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Review Article of Sleep Section

# Obstructive sleep apnea and multiple facets of a neuroinflammatory response: a narrative review

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**Background:** Obstructive sleep apnea (OSA) is a chronic, highly prevalent, multi-system and sleep disorder, which may contribute to cognitive impairment and a variety of structural and neurophysiologic changes. The focus on OSA is warranted given its recognized links with major psychiatric and neurologic disorders, including Alzheimer's disease. Some preliminary studies suggest a dual effect of the inflammatory response in OSA. Neuroinflammation may present with initial, potentially adaptive and homeostatic, and later, a more distinctly maladaptive, precipitating and perpetuating role.

**Objective:** We here propose and argue in favour of the inflammatory process in the brain as a likely binding mechanism behind at least some effects that OSA may have on the brain and its function. Several OSA-triggered molecular and cellular events, that could lead to a neurodegenerative cascade, are similarly discussed.

**Methods:** This perspective reviews the body of literature that investigates potential links between the inflammatory processes in the brain and the OSA. A special emphasis is placed on a potential role for neuroplastin, a novel transmembrane synaptic protein involved in the neuroplasticity and known to be differentially regulated in the OSA.

**Conclusions:** The intricate interplay between neuroinflammation and other mechanistic correlates of OSA add to the evidence that neuroinflammation may be a key target for future therapeutic strategies in a number of comorbid disorders. The future studies will need to answer whether it is sleep fragmentation (SF) or intermittent hypoxia (IH) which may drive any such neuroinflammation.

**Keywords:** TLR2; neuroplastin; sleep; neuroinflammation; obstructive sleep apnea (OSA)

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## Inflammation and sleep-disordered breathing

Obstructive sleep apnea (OSA) is the second most prevalent sleep disorder (1), with higher prevalence in elderly and obese people (2) and incidence of 24% men and 9% of women in 30–60 age group, with further increase in incidence of up to 40–60% for both genders aged sixty five and above (3-5).

Traditionally, the main instigators of OSA-related ramifications have been considered to be the intermittent hypoxia (IH) and sleep fragmentation (SF) (6). However, a more complex picture of OSA-induced injury is emerging (7). The current consensus is that the extent of the associated functional deficits in OSA is likely decided by an intricate interplay of all maladaptive and homeostatic adaptive processes in the brain (7,8). These arguably may include a neuroinflammatory response, along with an individual genetic disposition, a chronic low-grade systemic inflammatory state (2) and any present co-morbidities. In support of the idea that inflammation may play a pivotal role in any such interaction, several studies have highlighted the possible role of a systemic chronic low-grade inflammation in OSA patients (9-11). The presence of inflammatory process is evident by increased levels of the pro-inflammatory cytokines tumor necrosis factor-α (TNF-α) and interleukin 6 (IL-6) that promote the innate immunological response (10). It should be noted that the very definition of chronic low-grade inflammation remains elusive, and that its use commonly refers to states defined by chronically increased inflammatory markers of the innate immune system [i.e., C-reactive protein, IL-6, TNF-α, white blood count (WBC), neutrophils] (10,12).

In past preclinical studies, the mimicking of the OSA-related mechanical stress in the upper airway has been shown able to induce a localized inflammatory cascade (13). For example, SF has been linked to increased upregulation of TNF-α in mice, and, in pediatric OSA patients, this increase has been reported as directly related to the degree of SF and the body mass index (14,15). Similarly, IH strongly upregulates IL-6 production, which, along with the abundance of TNF-α, may additionally lead to the excessive sleepiness seen in OSA (16). When etanercept, an anti-TNF-α medication for rheumatoid arthritis, is offered to objectively sleepy OSA patients, significant symptomatic and measurable improvement is detected in their sleepiness (17). The magnitude of that improvement is three times higher than the reported of positive airway pressure (PAP), and proportional to the reduced TNF-α and IL-6 levels (17,18).

