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Review

Evidence of Neurodegeneration in Obstructive Sleep Apnea: Relationship Between Obstructive Sleep Apnea and Cognitive Dysfunction in the Elderly

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The incidence of dementia and obstructive sleep apnea (OSA) increases with age. Late-onset Alzheimer's disease (AD) is an irreversible neurodegenerative disease of the elderly characterized by amyloid β (Aβ) plaques and neurofibrillary tangles. The disease involves widespread synaptic loss in the neocortex and the hippocampus. Rodent and clinical studies suggest that OSA impairs the structural integrity of several brain regions, including the medial temporal lobe. Indeed, hypoxia, hypertension, hypoperfusion, endothelial dysfunction, inflammation, and oxidative stress noted in OSA patients also occur in AD patients. This Review highlights pathological commonality, showing that OSA upregulates Aβ, tau hyperphosphorylation, and synaptic dysfunction. Indeed, OSA and hypertension trigger hypoperfusion and hypometabolism of brain regions, including cortex and hippocampus. Several studies show that hypertension-driven brain damage and pathogenic mechanisms lead to an Aβ increase. The pathophysiological mechanism by which OSA enhances hypertension may be linked to sympathoexcitation, oxidative stress, and endothelial dysfunction. Strong pathophysiological similarities that exist between OSA and AD are underscored here. For example, the hippocampus is negatively impacted in both OSA and AD. OSA promotes hippocampal atrophy, which is associated with memory impairment. Cognitive impairment, even in the absence of manifest dementia, is an important independent predictor of mortality. However, several pathophysiological mechanisms in OSA are reversible with appropriate therapy. OSA, therefore, is a modifiable risk factor of cognitive dysfunction, and treating OSA prior to mild cognitive impairment may be an effective prevention strategy to reduce risk for cognitive decline and AD in middle-aged persons and the elderly.

Key words: Alzheimer's disease; obstructive sleep apnea; hypoperfusion; neuroinflammation; Abeta; tau hyperphosphorylation; cognitive dysfunction

There are two major types of sleep-disordered breathing (SDB), obstructive sleep apnea (OSA) and central sleep apnea (CSA). Among the two types of sleep apneas, OSA is the most common type, constituting greater than 85% of all cases of SDB; CSA is far less common (Morgenthaler et al., 2006) People with untreated OSA stop breathing repeatedly during their sleep because of recurrent collapse of the upper airway with inspiration, resulting in apnea, intermittent hypoxia (IH), oxygen desaturation, and arousal from sleep (Guilleminault et al., 1976). Generally, an apnea in adults is defined by a >90% decrease in respiratory airflow for 10 or more sec; however, there need not be a complete cessation of airflow.

SIGNIFICANCE:

Obstructive sleep apnea (OSA) can significantly affect physical and mental health, including cognitive health. OSA induces neurodegenerative changes resulting from two of its main and integral processes, intermittent hypoxia and sleep fragmentation. Because of the pathological impact of hypoxia vis-a-vis hypertension, hypoperfusion, impaired glucose metabolism, and adverse cardiovascular, neurocirculatory, and metabolic consequences, amyloid β generation and tau phosphorylation are upregulated, leading to memory/cognitive impairment and progression to Alzheimer's disease (AD). Furthermore, OSA-related inflammation and oxidative stress impair synaptic function and neural circuitry, leading to a decline in neuronal function in several key brain areas and, thus, inducing cognitive decline. Sustained OSA-promoted cognitive dysfunction overlaps with that noted in AD-associated cognitive impairment.

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Hypopnea is defined as a ≥50% decrease in nasal airflow with a ≥4% oxygen desaturation (Ward et al., 2013). Apneas and hypopneas have similar pathophysiology. SDB is defined as apnea–hypopnea index (AHI) ≥5/hr with symptoms or ≥15/hr with/without symptoms. Different hypopnea scoring rules can significantly influence the AHI and diagnosis of SDB (Ward et al., 2013; Heinrich et al., 2015). For example, using the American Academy of Sleep Medicine (AASM; 2007) recommended definition may lead to a lower AHI and less OSA severity compared with the previous standard (BaHammam et al., 2014; Nixon et al., 2014). The AASM definition for hypopneas is somewhat liberal, so it may lead to a higher AHI, with inclusion of less severe events. A discussion of different published hypopnea definitions and the implications of revised AASM rules on scoring apneic and hypopneic respiratory events is beyond the scope of this Review. Interested readers should consult appropriate articles on this topic (Thornton et al., 2012; Shahar, 2014).

Recent estimates suggest that up to 30% of men and 12% of women between 30 and 70 years of age are affected by OSA (Peppard et al., 2013). The prevalence estimates of moderate-to-severe SDB (AHI ≥15 events/hr) were studied in different age groups. These estimates were 10% among 30–49-year-old men, 17% among 50–70-year-old men, 3% among 30–49-year-old women, and 9% among 50–70-year-old women (Peppard et al., 2013). A polysomnographic study of 2,911 older men (76.38 ± 5.53 years of age) conducted by Ancoli-Israel and colleagues found prevalence of moderate-to-severe SDB to be 21.4–26.4% (Mehra et al., 2007).

Some of the long-term health problems associated with untreated OSA include hypertension, stroke, diabetes, cardiac arrhythmias, myocardial infarction, heart failure, and depression (Daulatzai, 2013a). OSA has been extensively reviewed elsewhere (Ryan and Bradley, 2005; White, 2005; Daulatzai, 2013a). Currently, the standard therapeutic option for the management of OSA is continuous positive airway pressure (CPAP). CPAP provides a continuous, stable, predetermined pressure of air that ameliorates negative pressure and keeps the upper airway from collapsing.

Alzheimer's disease (AD) is the most common neurodegenerative disorder affecting the elderly and is an escalating public health issue. During the early stages of disease, sleep disturbances and forgetfulness are generally the first presenting symptoms (Pace-Schott and Spencer, 2015). AD is characterized by progressive and gradual decline in memory and cognitive functions. Although familial early-onset AD is usually associated with gene mutations, the etiology of the sporadic late-onset form of AD is largely unknown. It has been emphasized in recent years that environmental factors and epigenetic alterations may significantly contribute to the process of AD (Daulatzai, 2010, 2012a,b, 2013a,b, 2014, 2015a–c). In 2000, prevalence of AD in the United States was estimated at 4.5 million, and this figure is projected to increase to 14 million by 2050 (Kelley and Petersen, 2007). OSA is common among the elderly and patients with AD, with >40% prevalence in those who are institutionalized (Ancoli-Israel et al., 1991a). Unfortunately, few interventions (behavioral or pharmacological) effectively delay progression in cognitive decline or improve memory and quality of life for AD patients.

