Neurochem Res (2012) 37:846–868
DOI 10.1007/s11064-011-0680-2

OVERVIEW

Dysfunctional Nucleus Tractus Solitarius: Its Crucial Role in Promoting Neuropathogentic Cascade of Alzheimer's Dementia—A Novel Hypothesis

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Received: 28 September 2011 / Revised: 16 November 2011 / Accepted: 15 December 2011 / Published online: 5 January 2012

Abstract The pathophysiological mechanism(s) underlying Alzheimer's disease (AD) still remain unclear, and no disease-modifying or prophylactic therapies are currently available. Unraveling the fundamental neuropathogenesis of AD is an important challenge. Several studies on AD have suggested lesions in a number of CNS areas including the basal forebrain, hippocampus, entorhinal cortex, amygdale/insula, and the locus coeruleus. However, plausible unifying studies on the upstream factors that involve these heterogeneous regions and herald the onset of AD pathogenesis are not available. The current article presents a novel nucleus tractus solitarius (NTS) vector hypothesis that underpins several disparate biological mechanisms and neural circuits, and identifies relevant hallmarks of major presumptive causative factor(s) linked to the NTS, in older/aging individuals. Aging, obesity, infection, sleep apnea, smoking, neuropsychological states, and hypothermia—all activate inflammatory cytokines and oxidative stress. The synergistic impact of systemic proinflammatory mediators activates microglia and promotes neuroinflammation. Acutely, the innate immune response is protective defending against pathogens/toxins; however, when chronic, it causes neuroinflammation and neuronal dysfunction, particularly in brainstem and neocortex. The NTS in the brainstem is an essential multiple signaling hub, and an extremely important central integration site of baroreceptor, chemoreceptor, and a multitude of sensory afferents from gustatory, gastrointestinal, cardiac, pulmonary, and upper airway systems. Owing to persistent neuroinflammation, the dysfunctional NTS exerts deleterious impact on nucleus ambiguus, dorsal motor nucleus of vagus, hypoglossal, parabrachial, locus coeruleus and many key nuclei in the brainstem, and the hippocampus, entorhinal cortex, prefrontal cortex, amygdala, insula, and basal forebrain in the neocortex. The neuronal and synaptic dysfunction emanating from the inflamed NTS may affect its interconnected pathways impacting almost the entire CNS—which is already primed by neuroinflammation, thus promoting cognitive and neuropsychiatric symptoms. The upstream factors discussed here may underpin the neuropathopgenesis of AD. AD pathology is multifactorial; the current perspective underscores the value of attenuating disparate upstream factors—in conjunction with anticholinesterase, anti-inflammatory, immunosuppressive, and anti-oxidant pharmacotherapy. Amelioration of the NTS pathology may be of central importance in countering the neuropathological cascade of AD. The NTS, therefore, may be a potential target of novel therapeutic strategies.

Keywords Alzheimer's disease · Neuroinflammation · Nucleus tractus solitarius · Hypoglossal · Vagus nerve · Sleep apnea

Abbreviations

α1-ACT	α1-Antichymotrypsin
Aβ	Amyloid beta
Ach	Acetylcholine
BFB	Basal forebrain
BP	Blood pressure
AD	Alzheimer's disease
AHI	Apnea hypopnea index
AP	Area postrema
APR	Acute phase response
BFB	Basal forebrain

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BMI	Basal metabolic index
BBB	Blood brain barrier
CBF	Cerebral blood flow
CCL2	Chemokine ligand 2
CD15	Immunological carbohydrate adhesion molecule
CIC	Circulating inflammatory cytokines,
c-fos	Proto-oncogene
CIM	Circulating inflammatory mediators
CNS	Central nervous system
COX-2	Cyclooxygenase-2
CRP	C-reactive protein
DMNV	Dorsal motor nucleus of the vagus nerve
DVC	Dorsal vagal complex
ERC	Entorhinal cortex
GMV	Gray matter volume
HIF-1	Hypoxia-inducible factor 1
ICAM 1	Intercellular adhesion molecule 1
IFNγ	Interferon gamma
IL	Interleukin
LPS	Lipopolysaccharide
MCI	Mild cognitive impairment
MIP-2	Macrophage inflammatory protein
NA	Nucleus ambiguus
NF-κB	Nuclear factor of kappa light polypeptide gene enhancer in B-cells
NTS	Nucleus tractus solitarius
NO	Nitric oxide
NOS	Nitric oxide synthase
NK	Natural killer cell
OB	Olfactory bulb
OFC	Orbitofrontal cortex
ON	Olfactory nerve
OSA	Obstructive sleep apnea
PC	Piriform cortex
PFC	Prefrontal cortex
p-tau	Hyperphosphorylated tau
ROS	Reactive oxygen species
TGF-β	Transforming growth factor beta
THP-1	Human acute monocytic leukemia cell line
TNF	Tumor necrosis factor
VCAM-1	Vascular cell adhesion molecule-1
VNS	Vagus nerve stimulation

Introduction

Alzheimer's disease (AD) is an aging-associated disease affecting about 10% of those aged over 65, and over 45% of those aged 85. The two pathological hallmarks of AD are amyloid plaques composed of aggregated β-amyloid (Aβ) peptide, and neurofibrillary tangles composed of hyperphosphorylated tau protein [1]. There is a progressive deterioration in cognitive and emotional functions in AD; unfortunately, as yet there is no definitive prophylaxis and/or curative treatment that stops and reverses the relentless neurodegenerative process of this disease. Progress in treatment strategies is hindered due to our poor knowledge of the fundamental upstream factors underlying the neuropathological cascade of this disease.

Aging is a biological process characterized by time-dependent, progressive, physiological declines and thus accompanied by increasing incidence of age-related diseases and attenuated CNS functions including those of sensory, motor, and cognitive. Aging has been suggested to be a state of chronic, low-grade molecular inflammation which links normal aging and the pathogenesis of age-related diseases [2–4]. Inflammation is considered pivotal in age-related physiological changes and the pathogenesis of many age-related diseases. Several studies implicate oxidative stress in the etiology of AD in man [2, 3, 5–10] and animals [8, 9]. Consequently, available data have established two facts: (a) aging-associated dysregulation of the immune system and (b) aging-associated alteration of redox status. Both processes inter-twine and exacerbate systemic inflammatory status, due to a wide variety of inflammatory mediators. Several studies have shown increased inflammation in old age [11–15]. Glial cells from old mice secrete more proinflammatory IL-6 and less of anti-inflammatory IL-10, compared to young adults [16]. An insidious close relationship exists between systemic infection → neuroinflammation → cognitive dysfunction in the aged [11, 17]. Stimulation of the peripheral innate immune system (e.g. with lipopolysaccharide, LPS) causes increased neuroinflammatory response in the brain of aged mice [18] and humans [16, 19]. Old mice [13] and old rats [20] infected with *Escherichia coli* possess increased hippocampal interleukin (IL)1β and several other inflammatory cytokines, and undergo deficits in hippocampal-dependent memory, in comparison with similarly infected younger animals. This is because systemic circulating inflammatory cytokines (CIC) have been shown to impair synaptic function/plasticity [21, 22] and decrease gray matter volume [23, 24]. Consequently, an increase in neuroinflammatory response may be correlated with susceptibility to cognitive impairment [25]. Further, there is strong clinical evidence that AD is accompanied by an inflammatory response involving peripheral cytokines including IL-6, TNF-α, IL-1β, IL-12 and IL-18 [14].

