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REVIEW

Targeting norepinephrine in mild cognitive impairment and Alzheimer's disease

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Abstract

The Alzheimer's disease (AD) epidemic is a looming crisis, with an urgent need for new therapies to delay or prevent symptom onset and progression. There is growing awareness that clinical trials must target stage-appropriate pathophysiological mechanisms to effectively develop disease-modifying treatments. Advances in AD biomarker research have demonstrated changes in amyloid-beta (Aβ), brain metabolism and other pathophysiologies prior to the onset of memory loss, with some markers possibly changing one or two decades earlier. These findings suggest that amyloid-based therapies would optimally be targeted at the earliest clinically detectable stage (such as mild cognitive impairment (MCI)) or before. Postmortem data indicate that tau lesions in the locus coeruleus (LC), the primary source of subcortical norepinephrine (NE), may be the first identifiable pathology of AD, and recent data from basic research in animal models of AD indicate that loss of NE incites a neurotoxic proinflammatory condition, reduces Aβ clearance and negatively impacts cognition – recapitulating key aspects of AD. In addition, evidence linking NE deficiency to neuroinflammation in AD also exists. By promoting proinflammatory responses, suppressing anti-inflammatory responses and impairing Aβ degradation and clearance, LC degeneration and NE loss can be considered a triple threat to AD pathogenesis. Remarkably, restoration of NE reverses these effects and slows neurodegeneration in animal models, raising the possibility that treatments which increase NE transmission may have the potential to delay or reverse AD-related pathology. This review describes the evidence supporting a key role for noradrenergic-based therapies to slow or prevent progressive neurodegeneration in AD. Specifically, since MCI coincides with the onset of clinical symptoms and brain atrophy, and LC pathology is already present at this early stage of AD pathogenesis, MCI may offer a critical window of time to initiate novel noradrenergic-based therapies aimed at the secondary wave of events that lead to progressive neurodegeneration. Because of the widespread clinical use of drugs with a NE-based mechanism of action, there are immediate opportunities to repurpose existing medications. For example, NE transport inhibitors and NE-precursor therapies that are used for treatment of neurologic and psychiatric disorders have shown promise in animal models of AD, and are now prime candidates for early-phase clinical trials in humans.

The locus coeruleus and norephinephrine

The locus coeruleus (LC) is the major subcortical site for the synthesis of norepinephrine (NE) [1]. The LC preferentially projects to the thalamus, hippocampus, the frontal and entorhinal cortices and, to a minor extent, most other brain regions. Due to its extensive innervation of multiple forebrain regions and the widespread distribution of noradrenergic receptors, the noradrenergic system is involved in many behavioral and physiologic processes. The role of the LC noradrenergic system in cognitive processes, arousal and wakefulness is covered in several extensive reviews [2-6]. In addition to declining with normal aging, altered NE transmission has been reported in major brain disorders in psychiatry (depression, attention deficit disorder, Tourette's, psychosis, post-traumatic stress disorder), neurology (epilepsy, Parkinson's, Alzheimer's disease (AD)) and sleep [7,8].

Locus coeruleus loss in Alzheimer's disease

Extensive LC degeneration is nearly universal in AD [9-13] and is among the earliest pathologies [11,14,15], with LC neuropathology detectable as early as 10 years before neurocognitive signs [16-18]. Alterations in NE have long been known to be linked to cognitive, mood

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and neuropsychiatric symptoms [6,19-24]. A number of studies have also demonstrated significant correlations between LC cell death (or decreased cortical NE levels) and severity and duration of dementia in AD [25,26]. Neurofibrillary changes in the LC occur in prodromal stages of AD (that is, mild cognitive impairment (MCI)), and even in some young, cognitively normal individuals [16-18], preceding amyloid-beta (Aβ) deposition. However, whether the LC represents the initial site of pathology or reflects a nonspecific response to brain insults is still under debate [27].

An additional complication is that compensatory changes in the degenerating noradrenergic system appear to occur in AD; despite decreases in tissue forebrain NE in AD, surviving LC neurons show increased abundance of mRNA for tyrosine hydroxylase, the rate-limiting NE biosynthetic enzyme, sprouting of dendrites and axonal projections [28], and increased cerebrospinal fluid levels of NE are observed in AD patients [29-32]. The knowledge gaps present in these areas highlight the need for additional investigations into the mechanism by which LC loss contributes to AD.