Atrophy, degeneration, and progressive loss of neurons (referred to here as *neurodegeneration*) are prominent in neurodegenerative diseases, including AD, Parkinson's disease, amyotrophic lateral sclerosis, Creutzfeldt-Jakob disease, and Huntington's disease. The outstanding risk factor for developing neurodegenerative diseases, and certainly AD, is aging. The characteristic neuropathological lesions in AD are senile plaques formed by amyloid β (Aβ) and located outside neurons and neurofibrillary tangles (NFTs) comprising abnormally hyperphosphorylated tau protein and located within neurons (Su et al., 1996; Zhao et al., 2010). Aβ is considered to be the noxious etiological agent (as per the amyloid cascade hypothesis) that may trigger synaptopathy, glial (including microglial and astrocytic) activation-related inflammatory response, neuronal ionic dyshomeostasis, oxidative damage, tau hyperphosphorylation (because of altered activities of relevant kinases and phosphatases), and eventual neuronal death (De Felice et al., 2007). In neurofibrillary degeneration pathology, hyperphosphorylated tau protein accumulates in neurons as paired helical filaments in NFTs, induces abnormal cellular metabolism, and causes neuronal death. NFTs are associated with memory and cognitive dysfunctions (Goedert, 1993; Wes et al., 2014).

AD pathology starts years or decades prior to clinical diagnosis. This Review focuses on the significance of OSA-related IH signaling and upregulation of differing pathophysiological mechanisms, including hypertension, endothelial dysfunction, hypoperfusion, glucose dyshomeostasis, inflammation, oxidative stress, and neurotoxicity. These are posited to trigger memory and cognitive dysfunction prior to frank AD. This Review underscores OSA-related evidence relevant to AD and emphasizes a link between the role of OSA in triggering neuronal pathology (dysfunction and degeneration) and the possible pathogenesis of cognitive dysfunction in AD.

PREVALENCE OF OSA IN THE ELDERLY

Advancing age is characterized by a decline in physiological functions. It is a complex state, characterized by accumulation of pathology (Federal Interagency Forum on Aging Related Statistics, 2010). Consequently, aging is a disadvantageous factor because most major diseases, including cardiovascular disease, cancer, and dementia, are strongly age related. There is a higher prevalence of OSA among the aged, which is an important risk factor for this condition (Mehra et al., 2007; Peppard et al., 2013). The mechanisms whereby aging increases the risk of OSA are not completely understood. However, some of the most well-recognized factors in OSA pathogenesis during aging include a highly collapsible airway, an ineffective upper airway dilator muscle activity/responsiveness (i.e., of genioglossus), a low respiratory arousal

threshold, and an unstable ventilatory control system (Malhotra et al., 2006; Wellman et al., 2011; Eckert et al., 2013). Aging increases OSA in postmenopausal women as a result of loss of the ventilatory drive of female hormones (Redman et al., 2003; Resta et al., 2004; Davenport et al., 2012). Elevated oxygen desaturation index ($\geq$15 events/hr) in older women was found to be associated with increased risk of developing mild cognitive impairment (MCI) or dementia (Yaffe et al., 2011; Bayer et al., 2015). Indeed, aging is the most important risk factor for AD.

OSA, CSA, and mixed sleep apneas have been recognized as common occurrences among the elderly. Aging per se is associated with a decrease in sleep quality, and SDB may further disrupt the sleep architecture in older individuals who suffer from lung conditions (e.g., chronic obstructive pulmonary disease; COPD; Soler et al., 2015). Increasing age is associated with the risk of developing SDB (Ancoli-Israel et al., 1991a,b, 1993, 1995; Young et al., 1993; Malhotra et al., 2006; Mehra et al., 2007; Peppard et al., 2013). Furthermore, OSA has been associated with increased mortality among older adults (Janssens et al., 2000; Edwards et al., 2014). SDB occurs more frequently in AD than in the nondemented elderly, and its severity is correlated with the degree of cognitive impairment. Moreover, patients with SDB have been shown to have a younger age at onset of MCI and AD dementia (Osorio et al., 2015). The hypothesis of a causal relationship between SDB and AD, however, remains a subject of great interest.

OSA CAUSES HYPERTENSION

Significant strides have been made in the past 25 years toward understanding systemic hypertension related to OSA. There is a dose–response relationship between the severity of OSA and the odds ratio for development of systemic hypertension (Young et al., 2002). The exposure to clinically significant OSA is thought to be responsible for many of the long-term cardiovascular and cerebrovascular consequences (Somers et al., 2008), including systemic hypertension (Morrell et al., 2000; Nieto et al., 2000; Peppard et al., 2000; Lavie, 2005). Hypertension is characterized by endothelial dysfunction, arterial stiffness, and increased oxidative stress among untreated OSA patients (Montezano and Touyz, 2012). Adult rats that were subjected to IH demonstrated an increase in arterial pressure (Fletcher, 2001; Zoccal et al., 2007).

OSA patients are at increased risk of substantial dysfunctions in the cardiovascular system, including the development of sustained hypertension (Hoffman et al., 2004). Clinical (Narkiewicz and Somers, 1997; Leuenberger et al., 2005) evidence indicates increased sympathetic outflow as the main cause for sustained hypertension resulting from chronic intermittent hypoxia (CIH). Severe disturbances of cerebrovascular reactivity in OSA patients are associated with increased arterial stiffness, indicated by cerebral blood flow (CBF) hyporeactivity; the latter may impair cerebral circulation (Furtner et al., 2009). CBF is closely coupled to regional cerebral metabolism and is strongly modulated by hypercapnia and hypoxia that have widespread impact, including cardiorespiratory insults (Corfield and Meadows, 2006). Specifically, the CBF response to hypoxia was reduced by 42% (compared with healthy subjects; Foster et al., 2007). Previous studies have demonstrated impaired autoregulation of the peripheral vasculature in patients with OSA, which has been attributed to endothelial dysfunction and diminished bioavailability of nitric oxide (NO; Carlson et al., 1996; Kato et al., 2000; Imadojemu et al., 2002).

Epidemiological studies suggest an association between chronic blood pressure (BP) changes and AD (Lattanzi et al., 2015). In particular, there is growing evidence that hypertensive persons who have untreated and uncontrolled BP in midlife are more likely to develop AD later in life. This may be a result of ongoing cerebrovascular disease, hypertension, brain hypoxia, or hypoperfusion (Daulatzai, 2012b; 2013a,b). Moreover, high BP contributes to cognitive impairment by raising both oxidative stress and inflammatory response. Reductions in arterial blood O_2 levels will impose stress on all organ systems; however, the brain is particularly vulnerable to the effects of hypoxia (Dahl et al., 1994). OSA has been associated with pathological loss of cortical gray matter (Placidi et al., 1998; McKay et al., 2003; see below), suggesting that the nocturnal IH in OSA may be sufficient to damage brain tissue directly. Cognitive impairment is one of the important consequences of OSA, resulting in part from IH-related oxidative stress in cerebral tissues.

