Review Article
Fundamental role of pan-inflammation and oxidative-nitrosative pathways in neuropathogenesis of Alzheimer's disease in focal cerebral ischemic rats

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Abstract: Alzheimer's disease (AD) is a chronic progressive neurodegenerative condition of the brain, and it is the most common cause of dementia. Several neurobiological etiologies of AD are described in the literature. These include vascular, infectious, toxic, nutritional, metabolic, and inflammatory. However, these heterogeneous etiologies have a common denominator - viz. Inflammation and oxidative stress. Lipopolysaccharide (LPS) elevates the synthesis of proinflammatory cytokines and chemokines; chronically, together they trigger various pathological responses in the periphery and the CNS including dysfunctional memory consolidation and memory decline. Aging - the main risk factor for AD is inherently associated with inflammation. There are several age-related comorbidities that are also associated with inflammation and oxidative stress. Such co-prevailing aggravating factors, therefore, persist against a background of underlying aging-related pathology. They may converge, and their synergistic propagation may modify the disease course. A critical balance exists between homeostasis/repair and inflammatory factors; chronic, unrelenting inflammatory milieu succeeds in promoting a neuroinflammatory and neurodegenerative outcome. Extensive evidence is available that CNS inflammation is associated with neurodegeneration. LPS, proinflammatory cytokines, several mediators secreted by microglia, and oxidative-nitrosative stress in concert play a pivotal role in triggering neuroinflammatory processes and neurodegeneration. The persistent uncontrolled activity of the above factors can potentiate cognitive decline in tandem enhancing vulnerability to AD. Despite significant progress during the past twenty years, the prevention and treatment of AD have been tantalizingly elusive. Current studies strongly suggest that amelioration/prevention of the deleterious effects of inflammation may prove beneficial in preventing AD onset and retarding cognitive dysfunction in aging and AD. A concerted multi-focal therapeutic effort around the inflammation-oxidative-nitrosative stress paradigm may be crucial in preventing and treating AD. This paper informs on such relevant polypharmacy approach.

Keywords: Alzheimer's disease, aging, LPS, proinflammatory cytokines, neuroinflammation, oxidative stress, nitrosative stress, microglia, amyloid, tau

Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder of the aged characterized by the accumulation of amyloid-β (Aβ) and hyperphosphorylated tau (Ptau). These are present aggregated in amyloid plaques, and neurofibrillary tangles respectively - causing synaptic and neuronal loss, and enhancing cognitive dysfunction. AD is a multifactorial neurodegenerative condition and accumulating evidence has shown inflammation to be an integral part of its etiology [1-16]. A host of comorbid conditions are associated with aging; these include - endo-toxemia, type 2 diabetes, obesity, metabolic syndrome, obstructive sleep apnea (OSA), and sleep loss. All these conditions upregulate inflammation [17-24]. Indeed, several studies indicate that inflammatory mechanisms are upregulated by the above comorbid conditions. This diverse group of conditions induces primary and secondary mechanisms that upregulate inflammation and increase physiologic dysfunction in older adults. Inflammation is driven by interacting mechanisms including damage-causing proinflammatory mediators, reactive oxygen species (ROS), excitotoxicity, calcium perturbations/increase, and dyshomeostasis,

among others. These can be superimposed and synergistic, thus strengthening the deleterious pathophysiological state. There is supportive evidence for inflammation being an initial insult in cognitive decline. Indeed, dysfunctional cognition may also occur in the so-called normal elderly following: a) peripheral infection [25, 26], b) delirium due to general anesthesia [27, 28], and c) neurotoxic conditions affecting neurons, as in hypoxia/hypoxemia [29, 30] - all these are associated with inflammation.

Mild, higher levels of bacterial endotoxin (about ~1-100 pg/mL), persist in circulation in humans with adverse health conditions and unhealthy life styles such as aging, obesity, chronic infections, and chronic alcohol consumption and smoking [31-37]. The causes of mild but persistent increase in plasma endotoxin are several including compromised gut mucosal barriers, dysbiosis (i.e. altered commensal and pathogenic gram-negative microbiota ratio), and vasculature leakage. Lipopolysaccharide (LPS) found in the bacterial wall is present in the intestinal lumen and reaches the circulation causing metabolic endotoxemia. However, inflammation is upregulated when LPS binds to Toll-like receptor 4 (TLR4) [38]. The ongoing smoldering subclinical mild endotoxemia causing low-grade but persistent inflammatory response induces the generation of inflammatory cytokines/mediators [39]. The latter underlie the pathogenesis and propagation of various chronic conditions including obesity, cardiovascular diseases, diabetes, neurodegenerative conditions, and indeed inflammatory diseases [31, 40-48]. The pathways involving those mentioned above are being continually investigated and defined [49]. Given the deleterious pathological effects caused by inflammation, engendered by endotoxemia and proinflammatory mediators, therapeutic strategies should target this persistent pathological scenario to prevent and treat the above mentioned debilitating conditions.

Inflammation is meant to be beneficial to clear pathogen and phagocytose apoptotic cells/debris; however, when inflammation remains uncontrolled and becomes chronic, it leads to the production of neurotoxic mediators/proinflammatory cytokine that exacerbates neurodegenerative pathological outcome. Cytokines and Chemokines are proinflammatory proteins that mediate the body's immune response.

Their dysregulation is a cardinal feature in some pathological processes including the neuroinflammation, neurodegeneration, and demyelination. Pathologies in the CNS activate microglia that upregulates the production of these proinflammatory mediators, lead to glial and neuronal injury, and their death (see below). The above mentioned, therefore, orchestrates a scenario of imbalance between homeostasis-repair and inflammatory-neurodegenerative processes.

An excessive inflammatory response is characterized not only by elevated inflammatory cytokines, but by increases in mitochondrial dysfunction, reactive oxygen species (ROS), and nitric oxide (NO). Consequently, there may be damage to the systemic vascular endothelium, redox-glutathione depletion, and mitochondrial respiratory dysfunction causing reduction in ATP and $O(2)$ consumption. Although, ROS are essential as antioxidant defenses in cells; however, an excess of ROS production is harmful to homeostasis. The resulting cellular pathologies, therefore, are a function of mitochondrial dysfunction and an excess of oxidative stress damage. Hence, inflammation and oxidative stress are intertwined [50-54]. LPS-induced ROS signaling from mitochondria has been demonstrated to be critical in macrophage activation [55]. Conversely, antioxidants not only reduce mitochondrial damage, but they may also reduce interleukin-6 levels [54] and decrease LPS-stimulated proinflammatory cytokines [56].

