Elevated Cerebrospinal Fluid Norepinephrine in the Elderly can Link Depression and A Reduced Glymphatic System as Risk Factors for Alzheimer's Disease

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Abstract

Aging (>65 years) is clearly the greatest risk factor for developing late-onset Alzheimer's disease (AD), although the age of onset for an individual is unknown. Accumulation of plaques (Aβ) and tangles (phosphorylated tau) are believed to be the cause of AD and are considered the two major neuropathological markers of AD, and occurs well before the appearance of cognitive impairment. Reducing the incidence of AD by reducing the accumulation of plaques or tangles could have a profound effect on the predicted costs of caring for these individuals. To reduce the incidence or delay the onset of AD in the elderly population, risk factors or biomarkers need to be identified very early in the progression of the disorder to indicate when interventions should be initiated to prevent or slow the progression of AD. This review hypothesizes that depression in the elderly is a marker of depression because it suggests the noradrenergic nervous system in the locus coeruleus (LC) is malfunctioning. The noradrenergic neurons in the LC are malfunctioning because there is a loss of noradrenergic neurons due to early stage AD pathology. The minimal loss of LC neurons increases synaptic brain norepinephrine (NE) levels which precipitates depression and a reduction in the glymphatic system. The reduction in the glymphatic system would reduce the clearance of Aβ and tau from the brain, thereby enhancing the deposition of plaques and tangles in the brain and the development of AD.

Keywords: Norepinephrine (NE); Glymphatic depression; Central nervous system (CNS); Locus coeruleus (LC); Cerebrospinal fluid (CSF)

Introduction

Aging, is clearly the greatest risk factor for the development of late-onset Alzheimer's disease (AD) [1-3], with the incidence doubling every 5 years from ages 65 to 90 years [4], and an anticipated 7.7 million people by 2030 and 11-16 million by 2050 [5]. Therefore, reducing the incidence or delaying the onset of AD can have a profound effect in the coming years on the cost of caring for these individuals. Accumulation of plaques (Aβ) and tangles (phosphorylated tau) are believed to be the cause of AD and are considered the two major neuropathological markers of AD. Therefore, a great deal of emphasis over the past few years has been on the measurement of amyloid β (Aβ $_{1-42}$), total tau, and phosphorylated tau, neuropathological markers of AD in cerebrospinal fluid (CSF) in the elderly population as a biomarker. However, results using these neuropathological markers have been plagued by variability in values, limiting their usefulness as biomarkers for AD [6]. To reduce the progression of this disorder in the elderly population, other risk factors or biomarkers need to be identified and used to help determine when intervention in the elderly population should be given to prevent or reduce the incidence of AD. This review is not a comprehensive analysis of the potential risk factors or biomarkers that could be used to start intervention to prevent or slow the progression of AD. This paper focuses on the consequence of noradrenergic neuronal loss in the locus coeruleus (LC) that occurs early in the progression of AD on the development of depression and consequential reduction in the glymphatic system. Depression in the elderly has been described as a

risk factor for developing mild cognitive impairment or AD; however, a biological cause(s) linking changes in the noradrenergic system associated with AD to depression has not been identified. It has also been unclear how the presence of depression in the elderly could enhance the development of AD (i.e., increase the deposition of plaques and tangles). This short review hypothesizes that the early loss of noradrenergic neurons in the LC associated with early stage AD results in two important consequences: 1) depression and 2) a reduction in the glymphatic system in the CNS. The noradrenergic nervous system regulates the glymphatic system that is essential for the removal of toxic materials and soluble proteins, such as Aβ and phosphorylated tau from the CNS. Accumulation of insoluble Aβ and phosphorylated tau in the CNS can ultimately lead to AD. Therefore, the appearance of depression in the elderly may be a marker/risk factor for the development of AD because it would serve an indicator that the noradrenergic nervous system is malfunctioning (Figure 1).

