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# Adrenergic Drugs Blockers or Enhancers for Cognitive Decline ? What to Choose for Alzheimer's Disease Patients?

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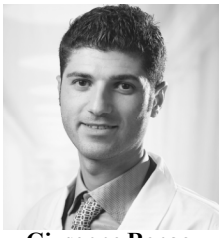
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**Abstract:** The adrenergic system has an important role in normal central nervous system function as well as in brain disease. The locus coeruleus, the main source of norepinephrine in brain, is involved in the regulation of learning and memory, reinforcement of sleep-wake cycle and synaptic plasticity. In Alzheimer's disease, locus coeruleus degeneration is observed early in the course of the disease, years before the onset of clinical cognitive signs, with neurofibrillary detected at the stage of mild cognitive impairment, preceding amyloid deposition. Thus, in the last years, a great interest has grown in evaluating the possibility of central adrenergic system modulation as a therapeutic tool in Alzheimer's disease. However, evidences do not show univocal results, with some studies suggesting that adrenergic stimulation might be beneficial in Alzheimer's Disease and some others favoring adrenergic blockade. In this review, we summarize data from both hypothesis and describe the pathophysiological role of the adrenergic system in neurodegeneration.

**Keywords:** Adrenergic receptors, Alzheimer's disease, beta-blockers, functional recovery, locus coeruleus, neurodegeneration.

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## INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia, affecting more than 20% of individuals over 80 years of age. It is a progressive neurodegenerative disorder clinically characterized by memory loss, cognitive impairment, emotional instability and changes in personality. The currently available therapeutic agents are only able to slow disease progression, with limited benefits. Thus, there is an urgent need to identify new potential drug targets that might have an impact on the natural history of the disease.

Pathologically, AD is characterized by the deposition of extracellular β-amyloid (Aβ) plaques, intracellular neurofibrillary tangles of hyper-phosphorylated tau protein, and neuronal death in the brain. Alongside, oxidative stress, inflammation, reactive gliosis and blood-brain barrier dysfunction contribute to induce accelerated neuronal degeneration and synaptic dysfunction [1]. The most well appreciated neuronal loss is in the entorhinal cortex, hippocampus, and basal forebrain. However, other areas are affected, including locus coeruleus (LC), the major source of noradrenergic projections to the whole brain.

## LC AND NORADRENERGIC SYSTEM IN AD

The LC nucleus, situated in the pons, has been the first neuromodulatory system to be delineated anatomically. It is connected to almost all brain regions (brainstem, cerebellum, diencephalon, paleo- and neocortex) with the exception of the basal ganglia. The LC is the unique source of norepinephrine (NE) in the brain, with a single neuron innervating different regions. The LC is part of the "ascending reticular activating system" and it plays an important role in the regulation of vigilance and sleep-wake cycles. Moreover, many reports have shown that LC is also involved in attention, synaptic plasticity, memory formation and retrieval, decision making and performance facilitation [2] (Table **1**).

In particular, it has been shown that rats with lesions of the noradrenergic ascending projections show cognitive dysfunction. Similarly, in primates the administration of the α2-adrenergic receptor (α2-AR) agonist clonidine impairs cognitive performance by reducing NE release [2]. In human studies using positron emission tomography (PET) imaging, it has been demonstrated that during rest, clonidine decreased the functional strength of connections both from frontal cortex to thalamus and in pathways to and from visual cortex. Conversely, during attentional tasks, functional integration generally increased and a drug-induced increase in the modulatory effects of frontal cortex on projections from LC to parietal cortex was observed. These results suggest that noradrenergic system mediates the functional integration of attentional brain systems and that noradrenergic drugs have differential effects on brain processes depending on subjects' underlying arousal levels [3].

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**Table 1. Summary of the main evidence on LC role in AD.**

| |
|---|
| • The LC is the unique source of NE in brain and it plays an important role in the regulation of vigilance and sleep-wake cycles. LC is also involved in attention, synaptic plasticity, memory formation and retrieval, decision making and performance facilitation |
| • NE has a crucial role in synaptic plasticity in terms of promoting long-term potentiation through the activation of β-AR in the hippocampus |
| • In AD, LC degeneration is observed early in the course of the disease. Some studies have indicated that a significant correlation exists between LC neurodegeneration and AD severity and duration |
| • LC degeneration contributes to AD development and leads to dysregulation of adrenergic receptors and exacerbation of Aβ-induced neuroinflammation |
| • The addition of LC lesion on top of mutant APP expression in mice seems to recapitulate more closely the neuropathological and cognitive features of clinical AD |