Locus coeruleus and norepinephrine in AD pathogenesis: preclinical studies

The strong correlation between LC degeneration, NE depletion and severity of AD in patients has prompted multiple studies of the contribution of LC dysfunction to AD progression through the use of animal models. The primary tool for studying the effects of LC degeneration and NE depletion *in vivo* is the neurotoxin *N*-(2-chloroethyl)-*N*-ethyl-2-bromobenzylamine (dsp-4), which reliably lesions the LC while leaving other aminergic systems intact. Transgenic mice that overexpress human amyloid precursor protein (APP) with familial Alzheimer mutations recapitulate many aspects of AD neuropathology and cognitive deficits, and have been used extensively to study AD. However, most of these mouse lines do not show the frank LC degeneration that occurs in human AD. To determine the functional consequences of LC loss in AD, therefore, several laboratories have used dsp-4 to lesion LC neurons in these transgenic mice.

In general, dsp-4 lesions of the LC exacerbate AD-like neuropathology and cognitive deficits, suggesting that LC degeneration plays a causal role in AD progression. For example, the first study to use this approach showed that dsp-4 lesions of the LC in APP23 mice resulted in increased Aβ deposition, neurodegeneration, neuronal loss, cognitive deficits and microglial activation, and reduced cerebral glucose metabolism [33]. Importantly, the effects of dsp-4 were confined to forebrain areas that received projections directly from the LC, while brain regions that receive noradrenergic innervation from non-LC cell groups were unaffected. APP/presenilin-1 (PS1) mice treated with dsp-4 displayed severe loss of norepinephrine transporter (NET) in the LC and cortex, along with a loss of noradrenergic innervation [34]. Lesioning of the LC induced accelerated amyloid deposition and neuron death with age, and more severe deficits in spatial memory compared with vehicle-treated animals [34]. The mechanism underlying the increased amyloid deposition appears to be related to reduced clearance, as occurs in sporadic AD [35], due to the inhibition of $A\beta_{1\text{-}42}$ (Aβ42) phagocytosis by microglia rather than an influence on APP production or processing [36]. NE has several strong influences on microglial function, and in general suppresses the production of proinflammatory cytokines and promotes the production of anti-inflammatory molecules. Thus, it is not surprising that dsp-4 treatment also exacerbates the neuroinflammatory response in multiple brain regions of APP/PS1 mice [36,37]. Interestingly, a recent study reported that in addition to increased Aβ deposition, dsp-4 lesions of the LC in APP/PS1 mice also resulted in olfactory deficits, another common and early pathology seen in AD patients [38].

Among the questions raised by these findings, an important issue with therapeutic implications is whether the effects of LC lesions in AD mouse models are due solely to the loss of NE itself, the loss of co-transmitters in LC neurons, collateral damage from the neurodegenerative process itself, or some combination thereof. To help resolve these issues, we recently crossed APP/PS1 mice with dopamine β-hydroxylase knockout ($DBH^{-/-}$) mice that lack the ability to synthesize NE but have intact LC neurons [39]. While APP/PS1 and $DBH^{-/-}$ single-mutant mice each displayed moderate hippocampal long-term potentiation (LTP) and spatial memory impairments, the two mutations had an additive effect, resulting in double mutants with severely compromised LTP and maze performance. Somewhat surprisingly, the genetic loss of NE had no apparent effect on AD-like neuropathology in the double mutant. Nondegenerative loss of NE produced by Ear2 knockout, which prevents the development of most LC neurons, also exacerbated LTP and memory deficits but had no effect on plaque deposition in APP/PS1 mice. However, dsp-4 worsened neuropathology in the APP/PS1, $DBH^{-/-}$ double mutant. Combined, these results indicate that the LC neuronal loss contributes to distinct aspects of AD; loss of NE itself impairs synaptic plasticity and cognitive performance, while the physical process of LC neuron degeneration exacerbates AD-like neuropathology.

In summary, combining expression of familial AD mutations with LC lesions or NE deficiency appears to more closely recapitulate the neuropathological and cognitive symptoms of AD compared with mutant APP expression alone, and implicates LC loss as a crucial component of AD.