The molecular mechanisms underlying the pathogenesis of sporadic AD are being unraveled on a continuous basis in the literature [1-24]. This enormous amount of data, however, are now available on their involvement in AD pathophysiology. Overall, the purpose of this review is to discuss key concepts of inflammation, immune-reactivity, and oxidative stress in the context of aging, comorbid conditions, neurodegeneration, and cognitive decline. This review describes the salient literature and discusses major studies regarding alterations in proinflammatory mediators and oxidative stress. There is an emphasis on heterogeneous disease conditions promoting neuroinflammation, and inter-relationship between neuroinflammation and neurodegeneration that may lead to cognitive impairment and AD. Additionally, an important pharmacological ap-

proach is described that may inhibit both inflammation and oxidative stress, ameliorate cognitive decline, and possibly treat AD.

Aging and inflammation

Aging represents a state of complex multifactorial pathways that involve an ongoing molecular, cellular, and organ damage causing functional loss, disease vulnerability, and eventual death [57]. Dysfunctional aging and an increased risk of death owe their origin to diverse unfavorable factors including genetic, epigenetic, and nongenetic including lifestyle and environmental factors [58].

In aging, there is a 2-4-fold increase in serum levels of inflammatory mediators such as acute phase proteins and cytokines. A variety of factors may maintain this low-grade inflammation; these include - increased adipose tissue, smoking, excess alcohol, indolent infections (asymptomatic microbial), and chronic disorders of gastrointestinal, respiratory, and cardiovascular systems [59-63]. The pathogenetic role of proinflammatory cytokines may conceivably constitute a link between dysfunctional physiology, dysfunctional aging, and co-prevailing persistent age-associated diseases [64].

Interestingly, compared with younger individuals, healthy aged persons may suffer impairment in their memory following deleterious events such as severe bacterial infection, surgery, or psychological trauma. These life events may trigger an increased and prolonged production of proinflammatory cytokines and neuroinflammatory response during aging. This has been shown to be due to sensitization/priming of microglia that is the source of this heightened proinflammatory response. An enhanced neuroinflammatory response may impair synaptic plasticity, and cause a reduction in Arc (important mediator of synaptic plasticity) and BDNF (brain-derived neurotrophic factor) - the important downstream factors. The above-mentioned mechanisms are crucial in impacting/decreasing long-term memory [65, 66].

There is an array of proinflammatory factors in addition to cytokines. These, e.g. include homocysteine, C-reactive protein (CRP) and alpha-1-antichymotrypsin (ACT). In a study, the correlation was studied between homocysteine and 6-year cognitive decrease, and the critical role

of Interleukin-6 (IL-6), CRP, and ACT. Higher homocysteine was negatively associated with lower information processing speed and a decline in cognitive function. The above negative association was highest in the presence of high level of IL-6. Similarly, higher CRP plus higher homocysteine were associated with decreased memory retention. Further, higher ACT plus higher homocysteine were also associated with lower information processing speed and faster decline. The above data reflect that a combination of inflammatory factors underlies cognitive impairment [67]. Furthermore, high serum CRP levels in association with high IL-6 levels were a significant risk factor for vascular dementia (VaD). Notably, just hyperhomocysteinemia (Hhcy) was correlated with increased risk of AD [68, 69].

LPS induces memory impairment in old mice compared to young animals [70-72]. Thus, disruption of cognitive processing [73, 74] in the old animals by LPS suggests that in old animals the hippocampus is vulnerable to cytokines, LPS, and an acute infection [75-82]. Importantly, LPS-challenged old animals had difficulty in locating the platform in Morris Maze test. This suggests that cognitive decline can be ameliorated when the neuroinflammatory response is minimized and kept under control [83].

As in neurodegenerative diseases, microglia is primed in aging also [84, 85]. Consequently, microglia in the aged brain respond to the inflammatory signals (e.g. infection) and generate more proinflammatory interleukin-1beta (IL-1β) for a longer duration than microglia in younger brains [17]. Indeed, LPS administration also resulted in an elevated proinflammatory cytokine response in the aged brain [84, 86, 87], as did *Escherichia coli* administration to older rats [82]. As well as higher proinflammatory cytokine response in the brain, LPS-injected aged mice demonstrated behavioral dysfunction, and a decline in hippocampal-dependent learning and memory - again compared with younger animals [84, 86, 88]. Similar to rodent data, acute cognitive impairments are common in the elderly humans (aged 65 years or older) suffering from peripheral infection [89, 90]. Hence, microglial cell priming, neuroinflammation, and dysfunctional physiological processes activate neuropathology in the aged brain [17, 91].
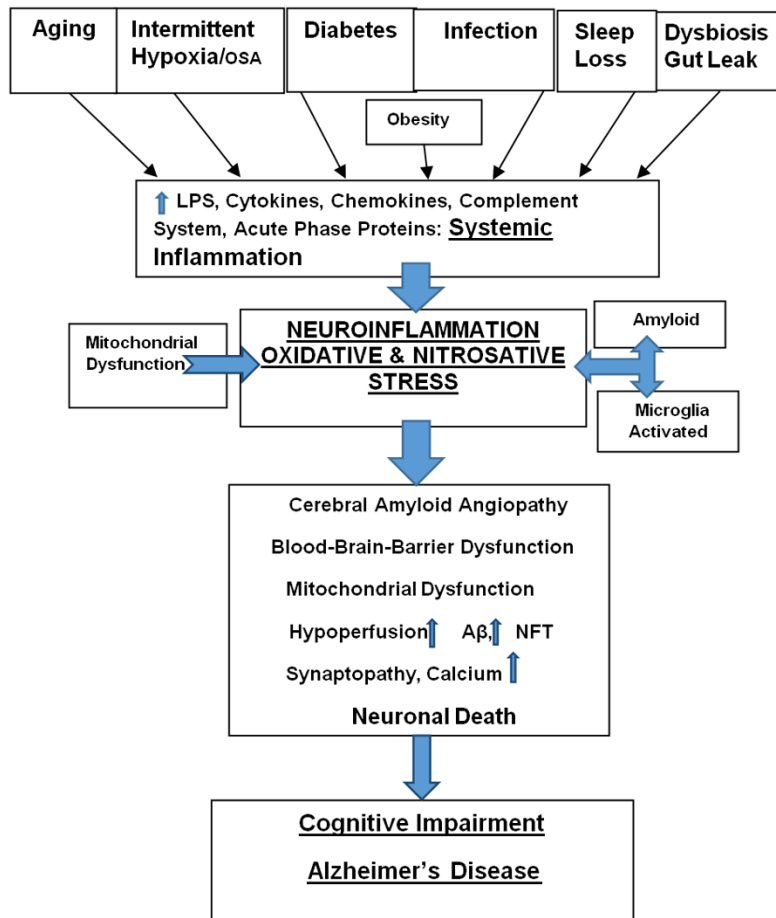
Figure 1. Schematic representation of the pathogenesis of cognitive decline in aging and AD. Aging in conjunction with several comorbid conditions/risk factors including obesity, hypertension, diabetes, hypoxia/OSA, infection, sleep loss and dysbiosis synergistically promote a complex inflammatory milieu. The latter is comprised of LPS, Cytokines, Chemokines, Complement System, and Acute Phase Proteins such as CRP - they are the components of systemic inflammation. The latter triggers neuroinflammation and oxidative-nitrosative stress mediated by activated microglia and amyloid. The above cascade leads to several pathologies including cerebral amyloid angiopathy, blood-brain-barrier dysfunction, mitochondrial dysfunction, and cerebral hypoperfusion. They lead to the accumulation of Aβ, NFT, and neuronal calcium causing neuronal death. An escalating neurodegeneration promotes cognitive/memory decline and AD.