More recently, another link between OSA and systemic low-grade inflammation has been proposed to occur via an acquired dysbiosis. The OSA-related IH increases the proportion of anaerobic bacteria in the microbiota, while the SF activates directly the innate immune system, and both assist in the increased intestinal permeability, that eventually promotes low-grade endotoxemia and chronic inflammation (19-22). These processes appear to develop even in mild severity cases of OSA (23).

An ever increasing body of literature also supports the notion that the mechanistic links between IH, SF and the pro-inflammatory cytokines could be regulated by the idiosyncratic genetic predisposition and the overall (epigenetic) impact of the environmental factors (10). For example, the *-174 G/C IL-6* gene polymorphism for IL-6 has been associated with increased IL-6 levels in OSA patients, but not the -572 G/C (24,25). Also, it has been further advanced that, in cases where CPAP treatment fails to get the pro-inflammatory cytokines under control, other known factors of low-grade inflammation such as obesity and cardiovascular diseases, which often coexist in OSA patients, likely explain that failure in statistical models (24,25).

The prevalence of OSA in patients with obesity/metabolic syndrome (MS) is estimated at 45–60%, and SF is known to promote obesity (26,27). Regrettably, even with the adequate treatment in place (e.g., with PAP), many of the patients report further weight gain (22,28). The MS (i.e., obesity, hypertension, hyperinsulinemia, glucose intolerance and dyslipidaemia) is in turn strongly associated with systemic low-grade inflammation mainly generated from the adipose tissue, and through the secretion of the pro-inflammatory cytokines and leptin resistance (29). Leptin is the satiety hormone, the interactions of which commonly lead to a reduction in calory intake. This effect appears to be decreased in OSA, which may further contribute to development of insulin resistance and diabetes type 2 in such patients (30). Ultimately, it is of note that MS also posits a cocktail of risk factors for cardio-vascular disease (CVD), and presents as the linkage between CVD and OSA, with low-grade inflammation as their shared mechanism (29,31).

Moreover, OSA has been linked to impaired synthesis, secretion, and timing of melatonin (32-34). Melatonin's beneficial role in suppression of development of insulin resistance, and thus its possible role in correction of ensuing metabolic dysregulation has been argued (35). Melatonin also plays the role in reduction of the formation of free oxygen radicals and prevention of mitochondrial dysfunction, which can lead to oxidative stress (36,37).

It also exerts a dual immunomodulatory function, with upregulation of the brain and muscle Arnt-like protein-1 (BMAL1) transcription factor, an established inhibitor of herpes simplex virus and influenza (38). Its role as an anti-inflammatory agent under conditions concerning senescence have similarly been argued, and its main effects appear to lead to reduction of pro-inflammatory cytokines and upregulation of the anti-inflammatory ones (39,40). Thus, even smaller modulation of this effective anti-aging agent might lead to reduction of its role against 'inflammaging' and contribute to a low grade systemic chronic inflammation in patients with OSA (41).

In this perspective review, we evaluate and appraise the current body of evidence which supports the notion that neuroinflammation may underly several pivotal functional and neuroanatomical effects of OSA on the brain. Moreover, we propose and argue for the potential role for the transmembrane synaptic protein neuroplastin in this process. We present the following article in accordance with the Narrative Review reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1231/rc).