Neuroinflammation is a key mechanism linking loss of locus coeruleus neurons and norepinephrine innervation with AD

Recent studies provide insights into the mechanisms by which LC dysfunction and NE loss facilitate AD pathogenesis. There is growing evidence suggesting that the inflammatory response induced and/or augmented by LC degeneration is a key mechanism contributing to the initiation and progression of AD pathogenesis. Microglia, astrocytes and endothelia are among the major targets of NE, and, under normal conditions, these cells control the delicate balance of the inflammatory response. In general, NE is an anti-inflammatory molecule; acting via β-adrenergic receptors, NE suppresses the expression of multiple proinflammatory genes, including major histocompatibility complex class II, TNFα, inducible nitric oxide synthase and IL-1β, while simultaneously promoting the expression of anti-inflammatory molecules such as NF-κB, inhibitory IκB, heat shock protein-70 and chemokine monocyte chemotactic protein-1 in astrocytes and microglia [7,40]. That NE deficiency results in undesirable proinflammatory effects is therefore not surprising.

One of the first pieces of evidence connecting LC degeneration and neuroinflammation in an AD model was reported by Heneka and colleagues [41]. Injections of Aβ42 in the cortex of rats induced severe cortical inflammation and the expression of several pro-inflammatory genes – including inducible nitric oxide synthase/nitric oxide synthase-2, IL-1β and IL-6 – within hours. This neuroinflammation was profoundly exacerbated when LC neurons were lesioned with dsp-4 prior to the cortical injection of Aβ42. In addition, dsp-4 pretreatment increased inducible nitric oxide synthase expression solely in neurons rather than in microglial cells, more accurately replicating the expression pattern seen in AD patients [41]. Augmented forebrain microglial and astroglial activation and proinflammatory gene expression that coincide with the development of other AD-like neuropathologies such as Aβ plaques were also obtained using dsp-4 and the APPV171 and APP/PS1 transgenic mouse models of AD [36]. LC lesions profoundly increased the Aβ plaque load, brain inflammation and spatial memory deficits concurrently in APP23 transgenic mice. In addition, dsp-4 treatment was associated with a switch in microglial cytokine expression from a neuroprotective anti-inflammatory profile to a proinflammatory and neurotoxic profile [33,36,42].

Because NE promotes microglia-mediated degradation and phagocytosis of Aβ in cell culture [43], another deleterious effect of LC degeneration on the neuroinflammatory response is the dysfunction of cellular machinery involved in Aβ metabolism and clearance. For example, in V717F APP transgenic mice, dsp-4 lesions of the LC produce a fivefold increase in Aβ plaques that is accompanied by microglial and astroglia activation and decreased expression of the Aβ plaque-degrading enzyme, metallopeptidase neprilysin [42]. Another study showed that NE suppressed Aβ-induced cytokine and chemokine production and increased microglial migration and phagocytosis in cell culture, while dsp-4 lesions prevented the recruitment of microglia to Aβ plaques and impaired Aβ phagocytosis in APP/PS1 transgenic mice [36].

A few epidemiological studies have investigated interactions between NE and neuroinflammation in AD. A small pilot study in a Spanish population found that a SNP associated with low DBH activity alone had no effect, but significantly increased AD risk in combination with SNPs in the IL-1A or IL-6 genes [44]. This result was partially confirmed and extended in an independent study with a larger sample population and wider patient demographics. This follow-up study reported a significant association between the low-activity variant of DBH alone and AD risk that was mostly attributable to males over the age of 75, and also replicated the interaction between DBH and IL-1A polymorphisms [45]. Interestingly, SNPs that are thought to increase adrenergic signaling have also been linked to a risk for developing AD. Individuals homozygous for the C allele of ADRB1 (the β1-adrenergic receptor) and the the T allele of GNB3 (the G protein β3 subunit gene), which are associated with increased cAMP levels and mitogen-activated protein kinase activation, have an increased risk for AD [46]. A Chinese case–control study found that a β_2-adrenergic receptor polymorphism which enhances responsiveness is also associated with the risk of sporadic late-onset AD [47]. These studies highlight the complicated nature of noradrenergic signaling in AD; activation of some receptor subtypes may suppress neuroinflammation and neuropathology, while other receptors may exacerbate aspects of the disease.