on BDNF; however, the combined effect of aging plus infection might disrupt BDNF production and its processing in the hippocampus. Indeed, inflammation-related BDNF reduction in synaptosomes may evoke long-term memory disruptions in aging [93]. BNDF is known to function in neuronal protection from dysfunction due to infection or injury; it plays a vital role in hippocampal plasticity processes. However, memory is compromised by deleterious effect of cytokines such as IL-1β. Thus, aging and inflammatory response in the brain depletes BDNF required to maintain memory-related plasticity processes at synapses in the hippocampus [94]. Minocycline, an inhibitor of microglial activation has been shown to restore significant LTP in middle-aged rats administered arthritis adjuvant systemically [95]. (Also, see below).

Heterogeneous comorbid conditions and inflammation: different roads but same destination

Various disease pathologies often co-exist in aging (**Figure 1**). The predisposition, interaction, and causation of these disease conditions in aging evoke different pathologies. However, since they have an impact on inflammation, it is important to appreciate their role in neuroinflammation in various age-related disease. In keeping with aging being a state of low-grade inflammation, the plasma concentration of LPS and its binding protein are significantly higher in older subjects [96]. This reflects the presence of metabolic endotoxemia, i.e. the presence of increased plasma endotoxin level in old age and metabolic disease [96].

Aging and comorbid age-related diseases might have an impact on synaptic plasticity in the hippocampus, to produce memory failures. For example, the LTP (long-term potentiation) induced in area CA1 (using theta-burst stimulation) is compromised by the combined effects of aging and infection [92]. Likewise, immune challenge e.g. employing intraperitoneal injection of *E. coli* disrupts hippocampus-dependent memory in aged (24-month-old), but not young (3-month-old), F344xBN rats. Synaptic plasticity and long-term memory strongly depend

Obesity and inflammation

It is well characterized that negative health outcomes are associated with high levels of fat within the abdominal cavity. Obesity enhances systemic inflammation and proinflammatory cytokines [97-99]. The visceral obesity-induced systemic inflammation is linked to the pathogenesis of insulin resistance [100], type 2 diabetes [101, 102], hypertension [103], and cardiovascular disease [104]. The adipose tissue is a rich source of metabolically active adipocytokines including leptin, plasminogen activator inhibitor-1, adiponectin, and resistin [105]. Also, adipose tissue in obese persons secretes high levels of some inflammatory cytokines including TNF-α, IL-6, and IL-8 [106]. Stem cells derived from adipose tissue of obesity showed hyper-responsiveness to hypoxia and strong nuclear factor-κB (NF-κB) activation that may, in turn, sustain inflammation [107]. Hence, NF-κB inhibitors might curtail the obesity-induced inflammation. Systemic inflammation is a precursor of neuroinflammation (see below). The neuroinflammation worsens central pathways of energy regulation/energy balance, perturbs nutrient metabolism, and triggers several disease states such as obesity, diabetes, and cardiovascular problems [108]. These conditions then impact physiological function/homeostasis and perturb neural regulation. Indeed, there is accumulating evidence that high-fat diet and obesity induce gliosis and inflammation in the human and rodent hypothalamus [109, 110], and perturb the hypothalamic function [111, 112].

Gut microbiota and metabolic endotoxemia-inflammation

High-fat consumption causes changes in gut microbiota, i.e. dysbiosis (an increase in pathogenic bacteria at the expense of commensals), and this generates high plasma concentration of LPS, termed metabolic endotoxemia. The latter has been correlated with a decrease in glucose intolerance, adiposity, oxidative stress, and mRNA expression related to macrophage infiltration in visceral adipose tissue. Of note, high-fat consumption strongly enhanced intestinal permeability via reduced expression of proteins of the tight junctions. This shows a close inter-connection between metabolic endotoxemia, inflammation, and intestinal permeability to LPS. Importantly, metabolic endo-

toxemia has been shown to upregulate both obesity and insulin resistance [20, 113]. Indeed, bacterial LPS is a triggering factor for the above disease states. Hence, LPS may be an important therapeutic target, and lowering plasma LPS concentration could be a viable strategy to ameliorate/retard metabolic diseases [20]. Further, favorable intestinal microbiota e.g. bifidobacteria prevent the deleterious effect of endotoxemia [19, 20, 31]. Also, therapeutic strategies involving weight loss and probiotic plus prebiotic intake can reduce inflammation, endotoxemia, and associated conditions e.g. insulin resistance [113].

Type 2 diabetes and inflammation

Epidemiological evidence links type 2 diabetes, obesity, hyperinsulinemia, and metabolic syndrome, to AD. There is an inherent association between the development of type 2 diabetes and elevated (but 'normal range') levels of circulating inflammatory mediators including CRP, and indices of insulin resistance (IR) [114]. Obesity, (mainly central obesity) is a strong mediator of insulin resistance and type 2 diabetes since it generates proinflammatory cytokines such as IL-6 [115]. The great majority of patients (90%) with diabetes have insulin resistance. Subclinical chronic inflammation has been implicated as an essential pathogenic factor in the development of insulin resistance and type 2 diabetes. Markers for this chronic inflammation include CRP, IL-6 and TNF-α (albeit at low level) [116]. Indeed, inflammation may trigger several mechanisms including insulin resistance and deficiency, impaired insulin receptor, impairment of insulin growth factor (IGF) signaling, glucose toxicity, dysfunctional advanced glycation end products and their receptors, cerebrovascular injury, and vascular inflammation [105, 117-119]. Furthermore, the proinflammatory effects of cytokines may involve specific intracellular signaling pathways such as the nuclear factor (NF)-dB, IκB kinase, (IKK), activating Protein-1 (AP-1) and c-Jun NH_2-terminal kinase (JNK), and impaired insulin signaling [21]. This provides important perspectives for treating insulin resistance, and glucose intolerance. The antidiabetic drugs that reduce insulin and insulin resistance may, in fact, reduce inflammation as well. Conversely, anti-inflammatory drugs (such as thiazolidinedione) may improve insulin resistance and glucose tolerance.