## Neuroinflammation in OSA

One of the important unresolved questions in the sleep medicine is whether its second most prevalent sleep disorder, OSA, may indeed also lead to inflammatory responses in the brain (5,6,42,43). This is of particular note as neuroinflammation has been argued to act as a shared archetypal mechanism in the pathogenesis of Alzheimer's disorder (AD), depression and several other major neurologic and psychiatric disorders with which OSA appears to share a complex bidirectional link (6,42,44). Our group has long argued that accumulating data does suggest that neuroinflammatory process occurs in OSA, and that it drives specific structural and behavioural changes known to afflict some susceptible OSA patients (42,43,45-49). More recently, we have been able to demonstrate that under OSA-like conditions in rodents, the neuroinflammatory response is indeed instigated in the forebrain and the septal nuclei regions, important cholinergic regions of the brain, with a later widespread and marked chronic component. Furthermore, we have demonstrated that subsequent structural changes develop in distinct neuroanatomical regions with monosynaptic connections to initial frontal and basal forebrain cortical sites of inflammatory response (6). It is widely accepted that acetyl-choline-mediated enhanced processing of sensory information underlies the cognitive process of attention, known to be impaired in patients with OSA (42). It has been argued that a variety of attention-related cognitive operations that together contribute to the detection and discrimination of stimuli are significantly impacted in OSA, and inflammatory processes in these regions may contribute to this (7,45). Moreover, as the integrity of attention processes contributes to the efficacy of higher-order cognitive functions such as learning and memory, it is perhaps unsurprising that these domains have been similarly shown as impaired in some patients with OSA (7,45). In addition, numerous behavioral studies have also implicated basal forebrain cortical cholinergic inputs in sustained attention functioning (50). Most notably, though, the neuroinflammation-driven changes were also shown to underlie several specific observed behaviours, including development of agitated (mal)adaptive behaviour under episodes of stress, and an increased ability to gain weight (6).

Several pivotal preclinical studies over the last several decades have similarly supported this notion. For example, data from rodent studies suggest that SF significantly increases systemic IL-6 serum concentration and hippocampal transcription of IL-6 in mice without further cognitive impairment (51). Further studies have shown that few hours of sleep deprivation can cause increase in astrocytic phagocytosis of presynaptic elements in mouse cerebral cortex, which could be a compensatory response to increased synaptic activity after prolonged wake. Moreover, there is indirect evidence, from both clinical and preclinical studies, that sleep loss may be similarly detrimental to oligodendrocytes, and to the production of myelin (52,53). It has been reported that chronic sleep loss can reduce myelin thickness (52). This effect may have important functional consequences in patients with OSA too, especially given the fundamental role of myelin in optimizing the information flow throughout the brain (53-55). Chronic sleep deprivation, in addition, activates microglia and their phagocytic activity (56). Another study that determined effects of sleep disturbance in mice showed increased IL-6 levels and induced microglial activation in hippocampus, but not in cortex, one and seven days after 24-hour long sleep disturbance (57). Mice (C57BL/6) exposed to chronic IH for 4 weeks showed elevation of Toll-like receptor 4 (TLR4), myeloid differentiation factor 88 (MyD88), TIR-domain-containing adapter-inducing interferon-β (TRIF), pro-inflammatory cytokines and oxidative stress which was ameliorated by concomitant atorvastatin administration (58).

On the other hand, in rats, chronic sleep deprivation

(21 days) results in anxiogenic behaviour and memory decline and in increased levels of pro-inflammatory cytokines (TNF-α, IL-1β) in hippocampus and piriform cortex, as well as increased expression of glial fibrillary acidic protein, GFAP and Iba1 (59). Another study showed that IH (2-min intervals, 10.5% $O_2$, for one, three, or 14 days) caused increase in gene expression of inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), TNF-α, IL-1β, and IL-6 in rat cortex, medulla, and spinal cord. Additionally, microglial TLR4 mRNA level was upregulated after hypoxia in a region- and time-dependent manner (60-62).