Recent biomarker studies in living subjects have also confirmed a proinflammatory state in AD [48-51]. Of note, increased proinflammatory and decreased anti-inflammatory markers account for the majority of changes detectable in a large panel of cerebrospinal fluid analytes in MCI and AD [49,50]. By promoting pro-inflammatory responses, suppressing anti-inflammatory responses and impairing Aβ degradation and clearance, LC degeneration and NE loss can therefore be considered a triple threat to AD pathogenesis.

Treatments that increase norepinephrine in AD animal models ameliorate AD-like pathology and cognitive decline

In vitro and animal studies have provided the most compelling evidence that increasing NE could have

beneficial effects on both AD neuropathology and cognitive symptoms. *In vitro* challenge of human acute monocytic leukemia cells (THP-1) with Aβ42 induced cytotoxicity and provoked a neuroinflammatory response that was dose-dependently attenuated by NE [52]. Treatment with cAMP or forskolin, a protein kinase A activator, had similar effects, suggesting that NE's protective effects were regulated, at least in part, via stimulation of β-adrenergic receptors and the corresponding activation of the cAMP/protein kinase A signaling pathway [52]. Another *in vitro* study in hNT neuronal and primary hippocampal cultures revealed a neuroprotective effect of NE against both Aβ42- and $A\beta_{25-35}$-induced increases in oxidative stress, mitochondrial dysfunction and cell death [53]. The neuroprotective effects were mediated by activation of β-adrenoceptor/cAMP signaling and also required the brain-derived neurotrophic factor/tropomyosin-related kinase B pathway, although some β-receptor-independent effects of NE persisted [53].

The earliest *in vivo* animal studies using noradrenergic pharmacotherapies focused on the α_2-adrenergic autoreceptor. The α_2-antagonists that enhance NE release, such as piperoxane, reversed memory deficits in aged mice as assessed by performance in a step-down inhibitory avoidance response task [54]. Another α_2-antagonist, fluparoxan, prevented age-related decline in the spontaneous alternation task (a test of spatial working memory) in APP/PS1 mice, although it had no effect in other memory tasks such as object recognition or the Morris water maze, and occurred in the absence of obvious concomitant change in pathology [55]. Drugs targeting other NE receptors and transporters have also been tested in animal models of AD. Desipramine, a tricyclic antidepressant that inhibits endogenous NE reuptake, induced the production of the anti-inflammatory cytokine monocyte chemotactic protein-1 [56]. CL316243, a selective β_3-adrenergic receptor agonist, rescued performance in a learning paradigm by chicks given intracranial injections of Aβ42 [57]. Recently, β-adrenoceptor activation of cAMP/protein kinase A signaling was found to reverse the synaptotoxic effects of human Aβ oligomers on LTP and behavior [58].

Compelling evidence in favor of noradrenergic treatments for AD has also been observed using the NE precursor, L-threo-3,4-dihydroxyphenylserine (L-DOPS). For example, L-DOPS restored the balance of the brain inflammatory system, facilitated microglial migration and Aβ phagocytosis, and reversed learning deficits in dsp-4 lesioned APP transgenic mice [36], and also partially rescued spatial memory deficits in the $DBH^{-/-}$, APP/PS1 double-mutant mice [39]. Treatment of 5xFAD mice, which have robust and early development of AD-like neuropathology, with a combination of L-DOPS and the NET inhibitor, atomoxetine, elevated brain NE levels, increased expression of Aβ clearance enzymes and brain-derived neurotrophic factor, reduced inflammatory changes and Aβ burden, and improved spatial memory [59].