The nucleus of the solitary tract (NTS) is an important brainstem nucleus where "initial integration" occurs of a wide variety of heterogeneous afferent inputs including gustatory, gastrointestinal, cardiovascular, and respiratory, to name a few. The brainstem circuits control several cardinal functions encompassing all above mentioned afferents, sympathetic and parasympathetic systems, neurotransmitter,

and hormonal systems; all these involve the crucial NTS [26–31]. The neuroinflammatory response in the CNS impacts the neocortex and the brainstem, and primes its different regions. Although the importance of neuroinflammation in AD is well recognized [14, 16, 19, 32, 33], however, as yet there is no unifying hypothesis on the initial upstream factors that provoke and exacerbate the fundamental neuropathogenetic steps of AD. The current thesis is the first to draw attention and emphasize that in the wake of CNS neuroinflammation in aging—it is the degeneration and neuronal apoptosis particularly within the dysfunctional NTS—that disrupts crucial CNS pathways. Since the NTS is reciprocally interconnected with almost the entire CNS, the dysfunctional NTS exerts deleterious impact on various essential neurophysiological functions in the vulnerable aged. Thus, mediated by neuroinflammation, the NTS is posited to occupy a central position in promoting the early upstream factors of neuropathogenetic cascade—that may cause cognitive decline in AD.

Evidence for Systemic Proinflammatory Cytokines/ Inflammation in the Elderly

Despite the normal immune surveillance and blood brain barrier (BBB) regulation, toxic substances, bacteria, and virus can enter the CNS, e.g. via transcytosis through endothelial cells-inducing cytokine and chemokine synthesis and causing neuronal dysfunction. The risk factors that increase proinflammatory cytokines and inflammation in the elderly include: (1) aging, (2) obesity, (3) infection, (4) cigarette smoking, (5) psychosocial Stress, (6) hypothermia, and (7) Obstructive sleep apnea, to name a few. The inflammatory insults can be acute, prolonged, repeated, and chronically synergistic. Further, the following evidence suggests that various stigmata including aging are associated with multiple cascades that arise from separate pathophysiological processes, each associated with dysfunctional cognitive sequelae.

Aging and Inflammation

During normal aging, dysregulated immune and inflammatory responses occur in both humans and animals. The NF-κB transcription factor and NF-κB-dependent gene transcription are activated in systemic inflammatory processes upregulating the transcription of the classical proinflammatory cytokines [2, 34–36], as well as other proinflammatory proteins such as adhesion molecules viz. VCAM-1 (P-, E-selectin) and ICAM-1 during aging [37]. The neurons of aged animals show greater vulnerability to CIC/neurotoxins than those of younger animals, thus reflecting a correlation between age-dependent inflammatory responses and an increased risk of neurodegeneration [38, 39]. The middle-aged (compared with young) individuals show increased sensitivity to acute LPS administration, upregulated neuronal c-fos immunoreactivity, and a lower tolerance development; they mount enhanced immune responses even to a lower dose of endotoxin [38, 40]. There is copious evidence of occurrence of high cholesterol, atherosclerosis, and inflammation in both aging and AD [41]. Noradrenaline is a well known anti-inflammatrory molecule. The findings of selective decrease in noradrenergic innervations of the hippocampal dentate gyrus (DG) and the frontal cortex (FC) [42] and neurodegeneration of LC neurons in the aging brains of amyloid precursor protein [APP(swe)] and presenilin-1 [PS1(DeltaE9)] mice mimic the neuropathology noted in the AD brains [43].

Obesity and Inflammation

There is substantial evidence that adipocytes are involved in inflammation [44] and obesity leads to reactive astrocytes, increased synthesis of adipokines [45], caspase-1 [46], proinflammatory cytokines such as TNF-α, IL-1β, IL-6, IL-8, IL-18, E-selectin, and a decreased synthesis of antiinflammatory cytokine IL-10 [46–48]. Obesity is associated with chronic low-grade systemic inflammation during mid- and late-life and increases the risk for neurodegenerative diseases including AD [49–51]. Higher BMI was associated with decreased gray matter volume [52–54]. In the Framingham Heart study, the relationship between obesity and cognitive dysfunction has been shown (Wolf et al. [55]). Several studies have described an association between atherosclerosis [56], high cholesterol, diabetes mellitus, obesity in midlife [57–61] and the incidence of AD.

Infection and Inflammation

The nose is said to be the air conditioner of the respiratory system; however, invading allergens/viruses/bacteria impact the airways negatively, and promote proinflammatory cytokine synthesis both locally and systemically. The most common infection in humans is viral respiratory tract infection (common cold) caused mainly by rhinoviruses. In acute rhinitis and influenza, viruses enter the nose/eye, initiate infection and trigger the release of inflammatory mediators, evidenced by the presence of TNF-α, IL-8, and MIP-2 in nasal secretions [62, 63]. The epithelial damage [64] may lead to secondary bacterial infection, local inflammation, microvascular leakage, degradation of extracellular matrix components, and activation of the innate immune system (to combat the bacterial invasion) [64–66]. An important source of circulating LPS and

proinflammatory cytokines in the aged is excess of gut microbiota and gut inflammation [67–69]. In addition, about 40% of persons over 60 years of age are known to have *Helicobacter pylori*, which causes peptic ulcers by damaging the mucous coating of the stomach and duodenum. Increased cerebrospinal fluid *H. pylori* antibody has been documented in Alzheimer's disease [70]. Many elderly take anti-inflammatory medication which is known to erode the lining of the gut. Both infection and inflammation are sources of neuroinflammation including that found in the NTS; see the section below on "Invading Pathogens Cause NTS Dysfunction". Even a single intraperitoneal injection of *E. coli* in the aged rats leads to specific deficits in long-term memory and long-lasting synaptic plasticity in hippocampus—this being strongly dependent on brain-derived neurotrophic factor (BDNF) [71].

Smoking and Inflammation

There is a positive association between tobacco smoking and increases in pro-inflammatory markers. A British study found higher CRP and fibrinogen levels in smokers relative to non-smokers [72]. Importantly, compared with never smokers, current cigarette smokers showed significantly higher levels of white cell count, hematocrit, blood and plasma viscosity, tissue plasminogen activator antigen, and fibrin D-dimer [72]. Another longitudinal study from Uppsala also found higher IL-6 levels in both current smokers and former smokers, compared to non-smokers [73]. A recent study has documented that chronic smoking is associated with inferior performance on measures of general intelligence, learning and memory [74].

Psychosocial Stress and Inflammation

Psychosocial stress alters innate immune function and aggravates inflammation. In mice, exposure to repeated social stress causes airway inflammation, altered corticosterone responsiveness [75], and augmented effects of LPS [76]. Further, in the absence of peripheral immune challenge, social disruption alone induced pulmonary inflammation and increased myeloperoxidase activity [77]. Remarkably, potentiation of CNS proinflammatory cytokine occurs in stressed animal [78]. Persons undergoing emotional stress of bereavement have an increase in IL-1β and TNF receptor II in orbitofrontal cortex (OFC) [79]. Acute stress elicits increased natural killer (NK) cell counts in PFC, and increased systemic levels of IL-1β and IL-6. Several data have reported that the stressors upregulate IL-6 gene expression in various brain regions, increase IL-1β and IL-6 into the circulation, and cause proinflammatory activation in neurons [78–80]. Further, various psychiatric stressors exert powerful impact on brainstem causing alteration in glutamate signaling genes SLC1A2, SLC1A3 and GLUL [81]. Interestingly, genome-wide transcriptional profiling conducted on healthy adults (25–40 year old) who grew up in low socioeconomic status early in life, showed activation of markers of systemic inflammation including IL-6, and immune activating transcription factor AP-1 activity [82]. In drug-free persons with major depression, gene set analysis showed up-regulation of a variety of proinflammatory cytokines, including interleukin IL-1α, IL-2, IL-3, IL-5, IL-8, IL-9, IL-10, IL-12A, IL-13, IL-15, IL-18, interferon gamma (IFNγ), and lymphotoxin α. This study found that the PFC showed evidence of local inflammation, oxidative stress, and apoptosis [83]. The age-related increases in IL-1β mRNA and protein are correlated with increased microglial stimulation, and this priming to an inflammatory phenotype may underpin enhanced neuroinflammation noted in aging [18], other age-related conditions, and psychosocial stress with potentially serious neuroinflammatory consequences. The above mentioned may also mediate the early neuropsychiatric and behavioral alterations noted in AD. Further, psychological stress has an inverse association with cognition [84].