Noradrenergic Neurons in the Locus Coeruleus in AD

AD is a progressive neurodegenerative disorder. My laboratory and others have demonstrated a substantial loss of noradrenergic cell bodies in the LC, the major source of noradrenergic projections to the whole brain, in postmortem brain tissue from AD patients compared to age-match control patients [7-11]. Braak and others [12-16] have examined postmortem tissue from a wide range of ages (1-100 years) of non-demented individuals, and noted the LC to be one of the first regions exhibiting early stages of neuropathological markers of AD. These data indicate the initial process for AD occurs many years before the onset of cognitive impairment. Since AD is a progressive disorder, it can be hypothesized that LC neuronal loss will be gradual and LC dysfunction will occur in the very early stages in the progression of
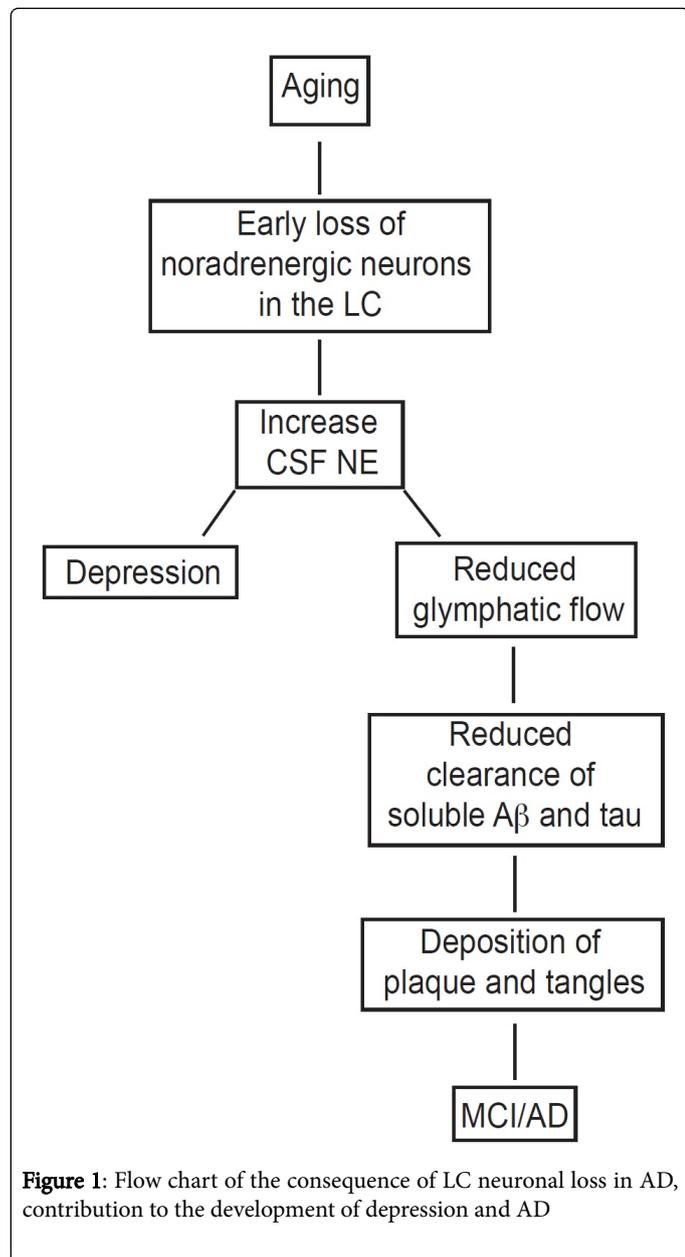
AD, when no symptoms of cognitive impairment are observed. If the noradrenergic nervous system is affected early in the progression of AD, it is logical to examine alteration in noradrenergic function in the elderly as a potential biomarker for AD.

Figure 1: Flow chart of the consequence of LC neuronal loss in AD, contribution to the development of depression and AD

Depression as a Marker of Altered Noradrenergic Function

The majority of AD patients exhibit neuropsychiatric symptoms (NPS), with depression being the most common NPS [17]. Interestingly, depression is mainly observed early in the progression of AD, when patients are demonstrating minor cognitive impairment or even before the appearance of any cognitive impairment [18-20]. The presence of depression in the elderly, but not depression earlier in life, has been hypothesized to be a risk factor for AD [21-31]. The presence of depression in the elderly cans double the incidence of AD [26] with aging. Depressive symptoms in the elderly are not explained by a

history of vascular risk factors [28]; and depression does not explain cognitive decline, or is associated with the cognitive decline [25].

Elevated LC Activity and CSF NE with Aging

Depression in late-life could reflect an altered noradrenergic system. The mechanism(s) underlying depression is unclear, although it is well established that the central noradrenergic nervous system is one of the neurotransmitter systems involved in mediating depression, in addition to serotoninergic and dopaminergic systems [32]. Initial belief was that depression was due to reduced noradrenergic function, but more recently the hypothesis of an increase in LC activity in depression has been postulated. This hypothesis has been supported mainly by studies that indirectly suggest an increase in LC activity in depression [33-39]. The most supportive data implicating increased LC activity in depression is the decrease in LC activity observed with the administration of antidepressant drugs and electroconvulsive therapy [40,41]. Also, several clinical studies have measured increased NE and its metabolite in the CSF of depressed patients [42-45], a change that reflects an increase in LC activity. Recently several laboratories have reported an enhanced central noradrenergic system in the elderly compared to younger adults, determined by an increase in CSF NE levels [46-48]. However, it is unclear if any of these elderly patients with an enhanced noradrenergic system also exhibited any degree of depression. Further work is necessary to establish a link between the enhanced noradrenergic activities in the elderly to depression.