The reduced cerebrovascular response to CIH in patients with OSA may contribute to elevated risk of hypoperfusion (Foster et al., 2007). Vascular risk factors, therefore, may impair cognitive functions and are therefore implicated in the pathogenesis not only of vascular dementia but also of AD (Fletcher, 2003; Feldstein, 2012). However, treatment of OSA with CPAP lowers mean BP and increases the CBF response (Hla et al., 2002; Montesi et al., 2012). The presence of SDB is associated with cognitive decline at an earlier age; however, it has recently been shown that CPAP treatment of SDB may delay progression of cognitive impairment (Osorio et al., 2015). Furthermore, there is evidence of the effectiveness of CPAP in reducing daytime sleepiness in AD patients with SDB (Chong et al., 2006).

OSA CAUSES INFLAMMATION

Inflammation is an important pathophysiological pathway that occurs during the development of several conditions described above, including cardiovascular disease in OSA patients. Recurring nocturnal episodes of hypoxia/reoxygenation noted among OSA patients appear to be partially responsible for the systemic inflammatory response. Increased values of systemic inflammatory markers, including C-reactive protein and fibrinogen, have been documented, emphasizing the involvement of inflammation in OSA (Wessendorf et al., 2000; Nadeem et al., 2013; Yardim-Akaydin et al., 2014; Fig. 1). Enhanced fibrinogen level in stroke patients with OSA suggests a

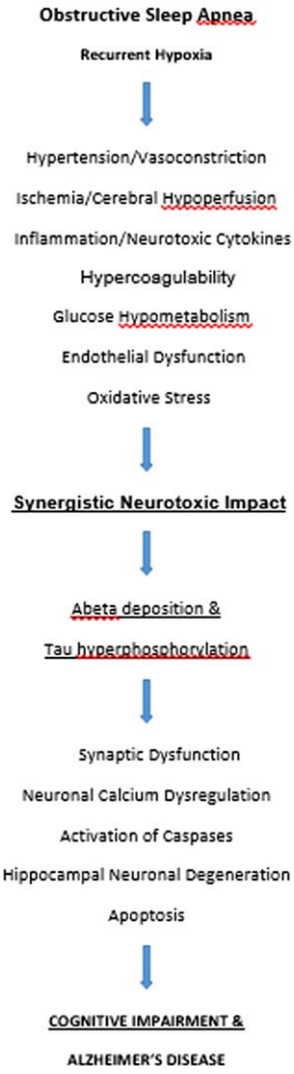

Fig. 1. Various dysfunctions associated with OSA that potentially contribute to cognitive decline. Repetitive hypoxia/reoxygenation and sleep fragmentation associated with transient cessation of breathing in OSA adversely impact a host of physiological functions and promote the upregulation of Aβ and tau hyperphosphorylation. These have a deleterious impact on cortical and hippocampal neurons, causing their degeneration and apoptosis; this leads to gray matter atrophy and memory/cognitive decline, the premier features of AD. Note that caspases are cysteine proteases. Caspases 8 and 10 are involved with the extrinsic apoptosis pathway that commences upon binding and activation of cell surface death receptors. Caspase 9, however, is involved in the intrinsic apoptosis pathway that results from the mitochondrial release of cytochrome C. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

possible pathophysiological mechanism for an increased risk of infarcts/stroke in OSA patients (Wessendorf et al., 2000). Such patients also possess an increase in proinflammatory cytokine interleukin 6 (IL-6; Medeiros et al., 2012).

There is considerable evidence that OSA is associated with a procoagulant state. Indeed, repeated apneas may lead to a hypercoagulable state that predisposes patients to thrombotic events by affecting hematological changes involving hemostasis via increased hematocrit, blood viscosity, platelet activation, clotting factors, and decreased fibrinolytic activity (Liak and Fitzpatrick, 2011). In addition,the integral glucose dysregulation in OSA has been found to be associated with chronic dysmetabolic fluxes and proinflammatory cytokines such as IL-6 (Pallayova et al., 2010).

OSA CAUSES IMPAIRMENT OF CEREBRAL PERFUSION

Marked changes in cerebrovascular control may occur during SDB, notably OSA, suggesting that the cerebral circulation may be vulnerable (Fig. 1). CBF velocity (CBFV) changes and vascular compliance were evaluated in patients with severe OSA by using transcranial Doppler sonography and cerebral pulse transit time. CBFV reactivity was significantly diminished in periods of consecutive respiratory events. The data also demonstrated loss of vasoreactivity and an increase of arterial stiffness, reflected by CBF hyporeactivity (Foster et al., 2007; Furtner et al., 2009). Furthermore, a reduction in CBF during non-REM sleep has been documented, despite a relative state of hypercapnia (Corfield and Meadows, 2006).

Cerebral ischemia is prevented via maintenance of cerebral perfusion pressure. Physiological fluctuations in perfusion pressure are compensated by cerebrovascular autoregulation. However, cerebral hypoperfusion may occur when there is 1) systemic hemodynamic failure in excess of the vasoregulatory capacity and 2) chronic dysfunctional cerebrovascular autoregulation. A close correlation has been shown between mean arterial pressure and CBFV, indicating that cerebral autoregulation is insufficient to protect the brain from rapid pressure changes in OSA (Bålfors and Franklin, 1994). The data show that nocturnal apneas are associated with profound changes in CBF. Apnea-induced hypoxemia combined with reduced cerebral perfusion may predispose to nocturnal cerebral ischemia in patients with OSA (Foster et al., 2007). Patients with OSA have decreased CBFV and delayed cerebrovascular compensatory response to changes in BP but not to CO_2. These perturbations are considered to increase the risk of cerebral ischemia during OSA (Urbano et al., 2008; Daulatzai, 2013a; 2015b).

Vasoneuronal coupling occurs as a result of CBFV variations during neuronal stimulation (Daffertshofer and Hennerici, 1995). However, there is significant neuronal dysfunction in OSA patients (see below); this may render vasoneuronal coupling suboptimal, thus enhancing CBFV abnormalities. The dose–response relationship between the severity of OSA and the odds ratio for development of systemic hypertension has been well documented (Morrell et al., 2000; Nieto et al., 2000; Peppard et al., 2000; Foster et al., 2009). Indeed, OSA patients with clinically significant disease may possess increased incidence of cardiovascular and cerebrovascular disease, and patients with advanced OSA may also have structural cerebral lesions (Foster et al., 2009; Almendros et al., 2011).

Indeed, an epidemiological association has been emphasized between OSA and the risk of stroke (Arzt et al., 2005; Yaggi et al., 2005; Foster et al., 2009).