Hypothermia and Inflammation

Hypothermia is a thermoregulatory response to systemic inflammation and metabolic deterioration in patients and experimental animals alike. Systemic infections/inflammation may alter the body temperature, and this may modulate the host response to infection. Hypothermic septic patients have a significantly worse outcome than the pyrexic or normothermic. Peri-operative hypothermia is common owing to anesthetic action, surgical procedures, and the drugs. The mechanisms regulating hypothermia are not fully understood, but NF-kappaB-dependent gene expression and cytokines such as TNF-α, IL-6, and IFNγ may be involved [85]. TNF-α functions as an endogenous cryogen inducing hypothermia and causes changes in cytokine generation comparable to those stimulated by zymosan, toxic shock syndrome toxin-1, or LPS. Further, hypothermia exerts stimulatory effect on TNF-α and IL-1β generation in primary monocyte cultures and the human THP-1 monocyte cell line, and that hypothermia causes changes in TNF-α and IL-1β mRNA accumulation. A threefold increase has been shown in reporter gene studies of the human TNF-α promoter at 32°C versus 37°C [85]. Flow cytometric analysis and simultaneous measurement of IL-1β, IL-6, IL-8, IL-10, IL-12p70, and TNF-α in monocyte culture of healthy humans showed higher levels in supernatant under hypothermic conditions [86]. Furthermore, mild hypothermia affects the balance of pro- and anti-inflammatory cytokines leading to a pro-inflammatory

state [87]. There is an age-associated increase in cytokines in hypothermics; proinflammatory IL-1β and IL-6, were higher in blood in aged endotoxemic mice (vs. the young) [88]. Hypothermia is a critical factor that causes deleterious impact on brain stem and neocortical functions. Additionally, hypothermia in the elderly promotes not only sensory and motor changes, but memory impairment as well [89].

Obstructive Sleep Apnea (OSA) and Inflammation

Snoring and OSA are caused by incomplete obstruction of the upper airway (UA) and up to 40% of the general population may suffer from these disordered breathing conditions. Snoring is associated with cytokine release from blood cells, and promotes inflammation [90]. Snoring involves vibration of the soft palate, pharyngeal walls, epiglottis and the tongue, and causes lesions of the UA mucosa, pharyngeal muscles, and their innervating nerves [91–93]. Therefore UA mucosa in snorers is edematous and inflamed. The levels of proinflammatory cytokines TNF-α and IL-6 are elevated in the uvula of nonapneic snorers, but are much higher in OSA [94, 95]. Mechanical vibration simulating snoring, triggered an inflammatory cascade in human bronchial epithelial cells, reflected by increased in IL-8 release [96]. Finally, higher BMI, alcohol consumption, and cigarette smoking exacerbate inflammation in snorers [97, 98]. Acute partial sleep deprivation as in OSA has been shown to result in weight gain/obesity [99] and increased risk of oxidative stress in OSA [100, 101].

In OSA, there is evidence of chronic systemic inflammation, evidenced by elevated levels of plasma CRP [102], soluble adhesion molecules [2], and leukocyte superoxide [103]. Further, there is an increase in levels of circulating ICAM-1, VCAM-1, and L-selectin in OSA [104]. Increased expression of adhesion molecules CD15 and CD11c from monocytes in OSA patients has been implicated in adverse effect on vascular proinflammatory/anti-inflammatory homeostasis [103]. The above has been confirmed by increased production of proinflammatory IL-4 cytokine, and a decreased production of IL-10 (anti-inflammatory cytokine), in patients with moderate to severe OSA (AHI of >10/h) [105]. An increase in lipid peroxidation and generation of reactive oxygen species (ROS) has been documented in OSA patients [106]. The ROS increase occurs in repetitive episodes of hypoxia in experimental animals also [107, 108]; the reoxygenation/reperfusion phase in OSA is said to be the culprit that promotes ROS production, oxidative stress, and neuronal apoptosis [108]. OSA has been shown to correlate with hypertension, which has been implicated in AD [109].

OSA is associated with unique cerebral alterations that may explain the behavioral and neurocognitive alterations observed. The vascular pathologies associated with OSA lead to the impairment of optimal cerebral perfusion [110] which has been emphasized to be a critical factor in the development of cognitive dysfunction [111]. Several studies have documented that hypoxia due to OSA causes neuropathological changes and cognitive/memory decline [112, 113]. The latter may result due to decreased oxidative metabolism in the brain, and impairment of neurotransmission. Different techniques including transcranial Doppler, event-related potentials, MR spectroscopy, and structural and functional MRI have clearly demonstrated changes in blood flow, metabolism, morphology, and activation in neurocognition-related brain regions in the OSA patients [114–139]. Decreased cerebral activation during the working memory task in OSA patients reflects that these individuals possess impaired cerebral responses during executive function [140–142].

OSA: Endothelial Dysfunction/Inflammation

Normal endothelium plays an important role in regulating vasomotor tone and maintaining inflammatory and coagulation homeostasis. However, these functions are altered in OSA patients [143–145]. OSA is characterized by vascular inflammation noted by upregulation of cyclooxygenase-2 (COX-2) and inducible NOS (iNOS) in endothelial cells [144]. Upregulation of COX-2 in OSA may increase superoxide production resulting in oxidative stress, increased platelet activation, and endothelial dysfunction/vasoconstriction [146]. In OSA, aggregation and adhesion of circulating leukocytes to the vascular endothelium causes blood vessel inflammation, cause endothelial cell apoptosis with impaired endothelial repair [105–107, 326]. The reasons for endothelial dysfunction in OSA are repetitive hypoxia/reoxygenation during apneas and hypopneas and oxidant-related microcirculatory endothelial dysfunction [144, 145]. There is reduced nitric oxide (NO) availability in OSA patients [143]; importantly, the decreased eNOS activity and increased nitrotyrosine production (byproduct of NO degradation) in endothelial cells provide direct evidence that bioavailability of NO is reduced in OSA patients [144]. This reduced NO availability in OSA impacts endothelial function thus enhancing vulnerability for disorders [143–146]. Even in healthy subjects, sleep deprivation causes a 50% decline in vasodilation reflecting reduced endothelium-dependent NO availability [147], increase in Proinflammatory cytokines IL-6, TNF-α, CRP, platelet adhesion thus promoting coagulation cascade [148–150]. NO is swiftly scavenged by ROS, producing the toxic metabolite—peroxynitrate. Thus as expected, nitrotyrosine expression is greater (than controls) in endothelial cells depicting the presence of enhanced endothelial oxidative stress [144, 145]. The endothelial oxidative damage and

ROS production with a decrease in NO perpetuate a cyclical pattern of endothelial injury [151, 152]. Hence, in OSA patients (those having AHI of >10) repetitive apnea/non-apnea episodes promote inflammation, adversely impact endothelial function, upregulate cell death receptors and mitochondria-dependent apoptotic pathways, that culminate in endothelial apoptosis [153].

Nucleus of the Solitary Tract (NTS)

The NTS is a compact network of neurons; it has copious afferent and efferent pathways that affect central homeostatic control. An array of extensive connections indicates that the NTS is a key structure for sensory, autonomic and neuroendocrine functions. CNS areas that receive a direct projection from the NTS project back to this nucleus. This nucleus contains an enormous range of neuroactive substances; indeed, most of those identified within the CNS are also found in the NTS, as neurotransmitters and neuromodulators [154]. The NTS undoubtedly is a nucleus of tremendous importance subserving extensive key interaction with almost every system of the body. Copious and well documented evidence is available on this brainstem hub nucleus and its influence/impact throughout the CNS. The NTS, the area postrema (AP), and the dorsal motor nucleus of the vagus (DMNV) nerve are components of the dorsal vagal complex (DVC).

