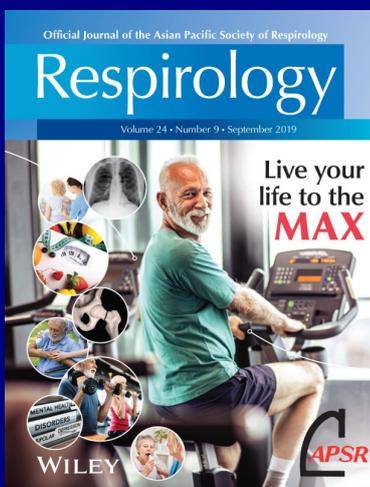
Authors: Nonomura K, et al.

Reference: Nature. 2017; 541(7636): 176-81.

URL: <https://doi.org/10.1038/nature20793>

Comments: Josef Breuer and Ewald Hering reported in 1868 that lung inflation causes a transient apnoea. Since then, the cellular and molecular mechanisms by which this 'Hering–Breuer reflex' is caused has long been unresolved. In this paper, the authors unveiled that Piezo2 is an airway stretch sensor mediating the Hering–Breuer reflex. The authors show that global and sensory neuron-specific ablation of the mechanically activated ion channel Piezo2 cause respiratory distress and death in newborn mice. Optogenetic activation of Piezo2⁺ vagal sensory neurons cause apnoea in adult mice. Further, induced ablation of Piezo2 in sensory neurons of adult mice causes decreased neuronal responses to lung inflation, an impaired Hering–Breuer reflex, and increase tidal volume under normal conditions. These phenotypes are reproduced in mice lacking Piezo2 in the nodose ganglion. Collectively, the results point that Piezo2 is responsible for sensing lung inflation to mediate the Hering–Breuer reflex.

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