Neuroinflammation has been argued to present a key linking element that interacts with the three neurobiological correlates of major depressive disorder too (63). Unregulated inflammatory response in the brain has been argued to lead to depletion of brain serotonin, dysregulation of the hypothalamus-pituitary-adrenal (HPA) axis, as well as to alteration of the continuous production of adult-generated neurons in the dentate gyrus of the hippocampus (63). In that background, it has been proposed that kynurenine pathway alteration and HPA axis dysregulation may have the common effect of increasing extracellular glutamate levels and glutamate neurotransmission, which can then impact adult hippocampal neurogenesis (63). This pathophysiological cascade appears to be correspondingly triggered during sleep deprivation (64), and it may present the common link between affective disorders, insomnia, OSA and neurodegenerative disorders, including Alzheimer's disease (AD) (42). Interestingly, an early antidepressogenic effect of the TLR2-dependant neuroinflammatory response in OSA has been demonstrated in the animal model, functionally linked to a distinct fronto-brainstem subcircuitry (6). In past, activation of a similar network in mice has been reported to favor effortful behavioral responses to challenging situations (65). For instance, a selective activation of a subclass of prefrontal cells that project to the brainstem has been shown to induce a rapid and reversible effect on selection of the active behavioral states (65). Based on this, it is tempting to argue that any such initial inflammatory response may play an adaptive role, and that it may initially help the organism to focus on continued trying to find its way out of a complex predicament (6). With time, however, any such prolonged behavioral response would conversely develop into an 'agitated' depressive profile, with strong maladaptive anxiety component (6). In keeping, similar mixed anxiety and depression endophenotype has been previously described in some patients with OSA (66), and it has been traditionally linked with higher suicide risks in depressed patients (6,67).

Taken together, and in spite of certain controversies, both preclinical, as well as human studies that investigated inflammatory markers in patients with OSA (68-84), increasingly indicate that there is reliable cumulative evidence supporting OSA as a low-grade chronic inflammatory disease which likely can also induce neuroinflammation and neuronal injury (10).

## Shared pathomechanism with neurologic and neurodegenerative disorders

Over the last decade, the links between OSA and earlier onset of neurodegenerative changes and cognitive decline have been emphasised (42,62,85-87). The additive effect of changes in sleep quality and structure, cerebral blood flow and the cellular redox status in OSA patients may contribute to cognitive decline, and may further aggravate AD and other neurodegenerative processes' (88) progression (42,44). Also, a recent meta-analysis suggests that patients with AD may have a five times higher chance of presenting with OSA than cognitively non-impaired individuals of similar age (44). Moreover, it has been similarly argued that around half of patients with AD will have experienced OSA at some point after their initial diagnosis (44). In addition, OSA prevalence increases with age (89-91), and a recent two-year longitudinal study showed an increase in markers of amyloid burden, a hallmark of AD in the cerebrospinal fluid (CSF) in elderly OSA patients (85,86). Furthermore, CSF levels of total and phosphorylated (P) tau (87), and inflammatory protein YKL-40 (neuroinflammation/astrocyte activation marker) predict poor sleep in cognitively healthy adults, older than 65 years, with increased Aβ42 CSF values (92). Studies have reported that patients with OSA are more likely to develop mild cognitive impairment (MCI) and AD at a younger age (93). In the same vein, a recent meta-analysis of longitudinal studies reported that individuals presenting sleep disturbances, such as insomnia, OSA, sleep-wake rhythm disorders, have a high risk of developing all-cause dementia, AD, and vascular dementia (94). Moreover, insomnia increased the risk of AD but not vascular or all-cause dementia, whilst OSA was associated with an increased risk of all-cause dementia, AD, and vascular dementia (94). Shared pathological findings between OSA and AD include sleep architecture disturbances, neurogenic neuroinflammation, changes in multipartite synapse and impaired clearance of toxic Aβ and tau (42). Several studies, including a recent cross-sectional study, suggest that there is

an increase in brain amyloid in OSA patients, in comparison to healthy controls (86,95,96). However, conversely, a number of studies have failed to report changes in CSF tau protein levels in patients with OSA (87,97). Nonetheless, it appears that OSA could act to induce a faster longitudinal increase in CSF tau levels in patients with MCI and AD (85,87). Distinct gender effects and links with a specific limbic phenotype of AD have also been argued (98). However, the exact molecular mechanisms leading from SF and apnoeic events to neurodegeneration remain unclear.