The NTS is located in the dorsal brainstem and is the primary site for termination and integration of sensory afferents, such as baroreceptor, chemoreceptor, nociceptors, and afferents from several key body systems, and from UA and tongue. The visceral afferents—i.e. abdominal sensory receptors project via the vagus (and glossopharyngeal) nerve to the DVC. The sensory afferents form synapses with one or more neurons in the NTS in a loose viscerotopic organization. Rostral NTS receives sensory inputs from the UA including the soft palate, epiglottis, pharynx, and the tongue. In intermediate NTS adjacent to area prostema and close to the midline, gastrointestinal inputs synapse, whereas respiratory tract and pulmonary sensory afferents synapse in lateral and ventrolateral regions of the intermediate NTS. Cardiovascular afferents synapse in the medial NTS [155]. In the most caudal NTS, however, cardiovascular, respiratory/pulmonary, and gastrointestinal afferents synapse mediolaterally as well [30, 156, 157]. Overlap of these heterogeneous sensory inputs increases in the caudal NTS where there is increased sensory convergence. Thus the NTS is the first CNS region for synaptic contact of the above afferents. The signal processing of sensory information from the heart, lungs, gut, UA, and the tongue at these synapses determines the output to all downstream NTS synapses in the reflex pathways. The second-order NTS neurons, therefore, integrate the sensory information including the vagal afferent inputs, spatially and temporally, orchestrate an efferent output, and transmit it to various interconnected foci—including the hypoglossal nucleus and the parasympathetic preganglionic neurons of the DMNV [158].

Various circulating inflammatory mediators (CIM), may directly or indirectly gain access and influence the activity of NTS neurons. Adjacent to NTS is the AP; it lacks a BBB and its prominent axons project to the NTS [158]. The AP provides an anatomical pathway whereby CIM can affect the NTS neurons. The caudomedial NTS also lacks a competent BBB, it possesses complexes of fenestrated capillaries and perivascular spaces which provide the NTS neurons direct exposure to blood-borne CIM. The brain is an immunologically competent organ and expresses constitutively a number of chemokines and chemokine receptors in neurons, astrocytes, microglia, and oligodendrocytes [159, 160]. Peripheral LPS challenge causes a hyperactive microglial response in the aged brain associated with higher induction of inflammatory IL-1 β and a significant increase in IL-1 β mRNA expression in the brain of aged mice [36]. Microglia produce IFN-γ during acute infection; they produce IFN-γ mRNA and MHC class II mRNA expression following stimulation with IL-12 and/or IL-18 [161]. There is evidence that inflammatory mediators can influence the brainstem neuronal function directly and the NTS itself is a primary CNS detector of cytokines [162]. Indeed CIM can influence NTS neuronal function directly through local synthesis of inflammatory mediators [163]. Thus binding of CIM, e.g. IL-1β to its receptors on the neuronal membrane, including those of the NTS, initiates signaling cascades upregulating transcription of genes including those of COX-2, TNF-α, and IL-6, and other mediators; these then recruit leukocytes and macrophages that release additional inflammatory cytokines [36, 159–164].

It is important to underscore that both afferent and efferent parasympathetic activity plays a crucial role in immunomodulation [165–167]. By having a "wandering" route through the body, the vagus (Xth cranial nerve) is uniquely equipped to provide an effective early warning system about the pathogenic presence, and feedback to the immune system when pathogens are cleared [165]. The majority of vagal fibers are sensory providing sensory information from a wide range of body systems; this includes relaying the detection/presence of pathogenic invaders [165–167]. It is in the NTS that the afferent and efferent components of the parasympathetic nervous system meet [168]. The NTS having neural-immune communication mounts a specific and effective response [165, 168]; through vagus it affects a broad array of physiological processes [169]. The NTS provides input to the DMNV, nucleus ambiguus (NA), hypoglossal and other

brainstem nuclei; these nuclei provide extensive efferent signals [170]. The efferent parasympathetic pathways constitute the "cholinergic anti-inflammatory pathway" [166, 171, 172]. Ascending from the NTS, the vagus reaches the parabrachial nucleus, thalamus, paraventricular nucleus, amygdala, hippocampus, insula, anterior cingulate cortex, and the PFC [173]. Chronic systemic/neuroinflammation may cause synaptic transmission perturbation and attenuate multitude of efferent signaling pathways from the dysfunctional NTS [170, 174–179]. A dysfunctional NTS would be deleterious to a multitude of CNS foci and body systems that have reciprocal projection to this nucleus. Taken together, the abovementioned studies suggest that the dysfunctional NTS may be responsible for promoting neuropsychiatric and cognitive disturbances noted in the elderly and in AD.

Disparate Afferent(s) and the NTS-Mediated Responses

Maintaining cardiorespiratory fitness (CRF) mitigates structural and functional brain changes related with aging, and preserves cognitive function [180]. Thus, higher CRF preserves brain volume thereby minimizing brain atrophy. In transgenic mice, exercise decreased neuropathology in both cortical and hippocampal regions decreasing amyloid load [181]. The relationship between lower CRF and brain atrophy is present in early AD [182]. This can be explained as follows: (1) CRF has the propensity to attenuate AD pathology and brain atrophy; (2) AD pathology inherently modifies/downregulates CRF; and (3) there is a possible underlying factor such as the dysfunctional NTS that downregulates CRF and enhances neuropathologic burden in AD. It is plausible that based on its functional status, the NTS may influence the CRF and related phenomena [183–186] (see below).

Owing to its immense importance, baroreceptor example is used here as a prototype. Delineation of multitude of afferent receptors vis-à-vis NTS is beyond the scope of this paper. However, some afferents and the involvement of the NTS have been described elsewhere in the above sections.

A number of epidemiological studies have shown a strong association between AD and cardiovascular risk factors, particularly hypertension. Hypertension increases with advancing age. Hypertension is a cardiovascular risk factor [187] which is associated with AD [59, 60, 188]. The densities of SP and NFT in hypertensive subjects are elevated compared to controls [189, 190]. The pathophysiological relationship between hypertension and cognition is important, in that, hypoperfusion and neurodegeneration are expected to be possible underlying mechanisms [191, 192]. Hypertension is also associated with disruptions in neurovascular coupling, decreased perfusion, vascular reserve capacity, microvascular disease, stroke, cognitive decline, and dementia. The baroreceptor reflex is a negative feedback system; baroreceptor stimulation decreases hypertension [193–200]. Conversely, NTS lesions are known to interrupt central baroreceptor pathways [196]. Artificial stimulation of baroreceptor afferents increases parasympathetic outflow but decreases sympathetic outflow to the cardiovascular system [193–200]. Indeed, age-associated changes in baroreflex regulation may involve NTS catecholaminergic mechanisms [201, 202] suggesting that any dysfunctional NTS physiology may contribute to altered regulation of parasympathetic discharge [203].

Cardiovascular system is affected by oxidative stress (ROS) and expression of subclinical proinflammatory TNF-α, IL-6, and CRP [204]. Increased sympathetic activation is a risk factor that potentiates cardiac hypertrophy, fibrosis, and the renin–angiotensin system [205–207]. However, enhancing vagal tone, via vagal nerve stimulation (VNS), exerts anti-sympathetic action through well characterized mechanisms [208–210]. Interestingly, in addition to anti-sympathetic effects, the vagal activation (a cholinergic effect) also mediates anti-inflammatory actions. In LPS-stimulated human macrophage culture, proinflammatory cytokines such as TNF-α, IL-1β, IL-6, and IL-18 were suppressed by ACh [211]. In LPS-induced endotoxemic shock, bilateral VNS ameliorated hypertension and prevented surging of plasma TNF-α [211]. Equally important, VNS mediated ACh release activates the endothelial dependent NO synthesis—a protective mechanism against hypertension and atherosclerosis [212]. Furthermore, a 3-month VNS stimulation improves Left Ventricular function and hemodynamics, together with normalization of TNF-α, IL-6 [213], and NO (mRNA and protein expression) [214]. The above mentioned suggests the possible in vivo importance of integrity of the NTS.

The NTS is extensively interconnected; this network may play an important role in several regulations/functions, in addition to cardiovascular system [195, 215]. Another example of the ubiquitous nature of the NTS is given below. The inflammatory signal induced by LPS reaches the preoptic anterior hypothalamic area (POA). Subdiaphragmatic vagotomy or abdominal perivagal lidocaine administration, or lidocaine injection into the NTS prevented the LPS action. These data suggest that LPS function is mediated by the vagus nerve which conveys the signal to the NTS that in turn stimulates norepinephrine release within the POA [216]. VNS stimulates both vagal afferents and efferents [217], and neural activation of NTS enhancing the brain-derived anti-inflammatory response [216, 218, 219]. The vagal nerve, therefore, is an important modulator of the immune system [172, 220]; it controls inflammation and modulates the immune response through a 'nicotinic anti-inflammatory pathway' dependent on the alpha7-nicotinic ACh receptor [221]. Vagus nerve commences from the NTS, and

supportive evidence of cognitive effects of VNS has been well documented [221–225].