Obstructive sleep apnea and inflammation

OSA is a common condition whose hallmark feature is intermittent hypoxia (IH). Chronic IH induces inflammation and directly triggers pro-inflammatory pathways [120-126]. Since obesity is associated with OSA, recent work has shown that IH leads to activation of inflammatory responses in human adipocytes [127]. The latter irrespective of being derived from either visceral or subcutaneous sites showed activated NF-κB DNA-binding activity in IH, compared with normoxic controls. IH upregulated proinflammatory gene expression and mRNA expression in adipocytes that were the source of significantly increased secretion of TNF-α, IL-6, and IL-8 [127]. Recurrence of IH resulted in cellular and systemic inflammation in the rat 3T3-L1 adipocytes. Both mRNA and protein levels of TNF-α, IL-6, and leptin, were significantly high in severe IH group; the level of these proinflammatory markers was proportional to the severity of IH [128]. In OSA patients, TNF-α and TNF-α/IL-10 ratio values were significantly higher compared with the control group; however, IL-10 was much lower. A meta-analysis of 51 studies found that the levels of systemic inflammatory markers were higher in OSA patients compared to control individuals [129]. Importantly, continuous positive airway pressure (C-PAP) therapy for a month decreased TNF-α level, while there was no change in the level of IL-10 [130]. The inflammatory response in IH rodents regarding serum levels of TNF-α, IL-6, and IL-8 showed progressive increment from onset to the 6th week, while the level of anti-inflammatory IL-10 decreased [131]. Further, soluble TNF receptor-1 (sTNF-R1) levels were significantly higher in the OSA patients then the controls [132]. However, three months of CPAP therapy lowered sTNF-R1 [133, 134].

Fibrinogen (a coagulation protein) is associated with inflammation, and long-term elevated plasma fibrinogen is linked to an increased risk of cardiovascular diseases (CVD). Compared to controls, fibrinogen is significantly higher in OSA patients [135], as is CVD. Plasminogen activator inhibitor-1 (PAI-1), is the principal inhibitor of tissue plasminogen activator (t-PA); it is higher in both OSA and CVD. OSA adversely affects circadian fibrinolytic balance, and t-PA has a pronounced circadian rhythm. This dysfunctional mechanism may be responsible for increased cardiovascular events in OSA

patients [136]. Another important inflammatory marker of systemic inflammation that is elevated in OSA is CRP [137-140]. However, obese OSA patients may contain other elevated proinflammatory cytokines e.g. IL-6, as well as CRP [141]. Six months of CPAP significantly reduced CRP [142].

An interplay has been suggested between OSA, sleep fragmentation, and neuroinflammation that may cause OSA-induced brain injury [29, 30]. There is accumulating evidence linking OSA with IR, glucose intolerance, and type2 diabetes [143-145]. Thus, OSA-induced proinflammatory cytokines such as TNF-α and IL-6 are associated with impaired glucose metabolism [143, 144]. Hence, chronic OSA could upregulate sustained glucose hypometabolism, inflammatory response, hypertension [146], ischemia due to endothelial dysfunction [147-149], white matter damage [150], and apoptosis in the hippocampus [151, 152]; conceivably, these would promote widespread pathology and trigger cognitive dysfunction.

Sleep loss and inflammation

There is insufficient sleep among people in our fast-paced stress-prone society. Sleep disturbance due to conditions such as OSA and short sleep duration increase inflammation. Insufficient sleep enhances blood pressure, glucose dysmetabolism, hormonal dysregulation, and inflammation [153]. Partial sleep deprivation (PSD) (compared with uninterrupted sleep) has been shown to cause significantly higher expression of TNF-α and IL-6 [154]. PSD also activated STAT family proteins; together they enhance the molecular inflammatory signaling pathways [154]. Circadian misalignment due to the wakefulness-sleep schedule perturbation conceivably causes a significant increase in TNF-α, and CRP [155, 156]. CRP is a recognized general marker for inflammation [157, 158]. Its serum concentration increases immediately after sleep restriction [159]. The CRP level increases, as expected, during both total and PSD conditions [158]. Indeed, long-term sleep restriction may cause increased production of cytokines including IL-β, IL-6, IL-17, as well as CRP [159]. One week of sleep restriction elevated not only mRNA concentrations of TNF-α and IL-1β but reduced endothelial-dependent vasodilatation in healthy individuals [160]. Interestingly, it has been documented

recently that decreased sleep may decrease immune function and increase susceptibility to viral infections [161].

Recent data have found that Aβ pathology is associated with non-rapid eye movement (NREM) sleep disruption impacting memory function in older adults. The study found that Aβ burden in medial prefrontal cortex (mPFC) correlated significantly with less NREM sleep, and more memory impairment mediated by impaired hippocampus-dependent memory consolidation [162].

Comments

Disparate aspects of inflammation: LPS, proinflammatory cytokines, and other mediators

LPS (present in the cell wall of Gram-negative bacteria) - a potent endotoxin enhances the levels of proinflammatory cytokines and activates both the neuroimmune and neuroendocrine systems [49]. It also blocks LTP in the hippocampus. Wistar rats administered LPS for three days showed increased level of expression of TNF-α, IL-1β, and IL-6 in the hippocampus (compared with controls). Following seven days of administration, however, Aβ level also increased in the hippocampus. LPS-induced cognitive dysfunction was verified in Morris maze test [163]. Interestingly, even a single injection of LPS impaired hippocampal-dependent learning (spatial learning) [164].

LPS infusion (1.2 mg/kg/day intraperitoneal) for 14 days induced sustained hypertension and a significant increase in plasma level of TNF-α, IL-1β, and CRP. This LPS-induced systemic inflammation was accompanied by activation of microglia, augmentation of TNF-α, IL-1β, or IL-6 protein expression, and O2 production in rostral ventrolateral medulla (RVLM) [165]. The above mentioned were blunted by administration of a cycloxygenase-2 (COX-2) inhibitor, an inhibitor of microglial activation (NS398), a cytokine synthesis inhibitor (pentoxifylline), or minocycline [165]. Neuroinflammation was also associated with a COX-2-dependent downregulation of endothelial NO synthase. The LPS-related pressor response was antagonized by minocycline, pentoxifylline, or tempol (SOD mimetic) [165]. An increase in serum LPS activity is associated with a host of pathologies including higher serum triglyceride,

obesity/metabolic syndrome, diabetes, increased blood pressure (mainly diastolic), and cardiometabolic disorders [19, 20, 31, 166-169]. Thus, LPS is linked to the development of metabolic and vascular dysfunctions supporting its role in evoking an immune response in their pathogenesis [166, 170, 171].