OSA CAUSES ENDOTHELIAL DYSFUNCTION

Significant data show that OSA upregulates endothelial dysfunction, including coronary endothelial dysfunction, and results in an increased propensity for cardiovascular events (Ryan et al., 2007, 2009). The pathogenesis of increased cardiovascular risk among OSA patients may involve diverse mechanisms, including sympathetic nervous system overactivity, oxidative stress (Büchner et al., 2011), activation of inflammatory and coagulation pathways, and metabolic dysregulation (particularly involving insulin resistance; Carlson et al., 1996; McNicholas and Bonsigore, 2007; Cassar et al., 2014; Daulatzai, 2015b). OSA is characterized by increased sympathetic activity that leads to systemic hypertension (Kato et al., 2000; Nieto et al., 2010); the latter is a well-known risk factor for endothelial dysfunction (Tang and Vanhoutte, 2010; Taddei and Bruno, 2015). Other factors responsible for endothelial dysfunction in OSA include obesity (Al Suwaidi et al., 2001; Ryan et al., 2007) and COPD (Moro et al., 2008). Mice subjected to an obesogenic diet showed greater inflammation, oxidative stress, and endothelial dysfunction (Badran et al., 2014).

In OSA, endothelial dysfunction may be related to CIH, sleep loss, and sleep fragmentation (Fig. 1). These conditions may increase the levels of various markers of inflammation and oxidative stress as well as those of increased procoagulant and thrombotic activity. The repetitive hypoxia–reoxygenation and repetitive arousals resulting in sleep fragmentation impair endothelial function in OSA (Atkeson and Jelic, 2008; Atkeson et al., 2009). There is a loss of normal homeostatic function in the blood vessels in endothelial dysfunction. This involves reduced availability of NO, which has major vasoprotective effects, including vasodilation, inhibition of platelet adhesion and aggregation, inhibition of leukocyte–endothelial adhesion, and inhibition of smooth muscle cell proliferation (Lurie, 2011a; 2011b). The reduced availability of NO in endothelial dysfunction in OSA is linked to vasoconstriction mechanisms involving angiotensin II and/or endothelin 1 (Fletcher, 2003; Narkiewicz and Somers, 2003; Cassar et al., 2014; Durgan et al., 2015).

COPD is characterized by low pulmonary function, inflammation, free radical production, and vascular dysfunction (Ives et al., 2014). COPD patients exhibit lower antioxidant levels (vitamin C and superoxide dismutase activity) but higher levels of oxidative stress (Ives et al., 2014). In addition to functional alterations, morphological changes such as endothelial denudation and endothelial cell apoptosis are observed in the pulmonary vasculature of COPD patients (Yang et al., 2008). Significant endothelial dysfunction exists in COPD patients (Yang et al., 2008; Maricić et al., 2013). Both OSA and COPD impart greater arterial stiffness, and this is also related in part to inflammation in both conditions (Patel et al., 2013; Badran et al., 2014). Furthermore, both COPD and OSA patients show lower NO (Foster et al., 2009; Maricić et al., 2013). Decreased NO availability and endothelial dysfunction might be related to the development of a number of conditions, including ischemic heart disease and hypertension (Kobayashi et al., 2015). Thus, COPD–OSA comorbidity could have synergistic effects and cause potential deleterious contributions in promoting cardiovascular and other outcomes.

OSA INCREASES OXIDATIVE STRESS AND MITOCHONDRIAL DYSFUNCTION

Hypoxia perturbs homeostatic cellular functions that are responsible for normal mitochondrial function and restorative processes involved in protein synthesis and gene regulation (Caine and Watson, 2000; Sun et al., 2002). CIH induces irreversible and functionally significant injury in neurons. NADPH oxidase has been implicated in inducing deleterious alterations in neurons. In contrast, neurons (e.g., in midbrain and pons) without detectable NADPH oxidase do not undergo the deleterious alterations. Additionally, inhibition of NADPH oxidase reduced neuronal injury (Zhu et al., 2007). Transgenic mice lacking Nox 2 (a catalytic subunit of NADPH oxidase) and mice with pharmacological inhibition of Nox 2 catalysis had resistance to oxidative stress (Zhu et al., 2007). Therefore, in hypoxia/reoxygenation of OSA, NADPH oxidase may enhance neuronal vulnerability. Furthermore, CIH episodes may negatively impact mitochondrial function because CIH causes mitochondrial swelling (Zhu et al., 2007). CIH-related mitochondrial injury is known to result in substantial NADPH oxidase activation and reactive oxygen species (ROS) production; the superoxide generation enhances hypoxia/reoxygenation-induced damage to neurons (Sims and Anderson, 2002; Schild and Reiser, 2005). These oxidative radicals in OSA lead to a breakdown of endothelial-derived NO and to exaggerated lipid peroxidation (Schulz et al., 2000; Lavie et al., 2004; Zhang and Veasey 2012).

OSA UPREGULATES GLUCOSE DYSHOMEOSTASIS

Glucose homeostasis is a prerequisite for neuronal energy maintenance and survival. Normally, the status of glucose/energy metabolism of the brain correlates with the level of functional neuronal activity. OSA is associated with distinct alterations in glucose homeostasis (Pallayova et al., 2010). Moderate-to-severe OSA may cause hypoxic damage to pancreatic beta cells, leading to their exhaustion and impaired secretory capacity over time. Furthermore, the impact of CIH, sleep fragmentation, and inadequate sleep quantity/quality (slow-wave sleep) may impair pancreatic β-cell function and cause glucose intolerance and insulin resistance (Spiegel et al., 1985; Zizi et al., 2010; Copinschi et al., 2014; Reutrakul and Van Cauter, 2014). The mechanisms responsible may involve the hypothalamic–pituitary–adrenal axis, circadian pacemakers, sympathetic nervous system activation, oxidative stress, and systemic inflammation (Drager et al.,

2010; Reutrakul and Van Cauter, 2014; Briançon-Marjollet et al., 2015). A recent Guangzhou Biobank cohort study that included 27,971 individuals concluded that cognitive impairment among older adults is associated with increasing glucose levels, even in the normoglycemic range (Jagielski et al., 2014). Brain-derived neurotrophic factor (BDNF) has antidiabetic properties, and reduced circulating BDNF is linked to dementia (Passaro et al., 2015). In the elderly, there may be a synergistic effect of cognitive decline and diabetes on reducing BDNF levels (Passaro et al., 2015).

OSA UPREGULATES OBESITY

There are several metabolic consequences of SDB. As described above, the presence and severity of OSA are associated with an increased risk of diabetes, hypertension, coronary artery disease, and stroke (Garvey et al., 2015). Metabolic syndrome (MetS), a cluster of risk factors that promotes atherosclerotic cardiovascular disease, consists of central obesity, insulin resistance, glucose intolerance, dyslipidemia, hypertension, and altered total body energy regulation. Excess caloric intake is indisputably the key driver of MetS, but other environmental and genetic factors may also play a role; in particular, CIH in OSA may induce or exacerbate various aspects of MetS. Clinical studies show that OSA can affect glucose metabolism, cholesterol, inflammatory markers, and nonalcoholic fatty liver disease (Mungai, 2010; Seetho and Wilding, 2014). OSA has been associated with the development and/or aggravation of obesity, dyslipidemia, and MetS (Lurie, 2011a). Inadequate sleep in OSA results in changes in insulin resistance and in hormone levels, leading to increases in appetite and development of obesity and type 2 diabetes (Pack and Pien, 2011; Seetho and Wilding, 2014). Exposing rodents to IH during their sleep phase alters circadian glucose homeostasis, impairs muscle carbohydrate uptake, induces hyperlipidemia, and upregulates cholesterol synthesis enzymes (Yokoe et al., 2008; Drager et al., 2010). Additionally, a high-fat diet may lead to progressive insulin resistance and inflammation. Mechanisms for these effects are not yet fully understood but are likely related to energy-conserving adaptations to hypoxia, which is a strong catabolic stressor. CIH may also contribute to the morbidity of MetS by inducing inflammation and oxidative stress. Indeed, metabolic disorders and OSA may be linked by sharing common intermediate pathogenic pathways, including alterations in autonomic nervous system regulation, increased inflammatory activity, and alterations in adipokine levels and endothelial dysfunction (Lurie, 2011b). Identification of OSA as a factor that may upregulate obesity should have immense clinical impact in terms of understanding and managing both disorders. (Jun and Polotsky, 2009).