Finally, the combination of advanced age in conjunction with other stigmata described above, and the dysfunctional NTS may interact in a complex pattern and provide pathophysiological impetus that leads to cognitive decline and dementia. The latter is promoted due to interactions between cortico-cortical and subcortical disconnection (synaptic dysfunction), neuroinflammation, altered cholinergic/NTS transmission, autonomic disturbance, dysfunctional vascular endothelium, altered regulation of blood flow, deposition of Aβ and NFT, and neuronal degeneration/death in several key brain areas. These attenuate decision-making, cognition and memory, thus promoting AD.

The NTS Vis-à-Vis Deficits in Known Key Brain Regions in AD

AD is multifactorial and heterogeneous and may involve more than one etiopathogenetic mechanisms. One of the major hallmarks of AD is the degeneration of BFB cholinergic neurons indicating an important role of the cholinergic system in learning and memory. Studies have emphasized the critical role of pro-inflammatory cytokines as common mediators of cholinergic neuronal damage [226]. In contrast to late AD, patients with mild cognitive impairment (MCI), apparently show no cholinergic neurodegeneration. There is abundant evidence that Aβ may trigger cholinergic dysfunction through action on α7 nicotinic acetylcholine receptors, affecting NGF signaling in cholinergic neurons [227, 228]. Mesulam concluded that "cholinergic loss is neither a primary pathogenetic factor of AD nor the principal correlate of its clinical manifestations" [229]. However, as the cholinergic dysfunction progresses, it does influence cognitive deficits. These observations are consistent with the clinical evidence that cholinergic therapies (use of cholinesterase inhibitors) alone are unable to treat AD.

A major feature of AD is the degeneration of noradrenergic locus coeruleus (LC) neurons [230–232]. LC is the sole source of noradrenaline (NA) to neocortex and the hippocampus [233]. Attention, memory, arousal, vigilance and mood are affected by NA signaling [233]. LC damage has been shown to upregulate gliosis and inflammation [234–237], excitotoxicity [238], oxidative stress [238, 239], and Aβ deposition in the hippocampus and neocortex [238]. LC degeneration has been shown to reduce NGF and/or BDNF in LC projection sites in AD [231]. Although NA agonists may improve cognition, their side effects would include tachycardia and other arrhythmias. Interestingly, the effect of AD on LC neurons was greater than that on the BFB cholinergic neurons [240]. When Aβ was injected in rat retrosplenial cortex, it caused a higher neuronal loss in the LC than in the BFB (nucleus basalis) [241]. Importantly, degeneration of NA neurons does not occur as a result of normal aging [242, 243]. Hypoxia has deleterious effect on neurons including those of LC and hippocampus [244–248]. They become persistently impaired after exposure to hypoxia/reoxygenation, modeling sleep apnea in adult mice [249]. The LC degeneration, therefore, is an event being closely associated with neuroinflammation and OSA. Vagal activation (or inhibition) has a correlated effect on the LC neurons, thus reflecting the influence of the NTS on the LC function [250].

The entorhinal cortex (ERC), located inside the rhinal sulcus in the olfactory area, is spatially associated with the amygdaloid complex rostrally and hippocampal formation caudally. The olfactory structures are the only primary sensory system components that have direct projections to the ERC; in addition, the cingulate cortex and thalamic afferents also innervates ERC [251]. Electrophysiological studies have confirmed the selective olfactory projection to the ERC [252–255]. The ERC forwards sensory information to the hippocampus via the perforant pathway and receives back the hippocampal information [256]. A substantial body of literature has documented that memory and learning deficits associated with AD are attributable to neuronal degeneration in the ERC. ERC ablations alone may produce memory deficits [257]. AD pathology begins in the ERC, and in AD the atrophy rate in the ERC is higher than in the hippocampus [258]. In mild cases of AD, 60% of the neurons are lost in the ERC, whereas 90% loss occurs in advanced AD [259]. The ERC atrophy precedes hippocampal atrophy and the ERC volume loss is dominant over the hippocampal volume loss in MCI [260]. Such preferential damage to the ERC contributes to the etiology of AD. ERC is particularly vulnerable to tau pathology in aging and following olfactory dysfunction. The upstream pathological factors in the latter (including infection, inflammation and environmental toxins) would have an adverse impact on ERC function. Further, there are projections from the NTS that may impact olfactory bulb function in AD [261–266]. The ERC lesion, therefore, would impair working memory and induce anterograde memory deficits [258–260, 267].

Metabolic and functional homeostasis in CNS is maintained due to the complex output of endocrine, autonomic, and behavioral control circuits. The functional relationship between the NTS neurons and a host of key foci and modulation of synaptic activity [170] identifies a pivotal role of the NTS in memory and cognition. Sensory signals from the cardiovascular, respiratory, gastrointestinal, and other systems (see the section on the NTS) are delivered to the NST; subsequently efferent signals arising within the NTS are relayed to various brain regions. The axonal

projections from the NTS to the hypothalamus and limbic regions is said to modulate behavioral arousal, and coordinate endocrine [268–273] and behavioral responses to stress (including infection and inflammation) [272, 273]. The potential physiological significance of these connections and mechanisms is immense in terms of central control of a vast array of functions. Finally, since stimulation of vagus nerve (arises from the NTS as mentioned above) has been reported to enhance memory in animals and humans, the underlying neuroanatomical-physiological substrate primarily responsible for modulating memory is the NTS. The dysfunctional NTS conceivably would lead to dysfunctional synaptic activity and may negatively impact memory in aging and AD [71, 201–203, 250, 264–266]. Accordingly, since the NTS may have an etiological role in AD, it represents an appropriate target for treatment of attention, arousal, cognition and memory dysfunction.

Discussion

Inflammatory Pathology in Aging and AD

Aging is a low-grade chronic subclinical state of inflammation that may promote age-associated diseases including AD. Ongoing inflammatory cascades may enhance pathologies including vascular endothelial cell damage, ischemia, hypoxia/hypoxemia, and cardiovascular conditions [2–4, 11–13, 18, 36, 164]. These may further exacerbate the expression of proinflammatory cytokines in the elderly [106–108]. Systemic inflammation has an impact on the microglia and switches them to a primed phenotype. Thus activated microglia become hyperresponsive to inflammatory stimuli [3, 18, 36, 164] in the aged CNS; they release proinflammatory cytokines that may exceed the anti-inflammatory mediators [22, 38, 39] and promote neurodegeneration [109, 274–277]. In both humans and transgenic mouse models of AD, the increased inflammatory modulators are correlated with the onset of AD neuropathology [109, 276, 277]. The former include the proinflammatory cytokines such as IL-1β, IL-6, TNF-α and TGF-β, chemokines, the complement pathway, coagulation factors; α-2-macroglobulin and α1-ACT (acute-phase reactive proteins) [25]. The Rotterdam Study (6,713 subjects) found a relationship between elevated levels of α1antichymotrypsin, CRP, IL-6, soluble ICAM and VCAM, and an increased risk for AD [278].

