Norepinephrine in Neurodegeneration: A Coerulean Target

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Alzheimer’s (AD) and Parkinson’s (PD) diseases are the two most common neurodegenerative disorders in older adults. Currently over 6 million Americans have been diagnosed with AD or PD, and this incidence is expected to increase dramatically in the near future [1,2]. Many recent advances in medicine have increased lifespan, and consequently an aging population has contributed to the burgeoning load of persons suffering from AD and PD. Both disorders are in the top 15 leading causes of death in the United States [3], and have no effective cures nor treatments that alter their progression. Since clinical diagnosis often occurs many years after the onset of neurodegeneration, early detection of neuropathological features and potentially overlooked prodromal symptoms may benefit future treatment strategies.

AD and PD patients both exhibit pathology and loss of locus coeruleus (LC) norepinephrine (NE) neurons prior to current clinical diagnostic criteria [4,5]. Novel assays or biomarkers could be used as early identifiers and directives for early treatments in AD or PD. This will be important for applying treatments that could reduce symptoms, increase productive lifespan, and alter disease progression. Below we briefly highlight evidence for the brain nucleus LC as a candidate early biomarker for these neurodegenerative disorders. We also point to certain functions of the LC-NE system primarily in the cognitive domain, as early intervention targets for both AD and PD treatments.

LC is the sole source of NE throughout cerebral cortex. These neurons project to parietal, temporal and frontal lobes [6,7], all of which are areas prominently involved in cognitive functions and susceptible to pathology in neurodegenerative disorders. Within the CNS, there is a caudorostral progression of degeneration in both AD and PD; pathology and loss of LC-NE neurons occurs very early (e.g., preceding loss of dopamine neurons in PD) [5,8,9]. Patients with AD and PD show depleted cortical NE [10,11]. Compensatory responses to LC loss by residual NE neurons or alterations in NE receptor expression in target regions may also disrupt network functions modulated by NE and affect behavior. NE has well known neuromodulatory effects in cortical targets, loss of which may disrupt network functions in relatively intact circuits and increase susceptibility of target neural populations to subsequent insult.

LC-NE neurons innervate both substantia nigra dopamine (DA) neurons and nucleus basalis (nbM) cholinergic (Ach) populations, which are critically susceptible to neurodegeneration in PD and AD, respectively [12]. The loss of excitatory NE input to nbM Ach and ventral tegmental area DA neurons by LC-NE projections may contribute to decreased cortical Ach and DA levels in these disorders [11,13-15]. In animal models of PD, loss of NE-LC innervation increases toxic injury and substantia nigra DA neuron cell death [16]. In addition, NE loss may exacerbate effects of DA loss, e.g., LC-NE lesions increase motor dysfunction and dyskinesias in models of PD [17]. Finally, in animal models of AD, LC loss exacerbates amyloid load, cholinergic cell loss, and memory impairment, whereas supplementing NE levels modulates neuroinflammatory processes to reduce amyloid load, presumably by altering expression of pro-inflammatory cytokines regulated by adrenergic receptors on microglial cells [18-20]. In humans LC-NE pathology is posited to begin many years, if not decades, before clinical diagnosis. LC degeneration in AD and PD is present in prodromal phases and during early symptoms [5,21], making identification of LC loss an attractive potential early biomarker for diagnosis, monitoring and interventional strategies. LC-NE degeneration may contribute to many features common to these disorders including mood, sleep and cognitive dysfunction seen early in AD and PD [4,22,23].