OSA CAUSES STRUCTURAL ALTERATIONS OF THE BRAIN

OSA and White Matter Changes

OSA is accompanied by several cardiovascular and neuropsychological dysfunctions, presumably induced by CIH and its deleterious impact on the brain. Repetitive episodes of hypoxia, hypercapnia, and BP elevation during OSA induce neural damage, including that involving axons (Lüdemann et al., 2001) and white matter (Kiernan et al., 2011). Almost 50% of hypertensive population showed white matter disease on magnetic resonance imaging (MRI; Kiernan et al., 2011). Seventy-one percent of OSA patients showed clinical signs of polyneuropathy (vs. 33% in controls). The differences were significant and were not attributable to confounding risk factors for polyneuropathy. The severity of axonal damage in OSA patients correlated with nighttime, with an O_2 saturation below 90%. Thus, CIH in OSA is an independent risk factor for axonal damage of peripheral nerves (Lüdemann et al., 2001).

Diffusion tensor imaging (DTI)-based mean diffusivity (MD) procedures are useful in detecting neural pathology. In comparison with controls, global brain MD values were found to be significantly reduced in OSA. Multiple brain regions, including medullary, cerebellar, prefrontal and frontal, temporal, occipital, limbic, and insular as well as basal ganglia, cingulum bundle, external capsule, corpus callosum, and corona radiate, showed reduced regional MD values in OSA patients. The significantly reduced global brain MD values in OSA are considered to reflect axonal, glial, and other cell changes in these areas and to indicate ongoing pathological processes in OSA (Kumar et al., 2012).

Radial and axial diffusivity maps calculated from DTI data indicated myelin or axon status resulting from diffusion being perpendicular (myelin) or parallel (axonal) to fibers. Global radial and axial diffusivity values were significantly reduced in OSA. Moreover, radial (myelin) diffusivity reduction was more than axial (axonal), indicating that myelin is more affected than axons in OSA. This possibly is due to myelin being more affected than axons because of increased myelin sensitivity to hypoxia and its suboptimal perfusion (Kumar et al., 2014). These declines in myelin and axonal measures were present in the dorsal and ventral medulla, cerebellar cortex and deep nuclei, basal ganglia, hippocampus, amygdala, corpus callosum, insula, cingulate and medial frontal cortices, and other cortical areas (Kumar et al., 2014). This injury appears widespread in OSA, involving medullary respiration-regulatory, cognitive, and autonomic control areas. Impairment of white matter integrity in several vulnerable areas in untreated OSA correlates with systemic hypertension, inflammation, and CNS structural damage (Kim et al., 2013; Chen et al., 2015). Thus, early treatment of OSA could reduce not only the risk of the above-described pathologies but white matter pathology as well.

OSA and Gray Matter Atrophy

MRI studies have also demonstrated substantial gray matter loss in several cortical regions among OSA patients (compared with normal controls; Macey et al., 2008). Cortical gray matter atrophy (GMAT) occurs in

hypertension (Celle et al., 2012). OSA subjects showed altered functional MRI signals in the thalamus, sensory cortex, supplementary motor cortex, cerebellar cortex and deep nuclei, cingulated cortex, medial temporal cortex, insula, right hippocampus, and midbrain (Macey et al., 2006). Other studies with OSA patients have documented significant GMAT in the parahippocampus (Morrell and Twigg, 2006), right insular gyrus, left gyrus rectus, left precentral gyrus, bilaterally in superior frontal gyri, frontomarginal gyri, anterior cingulate gyri, caudate nuclei, inferior temporal gyri, thalami, amygdala, hippocampus, and some lobules of the cerebellum (Joo et al., 2010). Similarly, other studies have also found GMAT in the frontal and temporoparieto-occipital cortices, thalamus, hippocampus, and some regions of the basal ganglia (in the right hemisphere) and of the cerebellum (Yaouhi et al., 2009). Furthermore, GMAT was reconfirmed in right and left hippocampus, right and left caudate, lateral temporal areas (Torelli et al., 2011), entorhinal cortex, left posterior parietal cortex, and right superior frontal gyrus (Canessa et al., 2011) in OSA patients.

COMMENTS AND PERSPECTIVE

The clinical manifestations of AD are associated with the pathological hallmarks of the disease that include extracellular amyloid plaques, intracellular NFTs, synaptic loss, and neuronal degeneration. Aberrant hyperphosphorylation of tau protein is the main constituent of NFTs. The amyloid plaques are composed of Aβ peptide surrounded by reactive astrocytes and activated microglia (Swerdlow, 2007; Pimplikar et al., 2010).

Currently, it is considered that sporadic late-onset AD arises through interaction among genetic, epigenetic, and environmental factors (Daulatzai, 2015a; 2015b). Such gene–environment interaction would involve deleterious environmental exposure in the presence of a susceptibility gene (Chouliaras et al., 2010; Daulatzai, 2015a,b). Various deleterious environmental exposures that can contribute to AD risk may include aging, hypoxia, unhealthy diet and nutrition, alcohol excess, some metals, pesticides, diabetes, hypertension, inflammation, brain trauma, and education level (Seshadri et al., 2002; Fleminger et al., 2003; Carrillo et al., 2009; Daulatzai, 2010, 2012a,b, 2013a, 2014, 2015a–c; Zhang and Le, 2010; Sivanandam and Thakur, 2012). However, among environmental exposures, CIH resulting from OSA may be one of the most potent in triggering the development of cognitive dysfunction/AD (Daulatzai, 2010, 2012a,b, 2013a,b, 2014, 2015b; Zhang and Le, 2010; Fig. 1).

Hypoxia Upregulates Neurocognitive Impairment

A number of comorbidities, including hypertension, diabetes, and stroke, may influence cognitive changes in OSA patients. These conditions can impact neural vasculature and result in neural damage, leading to cognitive impairment. The hypoxia signal transduction pathway is implicated in playing a cardinal role in ongoing neurodegeneration (Halterman et al., 1999). Neurons in the hippocampus and other neocortical foci have been shown to be selectively affected by cerebral hypoxia/ischemia (Pulsinelli et al., 1982; Chen et al., 1998; see Daulatzai, 2013a,b).