Aging Decreases NTS Volume

Applying strict exclusion criteria, 152 "healthy older adults without any disease", (mean age = 66), except for "undiagnosed sleep-related breathing disorders (SRBD)", and an AHI of 21 ($\pm$15) for males, and 16.7 ($\pm$12.9) for females, were studied [279]. The absence of subjective daytime sleepiness and a lack of involvement of any cortical or subcortical structures in these elderly underscored their overall health. Furthermore, their whole brain Gray matter volume (GMV) scans obtained using voxel-based MRI morphometry did not differ significantly between subjects with and without SRBD. However, bilaterally, a significant inverse relationship was found between AHI and GMV in the pontomedullary zone—involving (1) NTS, (2) NA, and (3) the DMNV [279]. The symmetrical atrophy of these key brainstem nuclei was interpreted as a function of episodic hypoxic and sleep-disordered conditions. The GMV loss in specific brainstem nuclei in asymptomatic elderly reflects an ongoing silent subclinical anatomical and pathophysiological change. Apart from their subclinical breathing abnormalities during sleep, the only other abnormalities these elderly possibly suffered from were subclinical ongoing decreases in olfactory, gustatory, and somatosensory modalities of senescence [89, 280, 281], and aging-related inflammation rendering the brainstem nuclei dysfunctional, including the NTS. Conceivably, during aging decreases occur in sensory modalities (thalamocortical system) and this may affect the NTS $\rightarrow$ Hypoglossal $\rightarrow$ genioglossus activity, attenuating the pharyngeal patency; this would result in apnea/hypopnea and hence hypoxia/hypoxemia during sleep. The recurring intermittent hypoxic episodes during sleep may potentiate neuropathology in key brainstem regions, and neocortex including the parietal, temporal, and frontal lobes, and the BFB. Conceivably, these neuropathological alterations may underpin cognitive dysfunction.

Hypoxic Injury and NTS Pathology

The NTS is a pivotal region for regulating the set-point of arterial pressure; CIH has been linked to elevations of sympathetic activity and mean arterial pressure. A recent study reports that the NTS hypoxia increases arterial pressure [282]. Hypoxia stimulates the expression of inflammatory cytokines (TNF-α, IL-1β), chemokines (IL-8, MCP-1/CCL2), and adhesion molecules (ICAM-1) in the brain and in cultured human and mouse astrocytes, and brain endothelial cells [283, 284]. Hypoxia-induced upregulation of inflammatory genes is regulated by different transcription factors including activator protein-1, NFκB, and HIF-1. HIF-1 is an essential molecule that regulates oxygen homeostasis and mediates hypoxia-induced expression of proinflammatory mediators including IL-1β [284–286]. Astroglial cells are the most abundant cells in the brain and play an important role in the initiation and progression of hypoxia-induced neuroinflammation. OSA subjects suffer from microarousals and enhanced sympathetic activity; however, it is important to highlight

that age-related oxidative stress itself is sufficient to promote vascular inflammation even in the absence of other common risk factors [286]. Recent experimental data suggest that ROS and multiple proinflammatory pathways may converge on NF-κB to enhance its transcriptional activity, and induce endothelial activation in aged vasculature [286]. Furthermore, in the NTS neurons, hypoxia decreases the amplitude of excitatory postsynaptic currents [287].

Significant cognitive impairment occurs in patients with moderate to severe OSA, and this is correlated with tissue damage in regions involved in cognition. Various data have shown focal loss of grey matter volume (GMV) and hence neuronal loss in cognitively relevant brain regions in OSA/hypoxia [288]. In animal model of OSA, the cortical neuronal cell death due to CIH has been documented causing neurocognitive dysfunction [108, 289]. Neurocognitive dysfunction associated with sleep apnea has been documented in elderly patients with MCI [290]. Another mechanism analogous to CIH is the ischemic hypoxia/reperfusion-related reoxygenation, where enhanced ROS generation may cause damage. Decreased brain perfusion has been documented after apneic episodes in OSA patients [291]; further, hypoxia has been shown to cause severe pathology in the NTS neurons [292].

Neuronal Apoptosis in the NTS

OSA is characterised by repetitive obstruction of the UA during sleep due to failure of the principal dilator muscle genioglossus to oppose the pharyngeal collapse. The net result is a condition characterized by intermittent apnea and hypoxia. However, despite its great importance little is known about the pathways proximal/prior to genioglossus dysfunction and UA collapse. The important role of snoring/OSA in causing degeneration of UA afferent nerve fibers that impacts the sensory limb of the sensory-motor reflex has been emphasized [280, 281]. It was also pointed out that the NTS that integrates UA sensory inputs may be rendered dysfunctional owing to paucity of UA sensory stimulation. Since the NTS projects to the hypoglossal neurons [28, 29] it impacts the genioglossus function that causes UA obstruction/collapse → snoring to overcome the UA negative pressure → apneic hypoxia. The question still remains as to what causes the NTS dysfunction in the first place that evokes a cascade culminating in UA obstruction and snoring; the pathology of sensory nerve fibers of UA being downstream to snoring and pharyngeal suction collapse. It is posited here that it is the ongoing systemic inflammatory episodes (from disparate sources detailed above) and the resultant neuroinflammation which are the harbinger of neuronal dysfunction/degeneration in CNS in general, and the NTS neurons in particular. Consequently, neuroinflammation, ROS production, oxidative stress gene activation, protein oxidation, lipid and nucleic acid oxidation, alter the neuronal homeostasis in the NTS and other brainstem nuclei. This conclusion is supported by experimental studies employing ROS/Neuronal degeneration approach [293]. Consequently, neuroinflammation, intermittent/episodic apnea/hypopnea, and ROS/oxidative stress would synergize to augment the NTS pathology [19, 108, 292, 294, 295]. There is compelling evidence, therefore, to support the above explanation for neuronal dysfunction—and the epicentre of this pathology is the multifunctional highly interconnected NTS.

Hypoxia and other risk factors described above upregulate innate inflammation and neuroinflammation causing release of proinflammatory cytokines from several brain foci. OSA was found to be independently associated with TNF-α level [293]; this cytokine has been shown to alter synaptic transmission and plasticity [296], and it is a crucial mediator of neuronal cell death. The NTS is highly vulnerable to ischemia and/or hypoxia owing to its intense metabolic activity. Important data are available on the anatomic distribution of apoptosis of neurons and glial cells in the medullary nuclei of adult subjects who died of hypoxic injury [294]. The apoptotic index was: NTS 11.2, DMNV 6.8, and hypoglossal nucleus 6.6. In another study of human autopsied brainstems (15 adults, 25–58 year old), the percentage of TUNEL-positive neurons in the NTS was 8.5% and DMNV was 5.4%, and the apoptosis was ascribed to hypoxic-ischemic injury [295]. In a guinea pig model of intermittent apnea (mimicking closely to that occurs in humans) recent elegant studies have clearly documented that recurrent periods of apnea induce apoptotic neurodegeneration in nuclei throughout the brainstem [291]. Although apoptotic neurons were widespread, the highest density of apoptotic neurons was present in the facial, hypoglossal, ambiguus, DMNV, and the NTS [297]. In addition to the nuclei involved in the regulation of respiratory, cardiovascular, sleep/wake, and autonomic functions, a great number of apoptotic neurons were present in other areas of the pons and medulla as well. Since the NTS is a major coordinating center, apoptotic degeneration of neurons in this particular nucleus and those linked to this nucleus may contribute significant deficits in a number of functions throughout the CNS.

Invading Pathogens Cause NTS Dysfunction

In addition to inflammation, hypertension, diabetes mellitus, hypoxia/hypoxemia, and attenuated cerebral blood flow (CBF), the Intra-cerebral presence of microorganism is also an important risk factor in promoting cognitive dysfunction and AD. An invading pathogen may generate an inflammatory acute response and commence a cascade

of signalling mechanisms, including activation of cytokines, complement system, and recruitment of the immune cells to the site of inflammation. An example of recurring acute viral insult is herpes simplex virus type 1 (HSV1) that remains in a latent state in the peripheral nervous system. The life-long dormancy is punctuated by repeated activation (due to different stresses), reaching different brain areas such as frontal and temporal sites (known to be involved in AD)—and causing damage. The virus is ubiquitous infecting about 90% of adult population, and PCR has confirmed the viral presence in brains of the elderly with and without AD [298]. Other viri including influenza PR8 virus may gain entry via nasal and/or oral portals, promote CNS neuroinflammation, and cause widespread neuronal dysfunction, including those of the NTS. Similar to HSV1, hepatitis, HIV, West Nile virus, *Chlamydia pneumoniae* and *Borrelia burgdorferi* (to name just a few), are capable of causing CNS pathology [299], as are other bacteria [70]. Injection of pseudorabies virus in the rat genioglossus produced viral labeling in neurons of the hypoglossal and the NTS nuclei [300]. When present in the brain cells, microorganism(s) enhance microglial activation, cause release of neurotoxic agents, and lead to neuronal injury and degeneration. Thus stigmata such as cerebral infection, neuroinflammation, hypoxia/hypoxemia, and perturbed CBF are assumed to occur in the NTS, and may impact its neuronal function adversely. In order to gain entry into the NTS, any infection need not alter the integrity/permeability of the BBB. Microorganisms can cross the BBB and enter the brain through the so-called "Trojan horse mechanism" [301]. *Chlamydia pneumoniae* e.g. is known to reside in the peripheral blood monocyte and leucocytes, and could exploit the Trojan horse mechanism to enter the CNS over an intact BBB [302]. NTS is adjacent to the AP [158] and lacks a BBB; the AP has prominent axonal projections to the NTS, and provides an anatomical pathway whereby various circulating inflammation-causing mediators can gain access and affect the NTS activity.