To generate further proof-of-principle for the efficacy of NET inhibitors in AD, we took advantage of norepinephrine transporter knockout mice (NET KO) that lack the NET completely, and have elevated basal extracellular NE levels, similar to what might be observed with chronic NET inhibitor treatment [60]. We crossed the NET KO mice to APP/PS1 transgenic mice that overexpress mutant human APP and PS1 and develop age-dependent Aβ plaques, and examined AD-like neuropathology by western blot assay at 6 months of age and by immunocytochemistry at 1 year of age. As shown in Figure 1a, APP/PS1 mice that carry wildtype copies of NET (NET WT, APP/PS1) contain heavy plaque load in the hippocampus and cortex, as detected by immunohistochemistry using antiserum 2964 against fibrillar Aβ42 [61]. The Aβ levels were much higher in female NET WT, APP/PS1 mice compared with males (Figure 1b), as reported previously for APP/PS1 and other lines of APP transgenic mice (for example, [62]). Remarkably, plaques were almost completely abolished in littermate APP/PS1 mice that lack the NET (NET KO, APP/PS1). Similar results were obtained with western blots of brain homogenates (Figure 1b).

These results suggest that attenuating NET activity can reduce Aβ levels, perhaps by increasing phagocytosis or another NE-mediated mechanism described in this review. Interestingly, full-length APP and the C-terminal fragment of APP were also reduced. The reasons for this are not clear, but raise the possibility that a change in APP production or turnover contributes to the decrease in Aβ levels. Consistent with this finding, selective lesion of the ascending noradrenergic bundle with 6-hydroxydopamine in rats increased cortical APP [63]. Combined with the results that atomoxetine + L-DOPS reduces AD-like neuropathology and cognitive deficits in 5xFAD mice [59], these data support the use of NET inhibitors in AD patient populations.

While studies using NE pharmacotherapy in AD models show promise for disease treatment, these studies must be interpreted with caution because the effects of noradrenergic drugs are complicated by multiple adrenergic receptor subtypes with different distributions and signaling capabilities. There are a number of studies that suggest noradrenergic stimulation actually increases certain proinflammatory markers, and that some adrenergic receptor blockade can be therapeutic. Pharmacological activation of β-adrenergic receptors (especially β_2-adrenergic) increases mRNA and protein levels for IL-1B and 1L-6 in macrophages, microglia and brain parenchyma [64-66]. Administration of adrenergic

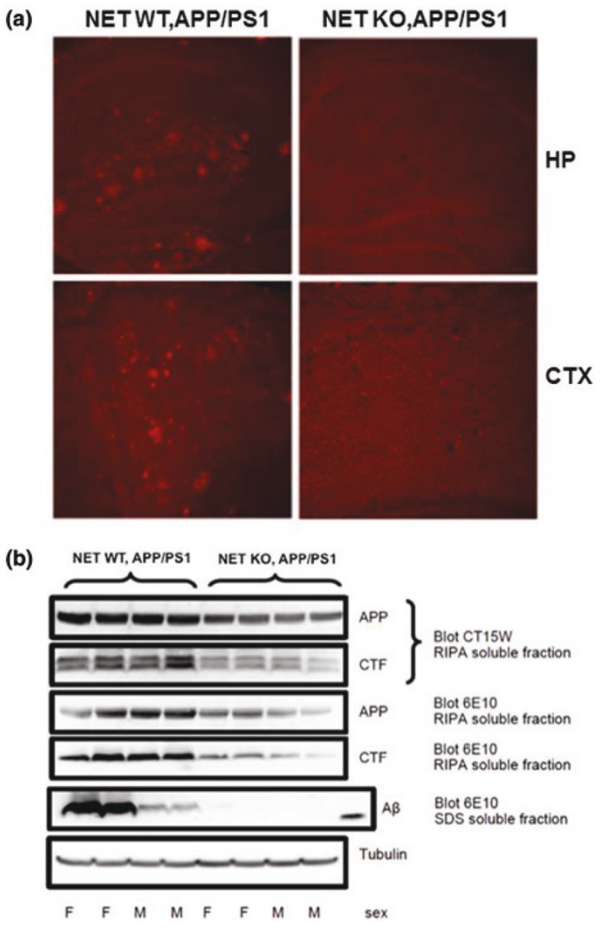

Figure 1. Enhancing norepinephrine may be a promising strategy to treat Alzheimer's disease. (a) Plaque deposition in the hippocampus (HP) and cortex (CTX) of 1-year-old APP/PS1 mice (NET WT,APP/PS1) and norepinephrine transporter knockout APP/PS1 mice (NET KO,APP/PS1) as detected by immunohistochemistry using antiserum 2964 against fibrillar Aβ42. **(b)** Abundance of full-length amyloid precursor protein (APP), the APP C-terminal fragment (CTF), and Aβ in male and female NET WT,APP/PS1 and NET KO,APP/PS1 mice at 6 months of age as detected by western blot using mAb 6E10 against amino acid residues 1 to 16 of Aβ. Tubulin was used as a loading control. Aβ, amyloid-beta; NET WT, norepinephrine transporter wildtype; PS1, presenilin-1.