In paucity of oxygen and in aging, hypoxia-inducible factor 1 (HIF-1) binds to its promoters/enhancers and activates several genes, including the one involved in cell death. Activation of the HIF-1 pathway via disparate risk factors such as age, hypoxia, hypertension, hypoperfusion, and neuroinflammation may facilitate Aβ deposition and contribute to AD pathogenesis (see below). Apoptosis has been documented in the CNS in aging (Anglade et al., 1997), OSA (Fung et al., 2012; Daulatzai, 2013a,b), and cardiovascular diseases (Zhang et al., 2004); it involves the activation of caspases that disintegrate the neuronal cell. CIH, an essential component of OSA, is associated with substantial hippocampal and brainstem damage, leading to impairments of neurocognitive, respiratory, and cardiovascular functions (Zhang et al., 2010; Fung et al., 2012). Although the precise molecular events leading to CIH-mediated neuronal cell death remain elusive, the oscillation of O_2 concentrations during CIH linked to hypoxia–reoxygenation and ischemia–reperfusion could increase cellular production of ROS (see below). Neurons may, therefore, undergo apoptosis in response to the above-described toxic processes (Revesz and Geddes, 1988; De Caro et al., 2003; Parenti et al., 2005).

OSA and Alzheimer's Disease—the Overlap

A wide range of cognitive deficits has been identified in untreated OSA patients; these may range from attention and vigilance to memory and executive functions. Exposure of the rodent to CIH is associated with age- and time-related neurodegenerative changes in brain regions and neurotransmitter systems, which are involved in learning and memory, attention, and locomotor activity (Row, 2007). In a sample of 100 patients with SDB (and without other comorbidity), declarative memory and working memory were both significantly and linearly compromised by hypoxemia and/or the respiratory disturbance index (RDI; Adams et al., 2001). Patients with even mild SDB may manifest a vigilance deficit in the absence of substantial sleepiness, performing significantly more poorly on visual vigilance and working memory than controls (Redline et al., 1997). Increases in RDI and increases in daytime sleepiness were found to be associated with increases in cognitive impairment (Cohen-Zion et al., 2001). Although CPAP improves the RDI, mean oxygen saturation, sleep quality, and daytime sleepiness ratings (compared with pre-CPAP values), the treated OSA individuals performed at a level comparable to controls on working memory storage functions; however, they still showed a significant reduction on tests of working memory (Lau et al., 2010). Indeed, some cognitive deficits, such as neuropsychological measures of complex attention, executive function, and psychomotor speed, were more resistant to CPAP treatment (Lau et al., 2010).

This is not surprising given that exposure to IH upregulates persistent and significant astroglial hyperplasia and hypertrophy and neuronal death in parietal brain cortex and hippocampus (Aviles-Reyes et al., 2010; Daulatzai, 2013a,b).

The prefrontal cortex (PFC) is affected negatively by sleep deprivation, and executive functioning is largely dependent on PFC activity (Drummond et al., 1999; Nilsson et al., 2005). Several studies have demonstrated that PFC activity is positively related to gray matter volume in medial temporal lobe in healthy older adults but negatively related in MCI and AD patients (Maillet and Rajah, 2013). Prefrontal sleep spindles mediate hippocampal episodic learning; they are reduced by over 40% in older adults, and dysfunctional sleep further contributes to cognitive decline (Fandakova et al., 2014; Mander et al., 2014). Thus, SDB is a condition that exacerbates metabolic (Drager et al., 2010) and CNS injury and compounds memory difficulty (Beebe and Gozal., 2002; Ayalon et al., 2009; Jackson et al., 2011; Sforza and Roche, 2012; Harper et al., 2013; Mander et al., 2013).

The performance of rats on a hippocampus-dependent spatial learning task is impaired after exposure to 72 hr of REM sleep deprivation (McDermott et al., 2003). Impaired spatial working memory occurs in rats when exposed to IH during sleep (Row et al., 2007). Long-term depression of excitatory synaptic transmission occurs in rat hippocampal CA1 neurons following sleep deprivation (Tadavarty et al., 2009). The underlying mechanisms of this hippocampal deficit involve membrane excitability and synaptic physiology in hippocampal CA1 pyramidal neurons and dentate gyrus granule cells (McDermott et al., 2003; Daulatzai, 2013b). It has been shown that neuronal excitability is severely reduced in CA1 neurons and that inhibition of long-term potentiation of synaptic strength occurs in both loci. These data emphasize that OSA and inadequate sleep produce several molecular and cellular alterations that profoundly impact hippocampal function. Patients with AD have a high prevalence of SDB, predominantly OSA. SDB is more frequent in vascular dementia (Guarnieri et al., 2012; also see Fletcher, 2003; Feldstein, 2012). The concomitant presence of OSA in AD patients can be deleterious (affecting nocturnal sleep and excessive daytime sleepiness) and can aggravate cognitive deficits (McCurry and Ancoli-Israel, 2003). This may be related to multiple pathophysiological factors, including damage to the cholinergic pathways and to the circadian pacemaker (in the suprachiasmatic nucleus; Vecchierini, 2010). Sustained OSA could therefore promote cognitive dysfunction in AD (Pan and Kastin, 2014), and these patients may manifest more severe symptoms and greater cognitive decline. Thus, OSA might represent an important treatable comorbidity in patients with AD.

As described above, the PFC is negatively affected by sleep deprivation (Drummond et al., 1999; Nilsson et al., 2005) and is one of the first regions to be affected in AD. There is evidence of dorsolateral prefrontal contribution to episodic memory impairment in AD (Wong et al., 2014). Similarly, hippocampus-dependent functions are impaired following sleep deprivation (McDermott et al., 2003) and in AD (Daulatzai, 2013a,b). This recognition of the presence of SDB and its impact in AD is important because potentially effective treatments are available to alleviate SDB (Gaig and Iranzo, 2012). Although OSA may aggravate cognitive dysfunction, OSA treatment may improve some cognitive functioning, although not in its entirety (Ancoli-Israel et al., 2008). However, a study (albeit on small number of patients) has documented that long-term CPAP treatment of patients with OSA and AD may result in lasting improvements in sleep, mood, and cognitive deterioration (Cooke et al., 2009).