Proinflammatory cytokines are key molecules that modulate immune responses. Their lack of reversibility in persistent inflammation would enhance dyshomeostasis [96]. LPS administration in the aged rats induces prolonged neuroinflammation and astrogliosis in the hippocampus (dentate gyrus) showing higher mRNA expression and protein levels of TNF-α and IL-1β [172]. The secretion of these proinflammatory cytokines increases several fold with daily consumption of alcohol in LPS-treated C57BL/6J mice [173]. Many disparate proinflammatory pathways may underpin aging and age-related diverse comorbid conditions (**Figure 1**). For example, the proinflammatory molecule eukaryotic translation initiation factor 5A (EIF5A) mediates stress-induced inflammation in diabetes [174]. EIF5A has been shown to upregulate inflammation by stimulating the translation of mRNA encoding inducible NO synthase (iNOS); the latter promotes inflammation-associated cell death. Inflammatory prevalence may be associated with the extracellular release of ATP that activates purinergic P2 receptors and promotes chronic inflammation [175].

Adipose tissue is an important source of inflammation and hypoxia triggers macrophage infiltration in adipose tissue [176-178]. The recurring cessation of breathing in OSA may promote adipose tissue hypoxia and upregulate inflammation in obesity. A major source of cytokine is adipose tissue; its expression of IL-6 is elevated in aging. Upon *in vitro* treatment of adipose tissue explants with LPS, IL-6 secretion was significantly increased in cultures from 24 months old aged C57BL/6 mice - compared to 4 months old young mice [179]. Further, treatment of these explants with physiological levels of IL-1β induced significant secretion of IL-6; this effect was age-dependent, reflecting a synergistic response of adipose tissues to IL-1β in the aged [179]. However, inflammation in obesity is also associated with elevated cortisol levels [180]. Such enhanced inflammatory

response in the obese aged may impact and alter the risk of other age-related comorbid conditions. Healthy obese adults with exacerbated inflammation markers such as CRP and fibrinogen may possess higher fasting glucose (prediabetes). However, these individuals with prediabetes tend to have prehypertension also [181].

Greater levels of serum IL-6 and CRP were associated with faster rates of cognitive decline over nine years among cognitively intact community-dwelling older women. This finding has been correlated with microvascular changes leading to myelin damage, pathological perturbations in neuronal axons, decreased neuron propagation, and impaired processing speed [182].

6,542 middle-aged adults were followed for 19 years prospectively; participants with a history of alcohol abuse, however, showed increased odds of developing severe memory impairment later in life [183]. In the animals, ethanol consumption upregulated basal gene expression of TNF-α, IL-1β, IL-6, and iNOS [184]. Alcohol-induced gut mucosal injury leads to marked increase in the permeability of the gut mucosa to macromolecules such as LPS. Consequently, the release of proinflammatory mediators such as TNF-α, and infiltration of inflammatory cells, e.g., neutrophils, lead to endotoxemia and systemic inflammation [185]. The leaky gut and associated inflammation upregulate depression also [186]. An increase in expression of inflammasome components (i.e. nucleotide-binding domain leucine-rich repeat proteins or NOD-like receptors - NLRP1, NLRP3, and caspase recruitment domain-ASC) and proinflammatory cytokines (such as TNF-α, MCP-1) occurs in the brain of alcohol-fed mice. An increase in IL-1β in alcohol-fed mice further activates inflammasomes [187].

It is well established that cytokines mediate immune and inflammatory responses. TNF-α and IL1-β enhance their mRNA levels as well as affect mRNA levels of other proinflammatory cytokines [188]. Thus, TNF-α and IL1-β induce each other, and indeed their own production [189]. When these cytokines are released into the extracellular space, they stimulate nearby neurons to produce TNF-α and IL1-β. Thus, cytokines render these neurons pathological and dysfunctional. Indeed, pathological neu-

rons produce proinflammatory cytokines and activate microglia [190-196].

The inflammatory process is integral to aging, obesity, IH, hypertension, malnutrition, diabetes, and depression (see above). Also, APOE4 genotype is known to potentiate the induction and regulation of inflammatory processes [197-199]. Furthermore, stress hormones may facilitate inflammation; the induction of TNF-α, IL-1β, IL-6, IL-8, IL-18, and CRP production may occur through the corticotropin-releasing hormone/substance P-histamine axis upregulation. Thus, a dysfunctional neuroendocrine-immune interface may play an important role in the pathogenesis of inflammation-related neuronal pathology and cognitive decline [200].

The effect of mild chronic Hhcy on proinflammatory cytokine levels in the brain, heart, and serum were investigated in rats. Results demonstrated an increase in TNF-α, IL-1β, IL-6, and the chemokine MCP-1 (i.e. CCL(2)) in the hippocampus, as well as an increase in IL-1β and IL-6 levels in the cerebral cortex. Also, an increase in prostaglandin E(2) in the hippocampus and serum of the rats has been documented [201]. These data suggest that homocysteine increase promotes inflammatory status that can contribute to neuronal dysfunctions [202, 203] and memory deficit [204]. Recent studies have corroborated these conclusions. Vascular dementia (VaD) is a frequent comorbidity with AD and is estimated to occur in as many as 40% of AD patients. The heterogeneous causes of VaD may include chronic cerebral hypoperfusion, microhemorrhages, hemorrhagic infarcts, or ischemic infarcts. MRI and histopathology revealed the occurrence of significant microhemorrhage, neuroinflammation, and elevated interleukin IL-1β, TNF-α, and IL-6, and the matrix metalloproteinase 2 (MMP2) and MMP9 in the Hhcy mice brain [202]. The Hhcy mice, not surprisingly, showed spatial memory deficit (assessed by the radial-arm water maze), and an increased risk for the neurodegenerative disease.

It is clear from the above mentioned that chronic inflammatory milieu would promote both vascular inflammation and neuroinflammation. The endothelium is the largest receptor-effector end-organ and maintains vascular homeostasis. Inflammation-related endothelial dysfunction is an important perturbation that precedes

and accompanies cerebral neuropathology. It leads to cognitive dysfunction as well as sudden cerebrovascular and adverse cardiovascular events. Several cell types infiltrate vasculature in inflammation; these include microglia, astrocytes, perivascular macrophages, and infiltrated peripheral immunocytes (T lymphocyte, B lymphocyte, and dendritic cells) [205, 206]. Hypertension also is a major cause of vascular inflammation. Spontaneously hypertensive rats subjected to hypoperfusion (via middle cerebral artery occlusion) showed immune cells of the peripheral blood infiltrated in the ischemic brain. These cells included neutrophils, monocytes, macrophages, and myeloid dendritic cells, lymphatic dendritic cells, microglia, and T cells [207]. This cellular recruitment, therefore, can aggravate damage to the brain tissue by releasing cytotoxic mediators, increasing vascular permeability, and disrupting blood-brain barrier (BBB) [208].