receptor antagonists *in vivo* can protect against the inflammatory response induced by a foot shock [67], peripheral bacterial challenge [68] or ischemia [69,70]. Nevibolol, a β_1-blocker, can also reduce amyloid production in TG2576 mice that have established amyloid and cognitive impairment, although it does not improve cognition [71]. One potential explanation for the dual beneficial and harmful effects of adrenergic receptor stimulation is that the loss of LC neurons coupled with the compensatory sprouting by surviving cells probably creates a situation where NE transmission is compromised in some brain regions, and overactive in others [6,19-24,28].

Clinical studies of pharmacotherapies that modulate norepinephrine in AD

Most clinical studies using noradrenergic pharmacotherapy to date have been primarily focused on treating the aggression and other behavioral disturbances that occur in many late-stage AD patients. β-adrenergic receptor antagonists (that is, propranolol) are somewhat effective in the treatment of aggression and agitation, which may be caused by NE overstimulation [72,73], while antidepressants inhibiting NE reuptake, such as the tricyclic imipramine, have been used to treat depression, which may be caused by NE deficiency [74]. Tantalizing pieces of evidence continue to support the idea of increasing NE to treat cognitive impairment in AD. For example, clonidine – which suppresses NE release by activating the α_2-adrenergic autoreceptor – impairs short-term recognition memory in patients [75], suggesting that facilitating NE release may be beneficial. The same group determined that clonidine could also enhance spatial working memory in AD patients [76], however, highlighting the complexity of these processes. Several clinical studies examining hypertension suggest that β-blockers may have therapeutic effects on inflammation and dementia. Dementia incidence and annual rate of cognitive decline tend to be lower in older patients that take β-blockers for hypertension [77-79]. The β_1-antagonists nevibolol and metoprolol have been shown to attenuate the release of atherosclerotic inflammatory markers such as soluble intercellular adhesion molecule-1 in humans after 1 year of treatment [80]. Since hypertension itself is a risk factor for AD, however, it is difficult to know whether the benefits of β-blockade are mediated by direct effects on neuroinflammation or are indirect effects mediated by control of hypertension.

Overall, the strong links between LC/NE loss in AD and disease progression in AD animal models combined with human clinical and preclinical data demonstrate the exciting disease-modifying potential of drugs that modulate NE levels. The urgent and essential next step is to translate these discoveries to humans. Although NE pharmacotherapies are widely used in medicine, drugs that regulate NE transmission in the brain could have complicated effects in AD. The integrity of the LC and pharmacological responsiveness in prodromal stages of AD are poorly understood. While preclinical studies suggest potential for NE-enhancing therapies to reduce neuroinflammation and amyloid burden and to ameliorate cognitive impairment, clinical observations in AD patients also suggest the potential to impact noncognitive symptoms of AD including mood, apathy, disinhibition, sleep, agitation and aggression [81,82].

Several NE pharmacotherapies are already used in clinical practice for a variety of neurological and psychiatric disorders, including attention-deficit disorder,

depression and orthostatic hypotension. NET inhibitors such as atomoxetine, a US Food and Drug Administration-approved drug that is a widely prescribed treatment for children and adults with attention-deficit hyperactive disorder, and reboxetine, approved in many countries around the world for depression, have been used safely in older subjects. The NE prodrug L-DOPS crosses the blood–brain barrier and has been used safely in Asia for several decades to treat hypotension. As mentioned above, treatment of 5xFAD transgenic mice (which accumulate amyloid burden at early ages) with a combination of L-DOPS and atomoxetine elevated brain NE levels, increased expression of Aβ clearance enzymes and brain-derived neurotrophic factor, reduced inflammatory changes and Aβ burden, and improved spatial memory [59].