Olfactory Nerve Transmits Infection to the NTS

The olfactory nerve (ON) is an important pathway for transmission of viruses into the brain owing to its direct contact with the environment. When influenza virus PR8 is intranasally introduced in mice, signals from the ON triggers the acute phase response (APR); however, the ON transection prior to influenza viral infection reduced the number of viral antigen-TNF-α- and IL1β-immunoreactive cells in the olfactory bulb (OB) and other interconnected brain regions [302]. As early as 15 h post-infection, the number of cells expressing TNF-α and IL1-β mRNAs and proteins increase in the OB, as well as in neurons within different regions of the brain including the amygdala, hypothalamus, and central autonomic system regions [302]. All above mentioned areas project reciprocally to the NTS (see section on NTS above).

Vagus Nerve Transmits Infection to the NTS

By having a "wandering" route through the body, the vagus is uniquely equipped to provide (a) an effective early warning system about the pathogenic presence, and (b) a feedback to the immune system when pathogens are cleared. Several studies have demonstrated that neurotropic viruses travels to the CNS mainly via the vagus nerve. In mice infected intranasally with influenza (either virus strain 24a5b or avian influenza A-H5N3), the virus travel to the NTS via the vagus nerve [303, 304], moreover, the nucleus primarily affected was the NTS [303, 304]. Following administration of the neurotropic avian influenza virus H5N1 in C57BL/6J mice, the virus is transmitted into the CNS via the vagus. Other infections including the fatal transmissible spongiform encephalopathies or prion disease spread from the periphery to the brain, through an oral route. The first target area in the brain of orally infected scrapie is the DMNV, followed rapidly by the NTS—again via the vagus nerve [305]. The above data clearly show that viri from the oral, nasal or lower respiratory mucosa are transmitted to the CNS via the vagus; they spread transsynaptically in the CNS inducing lesions in the brainstem nuclei, including the NTS. Thus, via vagus, microbes in the periphery are relayed to the NTS for mounting a specific and effective response; it is here in the NTS where the afferent and efferent aspects of the parasympathetic nervous system meet [168]. The efferent parasympathetic pathway forms "the cholinergic anti-inflammatory pathway" [166, 171, 172]. On the efferent side, since the NTS has direct and indirect connections to a wide range of neural structures in the CNS, it has the capacity to influence their physiological processes [165].

An Inflamed NTS Is a Dysfunctional NTS

Brain mRNA is replete with mRNA of systemic cytokines; systemic IL1-β e.g. increases brain IL1-β mRNA, and vagotomy (subdiaphragmatic) blocks this [306]. Interestingly, relative to control (saline), systemic administration of proinflammatory cytokines TNF-α or IL1-β also increased IL1-β, TNF-α and IL-6 mRNAs in the NTS, but did not increase the anti-inflammatory IL-10 cytokine [307]. Recent studies have implicated the microvasculature inflammation in the brainstem, specifically in the NTS, in the pathogenesis of hypertension [308, 309]. It has been shown that vessels within brainstem regions of hypertensive animals are inflamed and release ROS and cytokines;

these pathological messengers then alter neuronal activity in the NTS [310–314]. The inflammatory signaling molecules released from the brainstem microvasculature exert deleterious impact on neuronal excitability in the NTS; this then alters both the central set point of arterial pressure and its reflex control. Furthermore, the brainstem vessel inflammation conceivably elevates the resistance to blood flow thus causing inadequate perfusion. This then presents a scenario of sympathetically mediated hypertension in response to inadequate blood perfusion. Conceivably, the above pathology synergized with hypoxia and other risk factors negatively impacts the NTS activity further; an inflamed and dysfunctional NTS consequently may cause widespread disruption of many key physiological functions in both brainstem and neocortex.

Recent studies have shown high levels of proinflammatory molecules expressed in the NTS of the spontaneously hypertensive rat (SHR), an animal model of human essential hypertension. In the NTS of SHR, the gp39 precursor was up-regulated [310, 311]. The gp39 precursor is homologous to chitinase 3-like protein 1, also known as human cartilage-gp39 or YKL40. Although functional roles for gp39 precursor are not fully known, high levels of this molecule are present in many inflammatory conditions including rheumatoid arthritis, glioblastoma, inflammatory bowel disease, atherosclerosis, asthma, and indeed AD. Furthermore, gp39 precursor promotes chemotaxis, and an up-regulation of gp39 precursor in the NTS of the hypertensive rats reflects a pervasive inflammatory state that may attenuate neuronal activity in both inflamed NTS, as well as its interconnected foci [310–314]. In AD, the dysfunctional NTS may differentially affect functional integrity of its projected pathways/neurons, and compromise linked key brainstem nuclei, and neocortical regions including the hippocampus, BFB, hypothalamus, insula, PFC, amygdala, and other cortical regions. There are numerous examples of neural network degradation in aging and AD. Finally, it is untenable that the NTS remains structurally and functionally insulated from the pathological effects of local and distant neuroinflammation.

The Current Hypothesis

Several CNS areas including the BFB, hippocampus, ERC, amygdala/insula, and the LC are known to be lesioned in AD. To date, a plausible unifying hypothesis that links well characterized upstream factors and AD pathology encompassing heterogeneous dysfunctional regions in AD brain is not available. Based on well documented evidence, it is posited here that the NTS is a brainstem hub nucleus that has an enormous influence/impact throughout the CNS. The current article presents a novel NTS vector hypothesis that underpins several disparate biological mechanisms and neural circuits, and identifies relevant hallmarks of major presumptive causative factor(s) that link the NTS to AD neuropathogenesis.

The GMV decrease occurs in the CNS due to aging, inflammation, obesity, and hypoxia, as mentioned above. It is well documented that inflammatory and oxidative stress processes trigger cascade of neurodegenerative events including synaptic loss, neurotransmitter deficits, and neuronal dysfunction [315]. Input from the inflamed and dysfunctional NTS is deemed to negatively impact several foci, including the hypoglossal motor neurons. The dysfunctional hypoglossal activity causes genioglossal dysfunction, which provokes UA functional perturbations. To overcome the latter, snoring is employed as an effort to ameliorate UA obstruction that promotes periodic apnea, i.e. OSA. The resulting periodic UA obstruction/collapse and hypopnea/apnea cause intermittent hypoxia and hypoxemia. Chronic intermittent hypoxia/reoxygenation is toxic to neurons, which are already subjected to neuroinflammation and GMV. A synergistic effect of the above factors may exert deleterious impact and compromise the NTS function. Perturbations in the NTS activity cause dysfunctional processing of sensory afferents from the olfactory, gustatory, UA somatosensory, cardiovascular baroreceptor and chemoreceptor, as well as afferents from the gastrointestinal, respiratory, and other thoraco-abdominal viscera. The vagus arises from the NTS—a dysfunctional NTS may compromise and attenuate the efferent activity of the vagus; since vagus has an anti-inflammatory parasympathetic function—this will be attenuated as well. The projections from a pathological NTS (and the several nuclei it projects to, e.g. the LC, NA, DMNV, and parabrachial), to the PFC, amygdala, insula, BFB, ERC, and the hippocampus would conceivably compromise activity in the above CNS areas thus contributing to neuropsychiatric and cognitive pathology of AD (Fig. 1). An ongoing attenuation/compromise (over a period of decades) of function in many CNS pathways may result in widespread synaptic and neuronal perturbations, their disruption, degeneration, and eventual death.