Inflammation implicated in the etiopathogenesis of AD

Accumulating evidence supports the major role of inflammation in the etiopathogenesis of AD [209, 210]. As described above, proinflammatory mediators activate various signaling pathways that lead to neuronal injury (**Figure 1**). Neurons, glial cells, and vasculature are all implicated as being different cerebral components of neuroinflammation in AD, as are synapses [211-213]. Aβ-induced microglial cell activation (see below) triggers TNF-α or IL1-β cytokine synthesis and promotes neuroinflammation [214-217]. Systemic inflammation can upregulate neuroinflammation [218, 219]. In the preclinical stage of AD, systemic inflammation has been correlated with the development of AD [220, 221]. Indeed, early neuroinflammation occurs in the amnestic mild cognitive impairment (aMCI), underscoring that this pathology is a feature of prodromal cognitive decline [212, 222]. The expression of proinflammatory cytokines in middle age is an early risk factor and predictor of cognitive decline/ AD in old age [223].

The underlying primary event in the etiopathogenesis of AD has been emphasized in the data presented by van Exel et al. [224]. They [224] studied characteristics associated with genetic risk preceding AD development. They compared middle-aged offsprings of AD patients with offsprings of cognitively intact non-AD parents. The offsprings of AD patients showed enhanced proinflammatory responses (and increased hypertension). A greater proinflammatory response to inflammatory challenge found in the offsprings of AD patients, therefore, reflected their elevated genetic risk, and the susceptibility/predisposition to AD in the future. This was in keeping with well-documented alterations in innate immunity/inflammation found by other workers [210]. (Also, see above). Other susceptibility genes for AD include CLU, PICALM, and CRI [225, 226]; it is noteworthy that CLU codes for clusterin, and CRI, complement receptor 1, - and both are involved in inflammation/innate immunity.

It has been pointed out in the literature that LPS-induced inflammation promotes AD pathology by altering Aβ transport at the BBB [227] and decreasing the central clearance of Aβ [228]. Alteration of BBB effectively increases brain influx of Aβ but decreases its efflux [227]. It has been discussed above that low-grade systemic inflammation is rampant and accompanies aging and various comorbid diseases in AD [229, 230]. Obesity (e.g.) in aging is associated with significant systemic inflammation, that disruption BBB [231]. The resulting neuroinflammation and oxidative stress in the hippocampus likely contribute to the significant cognitive decline observed in obese aged animals. Both peripheral and central increases in proinflammatory cytokine levels result in increased Aβ1-42 in the hippocampus and cognitive deficits [232, 233].

The Honolulu-Asia Aging Study found that elevated CRP levels are related to a significantly increased risk for dementia [234]. The Rotterdam Study also reported a relationship between elevated levels of α-1 antichymotrypsin (ACT), CRP, IL-6, Intracellular adhesion molecule-1 (ICAM), and vascular cell adhesion molecule-1 (VCAM) - and an increased risk for AD [235]. Chronic inflammation (in 3xTg-AD mice) - related elevation of TNF signaling (in the hippocampus) [236], and intraneuronal amyloid and Ptau may promote neuronal death [236-238].

Inflammation-activated microglia and abeta exacerbation

Normally, Microglia is innate immune cells of the brain; they constantly scan the tissue,

respond to pathological signals, and protect CNS homeostasis. They encapsulate pathogenic foci and remove apoptotic cells/debris thereby defending the CNS tissue integrity. In neurodegenerative conditions, however, activated microglia and macrophages (peripherally-derived) take on strong proinflammatory function and generate proinflammatory mediators - including TNF-α, IL1-β, chemokines, complement factors, and other neurotoxic factors such as NO, ROS, and proteolytic enzymes. They all enhance Aβ production and plaque accumulation. Although microglia should be beneficial by generating anti-Aβ antibodies and stimulating clearance of amyloid plaques; the activated microglia promote Aβ pathology. Indeed, proinflammatory microglia develops in aging, traumatic brain injury, and neurodegenerative disease [239].

AD is characterized by Aβ plaques, neuronal atrophy, and degeneration in the hippocampus and cortex. Chronic inflammation contributes to the onset and progression of the above mentioned AD-related pathologies. Following intraperitoneal administration of LPS, C57BL/6J mice showed significantly higher levels of Aβ1-42 in their hippocampus with cognitive deficits [232]. Similarly, neuroinflammation attenuated memory retrieval (specifically impairing context discrimination memory via disruption of pattern separation processes) in hippocampus-requiring tasks in Sprague-Dawley rats [240]. OSA is a low-grade inflammatory condition associated with neuronal degeneration [29, 30] (see above). Exposure to IH induces low-grade neuroinflammation in the dorsal hippocampus of C57BL/6J mice. Chronic IH in conjunction with LPS elevated IL-6 mRNA, caused microglial changes, and enhanced cognitive impairment [241] (**Figure 1**).

A vicious cycle occurs between neuroinflammation and Aβ accumulation; activated microglia potentiates Aβ deposition and generates inflammatory mediators that in turn enhance Aβ level [242]. LPS administration induces a significant inflammatory response in both cortex and hippocampal formation in AD transgenic mice (see above); the resulting axonal pathology noted in these regions is secondary to increases in β-site of amyloid precursor protein cleaving enzyme (BACE-1) and soluble Aβ [212]. These AD-like data reflect that amyloidogenic axonal pathology and dendritic degeneration

arise from LPS-induced neuroinflammation [212]. Other studies have also shown myelin/axonal injury in the cortex following LPS administration and an increase in IL-1, Aβ protein precursor (AβPP), and Aβ [243].

Inflammation, AD pathology, and oxidative stress

Oxidative damage is a common and early feature of AD and other neurodegenerative conditions. Neuroinflammation implicated in cognitive decline enhances ROS and reactive NO species (RNS) that are neurotoxic. Oxidative stress plays an important role in neural injury and cognitive impairments [59, 60]. Oxidative stress can arise from several sources including disease state, IH/OSA, sleep restriction, unhealthy lifestyle including excessive caloric intake, malnutrition, and excessive alcohol consumption [29, 30, 59, 60, 146-149]. The nocturnal IH may induce the production of ROS and, therefore, cause local and systemic inflammation (**Figure 1**). ROS contributes to the "age-related cascade of neurodegeneration"; it contributes to accumulating oxidative damage in conjunction with protein aggregation, metabolic dysfunction, and inflammation [50-54, 97].

Thiamine deficiency (TD) induces a region-selective neuronal loss in the brain, accompanied by impairment of oxidative metabolism [244]. Free radical injury to the brain was assessed using CSF isoprostane concentrations (with age, sex, race, cigarette smoking, BMI, APOE ε4 allele, and CSF biomarkers of AD as confounders). The results were consistent with an age-related increase in free radical injury in the human brain. The concentration of CSF isoprostane has been shown to increase with age by approximately 10% from age 45 to 71 years in healthy, cognitively normal adults. Also, the CSF isoprostane concentration also increases by approximately >10% for every 5-U increase in BMI, as well as other life style modifications (e.g. smoking) [245]. The above studies highlight the importance of lifestyle modification (reducing high BMI and smoking) in decreasing free radical injury to the brain [245].