In clinical studies, atomoxetine has also been shown to improve working memory, response inhibition and other executive functions in patients with attention-deficit hyperactivity disorder [83-86]. Several small studies have examined atomoxetine treatment in older patients with neurodegenerative disease to assess safety, tolerability and symptomatic effects. Marsh and colleagues studied 12 patients with Parkinson's disease with doses up to 100 mg daily (mean tolerated dose 89.6 mg), with excellent safety, tolerability and improved executive function [82]. Weintraub and colleagues found that 80 mg once daily was well tolerated by Parkinson's disease subjects as a treatment for depression; only four of 29 patients withdrew because of adverse effects [87]. Although atomoxetine was ineffective for the treatment of depression in the study, atomoxetine was associated with improvement of global cognition. A 6-month phase II trial in mild to moderate AD tested up to 80 mg atomoxetine once daily in 47 subjects [88]. Although atomoxetine was well tolerated (only five subjects withdrew because of adverse effects), there were no significant improvements in cognitive function, global clinical impression or neuropsychiatric symptoms. However, this study was not powered for clinical efficacy and, more importantly, did not investigate the potential anti-inflammatory neuroprotective role of NE pharmacotherapy. Moreover, since patients with mild to moderate AD already have extensive neurodegeneration, most investigators now realize the best chance for neuroprotection will come from earlier intervention.

Logical next steps would therefore be to test NE pharmacotherapies for their potential anti-inflammatory and other neuroprotective mechanisms in phase II trials with individuals with preclinical or early clinical (that is, MCI) stages of AD. For example, it would be important to evaluate the effect of NE-based treatments such as atomoxetine and L-DOPS on biomarkers of AD pathology and inflammation [49,50,89,90]. A potential target would be cerebrospinal fluid inflammatory markers, which have been used successfully as surrogate markers of drug response in multiple sclerosis [91,92] and are among novel biomarkers that distinguish MCI and AD from other neurodegenerative diseases and correlate with both baseline cognitive impairment and subsequent cognitive decline [50].

In sum, there is a growing body of evidence linking LC neurodegeneration and altered NE neurotransmission to the pathogenesis of AD, in addition to the long-established links with cognitive and behavioral symptoms. Preclinical studies demonstrate that restoration of NE function has great potential to slow neurodegeneration by enhancing anti-inflammatory and suppressing proinflammatory responses, facilitating amyloid clearance and via other protective mechanisms. However, the complexities of NE signaling and multiplicity of effects of adrenergic receptor subtypes, together with the limitations of animal studies, underscore the importance of translating these studies to humans. The availability of clinically approved drugs that enhance central noradrenergic function provides a timely opportunity to repurpose their use to determine their potential as a novel disease-modifying therapeutic strategy.

This article is part of a series on *Cognitive enhancers for ageing and Alzheimer's disease*, edited by Howard Fillit. Other articles in this series can be found at http://alzres.com/series/cogenhancers

Abbreviations

Aβ, amyloid-beta; AD, Alzheimer's disease; APP, amyloid precursor protein; DBH, dopamine β-hydroxylase; $DBH^{-/-}$, dopamine β-hydroxylase knockout; dsp-4, *N*-(2-chloroethyl)-*N*-ethyl-2-bromobenzylamine; IL, interleukin; LC, locus coeruleus; L-DOPS, L-threo-3,4-dihydroxyphenylserine; LTP, long-term potentiation; MCI, mild cognitive impairment; NE, norepinephrine; NET, norepinephrine transporter; NET KO, norepinephrine transporter knockout; NET WT, norepinephrine transporter wildtype; NF, nuclear factor; PS1, presenilin-1; SNP, single nucleotide polymorphism; TNF, tumor necrosis factor.

Competing interests

TC, BK, MPK, TH, MTH, DW and AIL declare that they have no competing interests. WTH received one compensated meal from Eli Lilly as part of the Alzheimer's Association International Conference (under $100). WTH has patents pending on cerebrospinal fluid biomarkers for frontotemporal lobar degeneration and plasma biomarkers for AD. Some markers in these panels overlap with cerebrospinal fluid biomarkers to be measured in the atomoxetine trial.

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Author contributions

All authors contributed to the writing and editing of the manuscript. MTH and MPK generated the data presented in Figure 1.

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