Neuroinflammation—Amyloid Deposition and Neurofibrillary Tangles

Although Aβ deposition is considered a hall mark of AD, it occurs in unimpaired normal elderly as well [316]. This indicates that the time window for its slow rate of accumulation in clinically silent period may be quite large in the aged. An indolent sub-clinical inflammatory state persisting in the elderly (see inflammatory risk factors discussed above) causes neuroinflammation and cerebrovascular pathology in

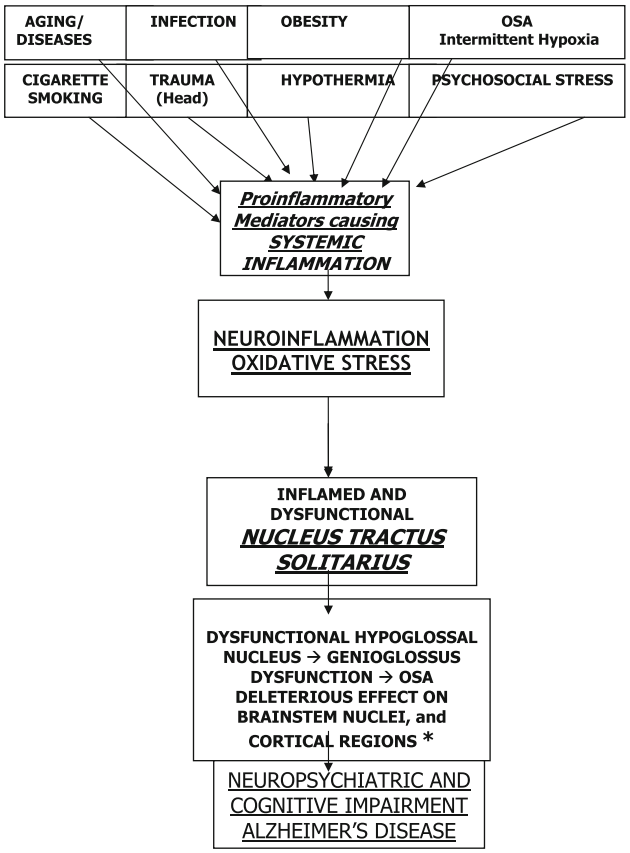

Fig. 1 Schematic representation of the hypothesis. Several risk factors in aging enhance proinflammatory cytokines inducing systemic inflammation. This promotes neuroinflammation; activated microglia further augment central inflammation affecting neuronal, glial and vascular endothelial cell functions. The *box* with the *asterisk* denotes that dysfunctional hypoglossal motoneurons cause genioglossus dysfunction resulting in upper airway obstruction/collapse. This leads to OSA, periodic hypoxia, and hypoxemia. Inflammation, intermittant hypoxia, and oxidative stress provide a rich milieu for the NTS inflammation and dysfunction. Being a central hub for disparate afferent processing, and owing to its widespread projections in the CNS, the dysfunctional NTS would negatively impact several key physiological functions, causing impairment in cognition and memory. The ongoing synaptic dysfunction and neuronal degeneration over a prolonged period (aging), promote neuropsychiatric and cognitive deterioration, and provoke Alzheimer's dementia

the vulnerable. This enhances priming of the microglia and astrocytes, infiltration of perivascular macrophages and peripheral immunocytes that may promote neuronal dysfunction/degeneration. These processes may cause reactive Aβ generation. In upregulated neuroinflammation, there is a mismatch between the level of Aβ synthesis and its removal by microglia; this may lead to further inflammation and excess of Aβ deposition. Thus, in neuroinflammation, Aβ formation/deposition is a downstream phenomenon. Furthermore, Aβ has been shown to functions as an antimicrobial peptide (AMP) being active against common and clinically relevant microorganisms [317, 318]. Since several infectious agents have been reported in CNS of the elderly and AD patients [70] (see the section on invading pathogens cause NTS dysfunction), Aβ may be synthesized as part of a response triggered by the immune system.

AD is characterized by neurofibrillar degeneration; the latter occurs as intraneuronal NFT in dementia. Hyperphosphorylated tau (p-tau) is considered to occupy a central position in AD neuropathogenesis. In Tg4510 mice, p-tau is associated with age-related microglial activation, and in normal aging up to 9 mo CD45+ microglia increase in parallel with tau pathology [319]. 1–3 month old young mice are capable of clearing soluble p-tau; however, in 5.5 month-old mice insoluble tau aggregates are present [319, 320]. In LPS injected APP mice, activated microglia cleared Aβ [321]. However, LPS-induced microglial activation exacerbated p-tau pathology in Tg4510 mice [319]. Interestingly, peripheral administration of LPS showed no changes of APP processing, while p-tau was increased in both hippocampus and the ERC [322]—important regions in AD pathogenesis. Moreover, proinflammatory cytokine IL-1β caused tau phosphorylation in neurons [323]. In 3xTgAD mice also, chronic TNF signalling enhanced p-tau causing neuronal death [324]. The above studies support the potential role of inflammatory mediators in enhancing p-tau pathology and underscore that inflammatory stimuli can and do facilitate tau phosphorylation potentiating taupathy. Similar results however have been obtained in rats undergoing chronic neuroinflammation following LPS administration [325]. Such a scenario may occur in the CNS and the NTS in particular, in the elderly and AD patients (who possess a chronic inflammatory state as delineated above). In sum, the dysfunctional NTS may affect the functional integrity of a large number of key pathways/synapses/neurons, and provoke cognitive dysfunction/dementia in the elderly.

Conclusions

The immune system and inflammation are implicated in aging and a wide variety of neurodegenerative conditions. Relatively common sources of systemic inflammation may be significant risk factors to potentiate neuroinflammation in the elderly. This would cause microvascular changes, switching of microglial phenotype and activity, and perturbation of physiological functions in the CNS including the key brainstem nuclei, viz. the NTS and the hypoglossal. Their dysfunctional activity results in genioglossal dysfunction that may leads to UA obstruction and intermittent hypoxia/hypoxemia. The latter has widespread impact on CNS structure and function by enhancing further inflammation and exacerbating GMV decrease in aging. Neuroinflammation plus intermittent hypoxia synergize to promote escalation of CNS pathology. The NTS is the

central integration hub for UA somatosensory, gastrointestinal, gustatory, baroreceptor, chemoreceptor, and several other afferents e.g. from the amygdala, PFC, and hypothalamus, as well as sympathetic and parasympathetic systems. On the efferent side, the NTS projects to most, if not the entire, CNS. A pragmatic hypothesis is posited on the neuropathogenesis of AD emphasizing the important role of upstream factors. The current hypothesis implicates the inflamed and dysfunctional NTS as an upstream central player in the neuropathogenesis of cognitive and neuropsychiatric impairment. In defining etiopathology of AD, the current hypothesis is the first to connect: Aging → proinflammatory mediators, neuroinflammation and oxidative stress → dysfunctional NTS → impaired function of hypoglossal nucleus → depressed genioglossal function and hence snoring/OSA → hypoxia and hypoxemia → further exacerbation of neuroinflammation/oxidative stress → widespread neuronal degeneration → global deleterious impact on key physiological functions in CNS → neuropsychiatric, memory and cognitive dysfunction → AD. Vagus arises from the NTS; the vagal function is anti-inflammatory and hence important in ameliorating inflammation and upregulating functions towards homeostasis. However, a dysfunctional NTS would compromise and attenuate vagal activity, resulting in increased CNS susceptibility to the effects of disparate pathological factors, and facilitating neuropathogenesis in aging and AD. The implications of the current perspective are considerable and future research is warranted.

Conflict of interest I have no conflict of interest.

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