There is a potential contribution by ROS to homocysteine-related neurotoxicity and neuronal damage. The latter derives from ROS as well as increased Ca^{2+} influx. ROS can be generated extracellularly by homocysteine [246] fol-

lowing excessive N-methyl-D-aspartate (NMDA) receptor stimulation [247, 248]. Importantly, SOD and catalase may offer protection from neuronal damage [247, 248].

Inflammation, AD pathology, and nitrosative stress

The OSA patients demonstrate decreased plasma levels of NO metabolites, and increased production of superoxide (by neutrophils and monocytes), isoprostane (in breath condensate) [249, 250], and exhaled NO (eNO), carbon monoxide (eCO), nitrates, and hydrogen peroxide (H_2O_2) [251, 252]. Oxidant stress and inflammation are potential mediators of IH-induced vascular dysfunction [253, 254]. There is direct evidence that OSA is a major determinant of endothelial dysfunction, inflammation, and elevated oxidative stress in obese patients [254]. Indeed, both ROS and RNS may lead to a breakdown of endothelial-derived NO and exaggerated lipid peroxidation [255-257].

IH induces inflammation and results in significant oxidative injury in sleep-wake regions of the brain; this is associated with hypersomnolence and increased susceptibility to short-term sleep loss. Compared to mice exposed to sham IH, those exposed to IH develop reduced mean sleep latency. Following two weeks of IH, the oxidative injury was present in regions of the basal forebrain and brainstem reflected by elevated isoprostane (22%), increased protein carbonylation (50%), and increased nitration (200%) [258].

Neuroinflammation enhances both ROS and RNS species [259] (**Figure 1**); both are neurotoxic and induce mitochondrial damage, upregulate caspases, increase calcium, and promote AD and other neurodegenerative diseases [260-262]. IL-1β and TNF-α in combination caused marked neuronal injury; their synergistic action being required to disrupt memory consolidation [263]. Brain cell cultures treated with TNF-α and IL-1β generated substantial amounts of NO. Blockade of NO production with an NO synthase inhibitor was accompanied by a marked reduction (about 45%) of neuronal injury - suggesting that NO plays a significant role in neurotoxicity. The addition of NMDA receptor antagonists to the brain cell cultures also blocked TNF-α and IL-1β-induced neurotoxicity (by 55%), implicating the involvement of

NMDA receptors in neurotoxicity [264]. Both intracellular and extracellular glutamate levels are elevated following TNF-α and IL-1β treatment. Pre-treatment with NMDA receptor antagonist MK-801 blocked cytokine-induced neurotoxicity [265].

Inflammation, AD pathology, and Tau

Tau phosphorylation and NFT are early hallmarks of AD. Neuroinflammation implicated in tau pathology [266] promotes tau, its aggregation and neurodegeneration in humans [267-270], as well as in animals [266, 271-275] (**Figure 1**). The above-mentioned progression of tau pathology following induction of brain inflammation was elegantly exemplified in hTau mice [266, 276]. Furthermore, blocking or enhancing IL1-β expression decreases [277] or increases [278] tau pathology, respectively. Importantly, the former ameliorates cognition in 3xTg-AD mice [277]. Several corroborative studies have documented inflammation preceding tau-mediated neuronal loss/neurodegeneration [271, 279]. Based on the above studies, it is emphasized that inflammation and activated microglia are essential in driving tau pathology and memory impairment [280]. However, tau pathology in 3xTg-AD transgenic mice may develop independently of Aβ generation [281, 282].

There is an age-related enhancement of Ptau species in the cortex and hippocampus of rTg4510 and other transgenic mice [281, 282, 289, 290]. Hypoglycemia enhances the AMPK-Akt-GSK3 pathway and tau hyperphosphorylation [291]. The central angiotensin II elevates Ptau levels via glycogen synthase kinase 3β (GSK 3β) and other tau kinases. However, Ptau and associated cognitive impairment were attenuated by losartan and the GSK 3β inhibitor [292]. These three conditions mentioned above are associated with inflammation (see above). Indeed, neuroinflammation upregulates p38 mitogen-activated protein kinase (MAPK), GSK 3β [278], and cyclin-dependent kinase 5 activity which potentiate tau phosphorylation [297].

The hippocampus in transgenic pR5 mice (expressing the pathogenic mutation P301L in the human tau gene) has a higher turnover of glutamate and glutamine - reflecting a hypermetabolic state [293]. Several data have identi-

fied stimulation of inflammation signaling pathway within the brains undergoing tauopathy [294-296]. Consequently, either reducing tau [283-285] or blocking neuroinflammatory pathways may serve as therapeutic targets to attenuate neurotoxicity/neurodegeneration and cognitive decline [286-288].

Neuroprotection-therapeutic approach employing polypharmacy

AD is a multifactorial condition in which a combination of many pathological pathways act synergistically and sequentially, evoking the neurodegenerative milieu. A single drug may not be efficacious - proverbially as "one size does not fit all". Hence, multicomponent approach (polypharmacy) may be required in potential therapeutic intervention to prevent neurodegeneration and affect AD pathology [298]. There are many therapeutic targets in the pathogenic cascade of inflammation (see above). These may include proinflammatory cytokines, complement system, oxidative stress, nitrosative stress, microglial activation, as well as amyloid and tau accumulation. The following suggested therapeutics may be required in a multicomponent treatment approach; indeed, they may be worthy of clinical trials.

1. It is essential that the immune homeostasis is maintained. High-dose intravenous immunoglobulin G (IgG) antibodies suppress inflammation. Its anti-inflammatory activity is associated with IgG crystallizable fragments [299]. Minocycline has also been shown to attenuate LPS-induced neuroinflammation [300] (see below).

2. MAPKs are implicated in the production of inflammation mediators. LPS treatment activates the MAPKs in both neurons and glia, promoting glia-derived neurotoxic molecules [301]. The p38 MAPK signaling cascade is activated in human AD brain tissue [302]; it is implicated in increasing proinflammatory cytokine levels by glia, following activation with Aβ. An experimental therapeutic "MW01-2-069A-SRM" - an inhibitor of p38 MAPK has been developed. This micromolecule is BBB penetrating, non-toxic, and orally bioavailable; it reversed higher proinflammatory cytokine levels in the hippocampus to normal level in the animal model [303].

3. Fructose-1, 6-bisphosphate (FBP - a glycolytic intermediate) reduced the expression of iNOS and inhibited LPS-induced NO production in a dose-dependent manner [305]. Although, FBP has anti-inflammatory and immunomodulatory properties, the underlying mechanisms of these functions have not been characterized.