We propose LC-NE loss in AD and PD may significantly contribute to cognitive deficits that characterize these disorders, as LC-NE is a critical ascending modulatory system that regulates prefrontal executive function. The cortical NE (from LC-NE pathway) is a core element in regulation of behavioral flexibility and executive functions [7,24-26]. Cortical executive dysfunction is a symptom often present in prodromal stages of both AD and PD, leading us to propose that such executive dysfunctions in early stages of these diseases are due, at least in part, to LC-NE degeneration that occurs early in these disorders. The predicted role of LC in cognitive sequelae of AD and PD is grounded in a comprehensive theory of LC function developed from basic research findings [27]. Work from our lab and others have identified two modes of LC-NE firing (phasic and tonic) that differentially regulate behaviors in cognitive tasks [27-31]. Specifically, a host of basic neuroscience findings indicate a role for LC-NE neurons in cognitive flexibility. Several studies find that depleted NE in PFC results in executive dysfunction, common to mild cognitive impairment, early AD and early PD [32]. Preclinically, such impairment can be resolved by manipulations that increase NE transmission, suggesting a possible pharmacological target [33-35]. Therefore we predict that loss of LC-NE neurons would cause deficits in cognitive flexibility, as is observed in PD [23,36]. Of course, other executive dysfunction may also be caused or exacerbated by LC-NE loss. Importantly, cognitive deficits in these disorders have significant impact on quality of life, life expectancy and caregiver stress [37], but are not treated by current PD medications, leaving cognitive impairment an unmet need for this severe and common disorder. Integrating studies on LC-NE cognitive function with pathology of model systems may identify novel insights for early diagnosis and early interventions to improve current therapeutic strategies. Together, these links for AD and PD with LC neurodegeneration indicate that early interventional strategies targeting LC-NE transmission may alter disease progression in addition to direct benefits on NE mediated...
symptoms. Indeed, NE has the potential to limit declines through its neuroprotective effects [16,38].

Using neuroimaging to identify the structural integrity of LC would significantly advance the study and treatment of both AD and PD. We therefore propose that LC-NE degeneration could be used as a biomarker for suspected AD or PD, allowing early, targeted NE-based interventions where appropriate. The LC has been observed in humans using an MRI protocol that has been shown to be sensitive to neuromelanin because the sequence reveals signal hyper-intensities in the LC and the substantia nigra [39], two regions where neuromelanin accumulates. The same sequence was used to demonstrate reduced ability to visualize the LC in PD patients [39]. Neuromelanin-containing LC neurons are fewer in number, have smaller neuromelanin granules, and are less densely packed in PD post-mortem brains compared to controls [40]. These results indicate that the LC-NE signal may be driven by the number of LC cells, possibly by the amount of neuromelanin, and could be used as a biomarker for AD and PD. The importance of an LC biomarker for tracking cognitive changes is underscored by the linkage of LC neuron loss to disease progression [41-46]. For example, PD patients with significant executive function impairment exhibited reduced post-mortem LC neuron counts compared to PD patients without significant cognitive impairment [47]. These findings strongly indicate that an LC biomarker can characterize the risk for cognitive decline. As LC neurons degenerate early, an LC biomarker could track the severity of LC decline and/or treatment effects.

NE modulation is a viable therapeutic target due to the proven safety and efficacy of NE modulators in other disorders, early involvement of LC in the neuropathology, opportunity for efficacy in other concurrent symptoms like mood and inflammation as well as potential impact on disease progression [48-50]. In terms of effectiveness of NE enhancers for cognitive dysfunction, very few trials have been undertaken in a small number of patients, with positive results that suggest more comprehensive testing in the future is warranted. For PD, the specific NE reuptake inhibitor atomoxetine recently led to improvements in clinical global impression scales of cognition in two separate studies [51,52]. Cognitive flexibility was not examined in these studies, but the findings are consistent with preclinical studies where atomoxetine improved cognitive flexibility deficits produced by specific LC-NE lesions in PFC [33]. In AD, increasing NE transmission increases electrophysiological correlates of attentional processing [54], which may provide benefits for cognitive dysfunctions. Evidence from 1) in vivo lesions in the LC-NE system and 2) preclinical studies highlights a role for LC-NE neuromodulation in early cognitive dysfunction, which points towards the use of NE modulation as a means for enhancing cognitive processing in both AD and PD patients.

Evidence is increasing for an important role of LC in AD and PD neurodegeneration [50,55,56]. We, and others, have argued that LC has a number of functions besides its roles in cognitive processing, including regulation of sleep, mood and neuroinflammation, all of which may benefit from NE-based therapies [19,57-59]. NE modulation of sleep, mood and neuroinflammation, all of which may benefit from NE-based therapies, particularly in early stages of neurodegenerative disorders, may enhance the opportunity for intervention strategies that could not only manage cognitive symptoms but may have disease-modifying effects on subsequent pathology.

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References