The dysfunction of the central noradrenergic system with aging could be attributed to the gradual loss of LC noradrenergic neurons that may also occur in the early stages of AD. Findings from Braak and others [15-19], as discussed above, indicate the LC exhibits early neuropathological markers associated with early-stages of AD, however, it is unclear when LC neurons begin to be reduced in response to these neuropathological markers. My laboratory has been investigating the effect of LC neuronal loss specifically on depression in a rodent model. In mice, LC noradrenergic neuron numbers are reduced by the direct administration of the noradrenergic neurotoxin 6-hydroxydopamine (6-OHDA) into the LC by stereotaxic surgery. LC administration of 6-OHDA results in a dose-sensitive loss in noradrenergic neurons, such that the larger the dose, the greater the degree of LC neuronal loss [49]. However, exhibition of depressive-like behavior in mice following LC neuronal loss was observed only when LC loss was minimal (approximately 25-40%). As the degree of LC neuronal loss increases further, the animals do not display depressive-like behavior. Importantly, the surviving LC neurons in animals treated with 6-OHDA that resulted in a minimal loss of LC noradrenergic neurons demonstrate increased activity (increased firing frequency, more irregular firing pattern, and a higher percentage of cells firing in burst) [49]. This pattern of increased LC activity is observed in the Wistar Kyoto rat [50], which is proposed to be an animal model of depression [51,52]. An increase in LC noradrenergic neuronal activity suggest an increase in norepinephrine (NE) release, though further research needs to verify increased NE release in the CNS with a minimal loss of LC neurons. The clinical implication of these results is that depression observed in the elderly population may be attributed to a minimal or modest loss of LC neurons.

Central Noradrenergic System and the Glymphatic System

A series of recent studies have described a brain "glymphatic" system analogous to the peripheral lymphatic system [53,54]. This glymphatic system involves the interaction of CNS interstitial fluid and CSF system that are essential to the removal of toxic materials and soluble proteins from the CNS [53,54]. The glymphatic system is "turned on" during normal sleep and substantially decreases during the awake state [55]. The neurotransmitter NE is a key regulator of the switch between sleep and wakefulness, with low CNS noradrenergic activity facilitating normal sleep and high CNS noradrenergic activity driving aroused wakefulness. The increase in CSF NE observed in the elderly [46-48] would hypothetically result in reduced glymphatic system activity, hence reduced removal of Aβ and phosphorylated tau, which could enhance the progression toward AD [56]. The noradrenergic receptor that appears to be modulating the glymphatic system is the alpha 1-adrenoreceptor (α1-AR). Treatment of awake mice with the α1-AR antagonist prazosin increases glymphatic flow almost to levels achieved during normal sleep [55,57,58]. Interestingly, in postmortem tissue from AD patients the α1-AR is significantly elevated in the prefrontal cortex and hippocampus [59,60]; however, it is unclear when the increase in α1-AR occurs with the progression of AD. An elevation in the α1-AR in the elderly would reduce the glymphatic system and the clearance of Aβ and phosphorylated tau, potentially accelerating the deposition of plaques and tangles associated with AD. In the 6-OHDA animal model of LC neuronal loss, 3 days after the administration of 6-OHDA into the LC there is a significant increase in α1-AR binding sites in specific regions of the mouse brain [61], suggesting that there is increased α1-AR activity in the CNS with a loss of LC noradrenergic neurons.

Summary

The incidence of AD is increasing every year and by the year 2030 there will be 7.7 million people with AD and 11-16 million by 2050 [5]. To reduce the prevalence of AD in the future, new interventions are required to target the early stages of AD to prevent or slow the progression of the disorder. Depression in the elderly has been proposed as a risk factor for AD for several years [7-11], but many clinicians felt the expression of depression in the elderly was not directly linked to AD. As outlined here, expression of depression in the elderly population may be linked to a malfunctioning noradrenergic system due to the loss of noradrenergic neurons in the LC [46,47]. The increase in synaptic NE due to malfunctioning noradrenergic neurons may due to (a) increased activity of the LC neurons associated with neuronal loss [49] and/or (b) to an increase in tyrosine hydroxylase, the rate-limiting enzyme in the synthesis of NE that is observed in the surviving LC neurons of AD patients [59]. These studies support the hypothesis that an enhanced noradrenergic system is present early in the progression of AD and associated with LC neuronal loss. With the recent description of the glymphatic system, there is now a potentially direct link between the enhanced noradrenergic nervous system and the diminished clearance of Aβ and phosphorylated tau from the CNS. Accumulation of plaques (Aβ) and tangles (phosphorylated tau) are believed to be the cause of AD and are considered the two major neuropathological markers of AD. The increase of noradrenergic activity that is observed in the elderly, which can precipitate depression, can also reduce the glymphatic system. Therefore, the presence of depression in the elderly, associated with a malfunctioning noradrenergic system can serve as a marker that the malfunctioning noradrenergic system could also be affecting the clearance of Aβ and tau which can result in the development of AD.

Acknowledgement

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