4. The peroxisome proliferator activated receptor-gamma (PPAR-γ) agonist pioglitazone inhibits iNOS activity in neurons and NO generation by microglia - following LPS-induced pathology [304]. Pioglitazone inhibits LPS-induced phosphorylation of p38 MAPK [304] and inhibits the expression of proinflammatory genes. It negatively regulates microglial activation and APP processing with a 27% reduction in Aβ1-42 level [306]. This has been corroborated by subsequent studies. Treatment of the triple transgenic 3xTg-AD mouse with pioglitazone (for four months) resulted in reduced serum cholesterol, improved learning, decreased hippocampal Aβ and tau deposits, and improved short- and long-term plasticity [307]. While pioglitazone is ineffective in multiple sclerosis, it has documented effectiveness in suppressing oxidative stress, NFκB signal activation, inflammation, and neuronal degeneration in other inflammatory conditions [308].

There is controversy surrounding common non-steroidal anti-inflammatory (NSAID) regarding its effectiveness in protecting against AD; several anti-inflammatory treatment trials have shown little to no effect on preventing or reversing AD. However, there may be reduced AD incidence after 2 to 3 years of NSAID use in asymptomatic individuals [309]. This, therefore, reflects that in addition to innate inflammatory responses, there may be other concurrent pathological pathways that may require treatment [310].

5. MitoQ is an antioxidant that protects mitochondria from oxidative damage/stress. MitoQ is a derivative of the antioxidant ubiquinone, with antioxidant and anti-apoptotic properties. In inflammatory condition, MitoQ decreased mitochondrial ROS in mice; it suppressed the NLRP3 inflammasome activation that is responsible for the maturation of IL-1β and IL-18 [311, 312]. It also decreased neurodegeneration by decreasing ROS production and lipid peroxidation, increasing MnSOD activity and glutathione

levels, and reducing protein and DNA oxidation [313]. Similarly, treatment with the mitochondria-targeted antioxidant, MitoTEMPO inhibited gut barrier dysfunction and suppressed colitis, thus enhancing barrier function and inhibiting proinflammatory cytokine generation [314]. Another important compound studied was mitochondria-protecting agent acetyl-L-carnitine (ALC). ALC enhanced SOD and reduced oxidative damage to the BBB [315].

6. ROS and RNS upregulate glia-mediated inflammation and cause neuronal damage. Minocycline significantly decreases hypoxia-ischemia (HI)-induced brain injury, owing to suppression of microglial activation and inhibition of neurotoxic factors and iNOS. It inhibits oxidative stress evidenced by an 8-isoprostane decrease in the minocycline-treated HI rat brain [316]. It has been shown to suppress pro-inflammatory NO following hypoxic upregulation [317]. Other studies on HI model also found that that doxycycline (a derivative of tetracycline, similar to minocycline) significantly inhibits neuroinflammation in several brain regions including the frontal cortex, striatum, and hippocampus; doxycycline inhibits TNF-α and IL-1β and augments BDNF [318, 319]. Interestingly, Aβ1-42 fibrils complexed with C1q (complement factor) upregulated proinflammatory cytokines in human microglia cell cultures, but minocycline decreased this production [320]. Furthermore, minocycline showed long-term neuroprotective property by improving cognitive impairment in the rat by inhibiting astrogliosis [321]. In a detailed analysis, it was shown that minocycline activated BDNF, and increased synaptic plasticity and synaptogenesis. Consequently, minocycline ameliorates cognitive deficits and upregulates neuroplasticity [322]. The above studies indicate that minocycline (and doxycycline) down-regulate microglial toxic factors and provide neuroprotection.

7. Rats subjected to IH (simulating OSA) show significant increases in levels of serum and hippocampal malondialdehyde (MDA, indicators of oxidative stress), mRNA levels of inflammatory mediators, and apoptotic cell death. Melatonin treatment significantly inhibited hippocampal MDA levels, and apoptosis was entirely prevented. It decreased expression of the inflammatory mediators including TNF-α, IL-1β, IL-6, iNOS, and cyclooxygenase-2, but enhanced expression of antioxidant enzymes including glutathione peroxidase, catalase, and copper/zinc SOD in the hippocampus. Thus, melatonin significantly attenuates oxidative stress and the pathogenesis of IH-induced hippocampal pathology [323-325]. Further, melatonin lowered both NO and eNOS and elevated the endothelial function [324]. The neuroprotective effect of melatonin is obvious from its attenuation of Aβ-mediated toxicity, and antioxidant and anti-amyloid effects. Further, it attenuated tau hyperphosphorylation [326]. A recent meta-analysis of randomized clinical trials concluded that "melatonin can be considered as a possible sole or add-on therapy in neurodegenerative disorders" [327]. From the above mentioned it is clear that the antioxidant, pro-mitochondrial (i.e. inhibiting mitochondrial dysfunction), anti-tau, and anti-amyloidogenic impact of melatonin recommends its utilization in aging, MCI, and AD - in conjunction with other selected therapeutic substances described here [328, 329].

A polypharmacy therapeutic approach may include melatonin, minocycline, pioglitazone, scavengers of ROS and RNS, as well as those that ameliorate mitochondrial dysfunction. Such a treatment strategy may: (A) reduce the synthesis of inflammation mediators and oxidants at multiple levels, (B) inhibit pathways involved in proinflammatory cytokine, ROS, and RNS signaling, and (C) attenuate mitochondrial and synaptic dysfunction.

Conclusion

The greatest risk factor in the neuropathogenesis of AD is aging. Several age-related comorbid conditions are important additive risk factors in upregulating inflammation and cognitive decline in aging. One of the mechanisms whereby LPS induces brain injury involves activation of TLR-4 on immune cells in neuroinflammation. This initiates activation of inflammatory cells and a generalized inflammatory response; this then results in several pathologies in the CNS including hypoglycemia, white matter injury, and cerebral hypoperfusion [59, 330, 331].

There is upregulation of proinflammatory cytokines, acute phase reactants, complement molecules, and other inflammatory mediators in AD brains; these are said to contribute the progression of neurodegenerative process. Both astrocytes and microglia are primed to

produce several neurotoxic factors in the chronic neurodegenerative state. Consequently, elevated cytokines and chemokines would heighten neuropathology in the vulnerable brain. Synergistic and superimposed insults from a host of sources (described above) would induce neuroinflammatory and neurodegenerative condition and escalate worse functional and memory/cognitive outcomes. Understandably, the mechanisms/pathways of the exaggerated pathological responses due to inflammation and oxidative-nitrosative stress should provide obvious potential targets for therapeutic intervention. The therapeutic neuroprotective strategy pointed out here suggests polypharmacy.

Finally, neuroinflammation exists in very early stages of AD. The neuronal toxicity promoted by chronic inflammation makes it a critical risk factor in the pathogenesis of neurodegenerative diseases in general and AD in particular. An essential goal for research today is to prevent and ameliorate inflammation and to reduce glial activation and neuronal toxicity/degeneration. A targeted therapeutic strategy to abrogate neuroinflammation is of paramount importance and may hold promise to prevent cognitive dysfunction and attenuate (possibly reverse) AD neuropathology.

Disclosure of conflict of interest

None.

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