Hypoxia Promotes Aβ Generation

Hypoxia can promote AD pathology through a molecular mechanism linking OSA-related metabolic dysfunctions and vascular factors such as hypoxemia and hypoperfusion (Innes et al., 2015). Hypoperfusion of brain is an important risk factor for AD (Austin et al., 2011; Mattsson et al., 2014). Cerebral hypoperfusion has a direct effect in upregulating expression of the amyloid precursor protein (APP) and in attenuating Aβ clearance from the brain (Sadowski et al., 2004; Austin et al., 2011). Compared with controls, patients with moderate-to-severe OSA show decreased cerebral perfusion in three well-characterized clusters. These are 1) bilaterally, the paracingulate gyrus, anterior cingulate gyrus, and subcallosal cortex as well as and the left putamen and the left frontal orbital cortex; 2) right-lateralized, the posterior temporal fusiform cortex, parahippocampal gyrus, and hippocampus; and 3) the right thalamus (Innes et al., 2015). It is significant that these are the brain regions that show regional gray matter volume decrease among OSA patients (Yaouhi et al., 2009).

Hypoxia rapidly induces HIF-1α expression, which enhances β-site APP cleavage enzyme 1 (BACE1) promoter activity, causing an increase in Aβ generation resulting from higher APP cleavages (Sun et al., 2006a,b; Guglielmotto et al., 2009a,b; Ogunshola and Antoniou, 2009). Indeed, hypoxia modulates the APP processing by facilitating both β- and γ-cleavage, resulting in a significant increase of Aβ generation in transgenic APP(swe) + PS1(A246E) mice (Li et al., 2009). Under hypoxic conditions, the plaque formations were not only significantly enhanced (1.5-fold) in APP23 transgenic AD mice but they were also larger compared with those of normoxic controls (Sun et al., 2006a,b). After hypoxia treatment, hypoxic mice showed significant decline in memory (Sun et al., 2006a,b). APP23 mice subjected to hypoxia increased the levels of Aβ40 generation by 358% and of Aβ42 by 185% (relative to controls), which facilitated the disease pathogenesis (Sturchler-Pierrat et al., 1997). Consistent with this, increased generation of both Aβ40 and Aβ42 correlated with an increase in endogenous BACE1 following hypoxia treatment (Zhang et al., 2007). These data demonstrate that hypoxia upregulates β-secretase

cleavage of APP and enhances Aβ production. BACE1 expression and its enzymatic activity are known to be increased in AD brains (R. Li et al., 2004; L. Li et al., 2009; Tamagno et al., 2012). Finally, hypoxia is an important risk factor for AD, and the incidence of AD may be highly associated with chronic hypoxic conditions (Jendroska et al., 1995; Kokmen et al., 1996; Moroney et al., 1996; Bazan et al., 2002; Qi et al., 2007).

Hypoxia Upregulates Tau Phosphorylation

A quintessential neuropathological lesion of AD is intracellular tau aggregation, and NFT may lead to neuronal cell death (Arnaud et al., 2006). Several kinases are implicated in hyperphosphorylation of tau. Hypoxia promotes the phosphorylation of tau via the extracellular signal-related kinase pathway, implicating hypoxia in tau pathology and neuronal degeneration (Fang et al., 2010). Numerous studies have emphasized that hypoxia increases tau hyperphosphorylation and drives AD pathogenesis (Sparks et al., 1995; Sparks, 1997; Zhang and Le, 2010; Daulatzai, 2012a,b; 2013, 2014, 2015a,b).

A decrease in glucose metabolism in the hypoxic and hypoperfused brain may trigger the process of neuronal degeneration in AD. Hypoglycemia increases neuronal tau hyperphosphorylation (Lee et al., 2013). Intracerebroventricular injection of streptozotocin (STZ) in Wistar rats selectively affected glucose transporter type 2-bearing cells (astrocytes) and interrupted glucose supply to neurons. STZ treatment increased the levels of phosphorylated tau via activated glycogen synthase kinase 3β (Lee et al., 2013). A sustained increase in intracellular calcium level, leading to activation of caspases, mediates the hypoglycemia-induced cellular damage (Cheng et al., 1991, 1992; Mattson et al., 1991). Disruption of microtubules secondary to hypoglycemia and altered calcium homeostasis may be the crucial processes that underpin neuronal degeneration (Cheng et al., 1991, 1992; Mattson et al., 1991). Indeed, hippocampus-dependent memory and spatial learning were impaired in hypoglycemic rats (Lee et al., 2013).

The release of catecholamines and the sympathetic activation of vascular smooth muscle via catecholamine are involved in the pathogenesis of hypertension in OSA (see above; Foster et al., 2010; Zlokovic, 2011; Muller et al., 2012). AD pathology may be triggered by impaired cerebral perfusion resulting from hypoxia, hypertension, and interrelated cerebral amyloid angiopathy; these may attenuate delivery of oxygen and glucose (Langbaum et al., 2012), impacting neuronal function (Foster et al., 2010; Zlokovic, 2011; Muller et al., 2012). There is compelling evidence for insulin resistance in OSA (Harsch et al., 2005; Steiropoulos et al., 2009). Indeed, cognitive dysfunction is a recognized complication of insulin resistance and hyperglycemia (Craft, 2007; Neumann et al., 2008; Steiropoulos et al., 2009; Sroriz-Filho et al., 2009). Chronic hyperglycemia and hyperinsulinemia stimulate the formation of advanced glucose end products, leading to an overproduction of ROS (Folli et al., 2011), which may accelerate tau hyperphosphorylation (Craft, 2007; Neumann et al., 2008; Sroriz-Filho et al., 2009; Steiropoulos et al., 2009).

Inflammation and Oxidative Stress Upregulate Neurocognitive Impairment in OSA

Overproduction of ROS and reactive nitrogen species (RNS) is deleterious. In a homeostatic state, both ROS and RNS are generated by tightly regulated enzymes, viz, NO synthase (NOS) and NADPH oxidase, respectively. In comparison with other tissues, the brain may generate more ROS because of its innate high oxygen consumption in conjunction with its high lipid content and redox metal ions (Floyd and Hensley, 2002).

Aging is characterized by a progressive decline in physiological functions and is accompanied by many pathological conditions, including an ROS increase. ROS are involved in age-associated damage to macromolecules, causing ROS-mediated oxidative stress and cell signaling dysfunction (Bouzid et al., 2015). Repeated episodes of low and high O_2 in OSA cause oxidant stress (Douglas et al., 2010). CIH in OSA patients perturbs cerebral circulation through NADPH oxidase-derived radicals (Douglas et al., 2010; Capone et al., 2012), and aging is the first and most important risk factor for AD; both are characterized by the elevated levels of ROS and the altered pattern of gene expression that cause impairment of several homeostatic cell functions (Swomley and Butterfield, 2015). OSA patients possess increased systemic markers of oxidative stress (Montplaisir et al., 1992; Carpagnano et al., 2002) and inflammation. Mitochondria and NADPH oxidase are the major sources of ROS in aging and OSA (Zhan et al., 2005); therefore, the generation of ROS is implicated as playing a role in neuronal dysfunctions in AD (Duranteau et al., 1998; Row et al., 2003; Chan et al., 2005).