Accumulating body of evidence suggests that various innate cellular adaptive and plasticity mechanisms are triggered in neurodegeneration and occur in an unregulated manner eventually aggravating neuropathologic and clinical findings (99). Moreover, when one considers some of the features of main AD pathological hallmarks, a clear convergence of at least two different types of tissue response to injury emerges: (I) reactivation of fetal phosphorylation pattern of tau protein, which contributes to cytoskeletal disorganization and impaired axonal transport; (II) immune reaction to amyloid formation and accumulation, which leads to chronic neuroinflammation and further structural and functional alterations and neurodegeneration (99,100).

Although typical neurofibrillary degeneration and amyloid deposits are being distributed in a specific spatio-temporal pattern in AD, they likely present common final points of long-lasting cellular changes in different neurodegenerative disorders and are triggered by mostly un-known cause(s). It has been long speculated that in understanding and elucidating the very early molecular alterations, one may learn how to unravel and prevent the formation of the core of several shared pathomechanisms of neurologic and neurodegenerative disorders (7,42). Having in mind that synaptic remodeling and plasticity is of pivotal importance for functions of brain tissue, and that dynamic cross-talk between neurons and different types of glial cells is involved in maintenance of synaptic homeostasis, searching for specific molecular mediators of neuron-glial interactions in (patho)physiological conditions becomes particularly promising line of enquiry. Indeed, several recent studies indicate new potential partners in such an interplay between microglia and neurons, namely TLR2 and neuroplastin. As reported by Polsek *et al.* (6), TLR2 is involved in initiating and modulating inflammatory response in specific brain areas in the murine OSA model. Moreover, immune response and structural changes triggered by microglial activation and TRL2 actions have been shown to influence on expression of several neuroplasticity markers such as neuroplastin. Transmembrane synaptic protein neuroplastin, which belongs to a family of cell-adhesion molecules (101,102), has been source of much attention since its discovery (103). Its role in long-term potentiation, synaptic plasticity and cognition has been widely acknowledged (104-107). Nonetheless, to date majority of neuroplastin actions have been predominantly reported in the preclinical studies, whilst just a few studies report on its expression and distribution in the human brain (108,109). More recently, however, neuroplastin has been argued as potential biomarker of AD progression, and its involvement in human hippocampal tissue reorganization has been demonstrated, i.e., plasticity response in the early AD neurodegeneration process (103,109). Arguably, a functionally relevant interplay between TLR2 and neuroplastin may form also through their intertwined intracellular signaling pathways. In keeping, it has been suggested that this interplay may occur through the same adaptor protein TNF receptor-associated factor 6, TRAF6 (110,111). Similarly, the early dysfunction of microglia-neuron cross-talk in OSA could also be a consequence of disturbed interactions between TLR2 and neuroplastin (6) (also see *Figure 1*). Given that TLR2 and neuroplastin share intracellular signaling cascade, and they are both involved in adaptive cellular mechanisms vital for neurons, i.e., regulation of immune response and synaptic plasticity it is tempting to argue that these membrane proteins may indeed play an important role in the bigger archetypal puzzle of brain's vulnerability to SF and oxidative stress (101,111).

## Conclusions and future directions

It is undisputable that cognitive and neurologic dysfunction occur in the majority of patients with OSA (7). The evidence towards its links with the major psychiatric and neurologic disorders is similarly accumulating (7). However, the exact nature of the mechanisms that cause these effects remain to be defined, as does the extent of the relationship and directionality between these factors and any potential inflammatory process in the brain. It is hoped that well defined future multimodal imaging studies, ideally performed in patients with OSA but without any overt co-morbidities, will enable us to finally resolve whether the neuroinflammatory process may indeed present in OSA.

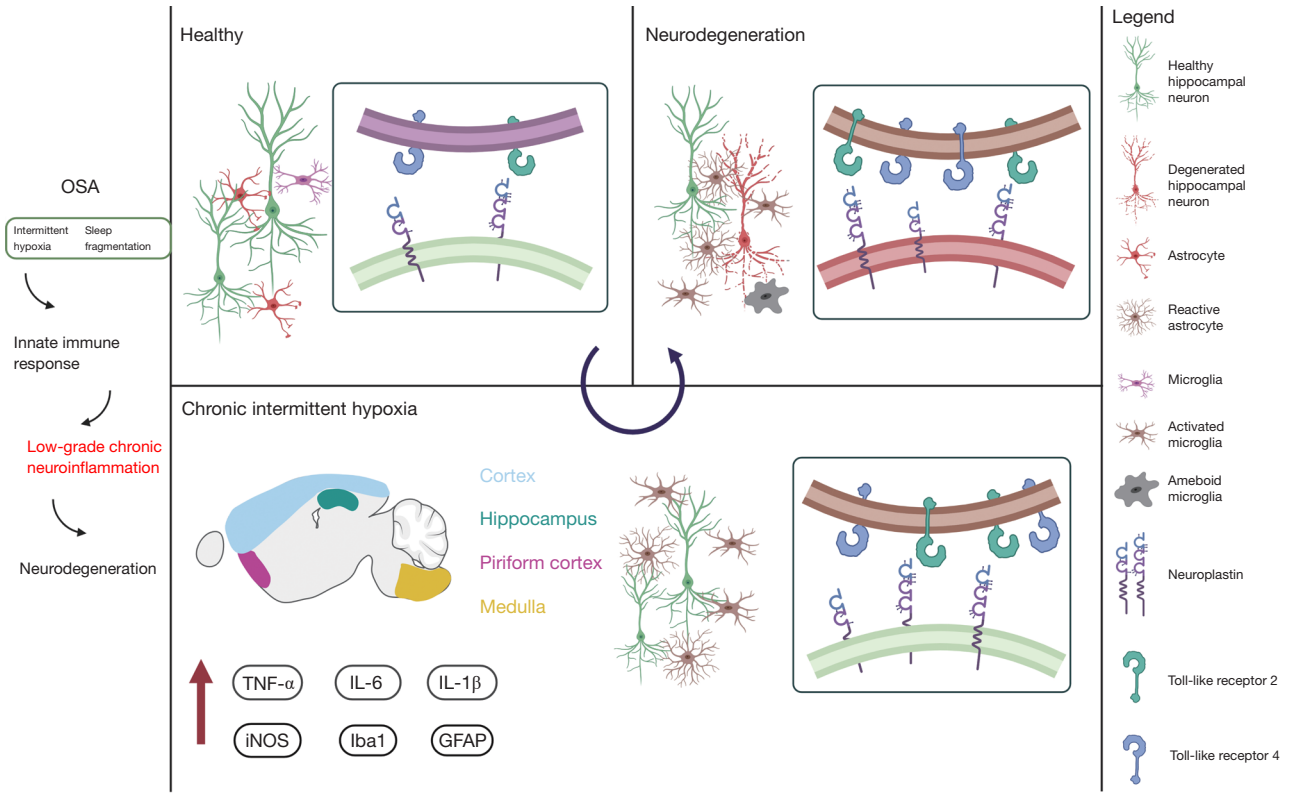


**Figure 1** Schematic sequence of hypothesized molecular and cellular events triggered by OSA, which may lead to neurodegeneration. Theoretic shared pathomechanisms encompass the following cascade of events: an initiation of a low-grade chronic neuroinflammation by increased secretion and expression of immune response mediators in specific brain areas. This may lead to the oxidative stress, with microglial and astrocytic activation co-occurring along increased pro-inflammatory cytokines production. Thus altered protein interactions between neuronal neuroplastin and microglial Toll-like receptors likely contribute to a complex mechanism of restoring tissue homeostasis, and they may further lead to a prolonged chronic activation of microglia and astrocytes. Such prolonged activation of glia cells likely leads and promotes dysfunction/failure of neuron-glia adaptive capacity, and instigation of further neurodegenerative processes and neuronal injury. Created with BioRender.com. OSA, obstructive sleep apnea; TNF-α, tumor necrosis factor-α; IL-6, interleukin 6; IL-1β, interleukin 1β; iNOS, inducible nitric oxide synthase.

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