Role of inflammation. Although the precise molecular and cellular relationship between AD and inflammation remains unclear, proinflammatory mediators are considered to activate signaling pathways that lead to neuroinflammation and neuronal injury (Suridian et al., 2015). Hypoxia has been proposed as one of the major triggers of macrophage (Pasarica et al., 2009; Fujisaka et al., 2013) and cytotoxic T-cell (Rausch et al., 2008) infiltration in tissues. Biochemical and neuropathological studies of AD provide clear evidence for an activation of inflammatory pathways involving systemic inflammation and neuroinflammation (Daulatzai, 2012a,b, 2014, 2015a,b; Mattsson et al., 2014). Several factors, including dysfunctional cerebral microcirculation, contribute inflammatory mediators; in turn, neuroinflammatory pathology further enhances inflammatory cytokines (Nagga et al., 2014; Lee et al., 2015; Yuan et al., 2015). Neuroinflammatory processes resulting from proinflammatory cytokines yield enhanced ROS and RNS (Daulatzai, 2014; 2015a,b) as well as other unknown components that have neurotoxic properties (Torres et al., 2011; Yuan et al., 2015). This proinflammatory milieu in the AD

brain is involved in the pathogenesis of neuronal injury, its degeneration, and apoptosis (van den Borst et al., 2011). When adult rats were exposed to intermittent hypoxia (2-min intervals, 10.5% O_2, for 1, 3, or 14 days), their cortex, medulla, and spinal cord showed rapid inflammatory gene expression depicted by increased mRNA levels of iNOS, cycloxygenase-2, tumor necrosis factor-α (TNF-α), IL-1β, and IL-6. Their microglial Toll-like receptor (TLR4) mRNA levels were strongly upregulated by hypoxia in a region- and time-dependent manner, and this coincided with peak inflammatory gene expression, suggesting that TLR4 may play a role in hypoxia-induced neuroinflammation (Smith et al., 2013; Yao et al., 2013).

Growing, corroborated evidence suggests that inflammation plays a significant role in the pathogenesis of AD. Several studies have examined the role of inflammation in tau pathology; tau phosphorylation was upregulated when inflammation was induced in 3×Tg-AD mice (Kitazawa et al., 2005; Lee et al., 2010). Gene delivery of the proinflammatory cytokine TNF-α into the brain of 3×Tg-AD mice upregulated phospho-tau (Janelsins et al., 2008). Indeed, it has been documented that tau pathology alone, without amyloid oligomers, can cause tau-mediated neurodegeneration (Lee et al., 2001; Bellucci et al., 2004; Jaworski et al., 2011). In 3×Tg-AD/BACE$^{-/-}$ mice, it has also been demonstrated that tau pathology occurs independently in the absence of Aβ generation (Winton et al., 2011). Furthermore, tau phosphorylation upregulated by angiotensin II in the rat brain was attenuated by losartan (Tian et al., 2012).

Role of oxidative stress. Oxidative stress is an early feature of AD and other neurodegenerative conditions. It plays an important role in neural injury and cognitive impairment (Daulatzai, 2012a,b, 2013a,b, 2014, 2015a,b). After hypoxia, the secondary injury mechanisms (see above) plus neuroinflammation and microangiopathy are posited to enhance vascular and parenchymal Aβ deposition and alter its clearance. Aβ activates astrocytes and enhances oxidative imbalance, mediated by neuroinflammation (Wirths et al., 2010). These vicious mechanisms may significantly enhance mitochondrial failure and amyloidogenic APP processing; Aβ accumulation, therefore, promotes both oxidative and inflammatory mechanisms, each accelerating the other. The abnormal production of proinflammatory cytokines and chemokines, the complement system, and ROS can disrupt neuronal function and cause loss of synapses and memory decline (Kljajevic et al., 2014).

OSA-related hypertension, oxidative stress, and the inflammatory milieu (described above) are associated with sustained metabolic stress, driving progressive cellular dysfunction and contributing to neuronal apoptosis, necrosis, and death (Emerit et al., 2004; Kljajevic et al., 2014). Cortical neurons treated in vitro with Aβ and concomitant hypoxic exposure show increased numbers of apoptotic neurons relative to treatment with Aβ alone (Egashira et al., 2002). This further emphasizes the deleterious effect of hypoxia itself that is related to neuronal death, a phenomenon observed in both OSA and AD brains. Decrease in oxygen supply to the brain causes depolymerization of actin filaments in neurons, decreased neuritic sprouting, impaired mitochondrial function, reduced expression of the proteins required to maintain synaptic connections, and, ultimately, neuronal death (Friedman et al., 1998; Breteler, 2000; de la Monte et al., 2000). Indeed, impaired oxygen supply and vascular disease have been emphasized to be involved in AD pathogenesis. Therefore, a synergistic deleterious effect of hypoxia, hypoperfusion, and neuroinflammation may be causally associated with promoting cognitive impairment/AD (Breteler, 2000; Kljajevic et al., 2014).

CONCLUSIONS

The number of patients with OSA and comorbid cognitive decline will rise significantly because of an increasingly aging population. Extensive data related to aging, obesity, and OSA indicate clear links among their pathophysiological mechanisms/pathways and cognitive decline (Fig. 1). Indeed, a history of hypertension caused by OSA may precede vascular dementia, particularly in the presence of heart disease and/or diabetes (Posner et al., 2002). CIH drives a number of the pathological mechanisms described above, including neuroinflammation and microangiopathy; these are related to enhanced Aβ deposition and tau phosphorylation. Aβ activates microglia and astrocytes and enhances oxidative imbalance, mediated by neuroinflammation. These vicious mechanisms lead to mitochondrial dysfunction and further amyloidogenic APP processing; thus, Aβ accumulation may promote both oxidative and inflammatory mechanisms, each accelerating the other. The abnormal production of proinflammatory cytokines and chemokines, the complement system, and ROS can disrupt synaptic function and upregulate neuronal dysfunction and memory decline.

A wide range of cognitive deficits has been identified among untreated OSA patients, from attention and vigilance to memory and executive functions. Indeed, OSA can have a broad impact on cognitive impairments, including sustained attention, working memory, visuospatial learning, motor performance, and executive function (Beebe et al., 2003; Ferini-Strambi et al., 2003). In particular, patients with OSA have been shown to have impaired judgment, prolonged reaction time, and vision problems, all of which can compromise activities of daily living, decision making, and driving ability (Sassani et al., 2004; Ellen et al., 2006). Behavior and mood can also be profoundly affected by a lack of adequate restful sleep in OSA, with increased irritability, aggressiveness, lack of attentiveness, and depression (Schröder and O'Hara, 2004).

Finally, the strength of the evidence presented here emphasizes an association between OSA-related pathological mechanisms and onset of memory and cognitive

dysfunction, which may progress to AD (Daulatzai, 2013a; Pan and Kastin, 2014). The current understanding of the pathophysiology of OSA and its cognitive impact suggests an early and chronic application of therapeutic modalities (Daulatzai, 2015b), including CPAP, to attenuate memory and cognitive dysfunction among OSA patients.

CONFLICT OF INTEREST STATEMENT

The author has no conflicts of interest to declare.

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