In addition to that, it is known that NE has a crucial role in synaptic plasticity in terms of promoting long-term potentiation (LTP) through the activation of β-AR in the hippocampus. Moreover, NE has been implicated in memory consolidation: rats experiments have shown that the administration of a β-AR antagonist two hours after learning resulted in amnesia if tested after 48 hours. However, if the β-AR blocker was administered immediately after learning, no effects were observed, suggesting a delayed role of NE in a late phase of long-term memory consolidation [4]. In addition to that, LC has been shown to take part to memory retrieval. In a functional MRI study in humans, subjects were presented with neutral faces in emotional or neutral contexts. The pupillary size measured during encoding was used as a modulator of brain responses during retrieval. Activation of the LC was observed during retrieval only following an emotional response during the encoding phase. Moreover, a psychophysiological interaction showed that amygdalar responses were more tightly related to those of the LC when remembering faces that had been encoded in an emotional, rather than neutral, context, suggesting that the coordinated action of the LC and the amygdala activates fronto-hippocampal networks that are essential for memory retrieval [5].

Moreover, NE has an important role as a vasoconstrictor, thus it is not surprising that this aspect has also been addressed in cerebral vasculature. Bekar *et al.*, by manipulating cortical NE output using the selective LC neurotoxin N-(2-chloroethyl)-N-ethyl-2bromobenzylamine (dsp-4) and inhibiting LC feedback inhibition with the α2-adrenergic antagonist atipamezole, were able to explore the role of NE in functional blood distribution kinetics. Indeed, these authors showed that the α2-adrenergic antagonist atipamezole results in decreased vessel diameter and that the NE-mediated decrease in vessel diameter improves synchronization both temporally and spatially in the sensory stimulation-mediated hyperemia with concomitant decrease in surrounding blood volume. These effects demonstrate that LC-NE enhances coupling of blood distribution changes with local oxygen demands and improves the ability to quickly redistribute blood to subsequently active brain regions, which is an important role for NE in optimizing neurovascular coupling. As LC neuron loss is prominent in AD, the diminished ability to couple blood volume to oxygen demand may contribute to their pathogenesis [6].

In AD, LC degeneration is observed early in the course of the disease, with LC neuropathology detectable 10 years before clinical cognitive signs. In particular, neurofibrillary tangles can be detected at the stage of MCI, preceding amyloid deposition. Some studies have indicated that a significant correlation exists between LC neurodegeneration and AD severity and duration [7]. However, it is still argued whether LC is one of the initial sites of AD pathology or it just reflects brain insults to other connected regions. Moreover, despite undergoing degeneration, surviving LC neurons show compensatory changes aiming at preserving NE output, such as increased levels of mRNA for tyrosine hydroxylase, the rate-limiting NE biosynthetic enzyme, and dendrites sprouting [7].

Further evidence on the role of LC degeneration in AD comes from studies replicating selective LC insults, through the administration of the neurotoxin dsp-4, which induces LC lesions while leaving other aminergic systems intact. In particular, to determine the consequences of LC degeneration in AD, dsp-4 has been administered to transgenic mice that overexpress human amyloid precursor protein (APP). Using this model, Heneka and collaborators demonstrated that, 6 months after dsp-4 administration, LC projection areas showed a robust elevation of glial inflammation along with augmented amyloid plaque deposits. Moreover, neurodegeneration and neuronal loss significantly increased, together with increased memory deficits; micro-positron emission tomography demonstrated reduced cerebral glucose metabolism, disturbed neuronal integrity, and attenuated acetylcholinesterase activity, globally suggesting that LC degeneration substantially contributes to AD development [8]. Additional data indicate that dsp-4 administration in transgenic mice also induced changes of α1-, α2-, and β1-adreneroceptor binding sites as well as increased micro- and astrogliosis in cortical and hippocampal structures. In addition, the expression of the pro-inflammatory cytokines CCL2 and IL-1β were induced and an elevation of Aβ1-42 levels in aged dsp4-treated APP/presenilin 1 (PS1) mice was observed. These data support the hypothesis that LC degeneration leads to dysregulation of adrenergic receptors and exacerbation of Aβ-induced neuroinflammation [9]. Recently, it has been reported that LC degeneration might also contribute to olfactory deficits that have been described in the early phases of the disease [10].

In another mouse model, APP/PS1 mice were crossed with dopamine β-hydroxylase (DBH) knockout mice, which are unable to synthesize NE but otherwise have normal LC neurons and co-transmitters. The impairments in spatial memory and hippocampal long-term potentiation displayed by young APP/PS1 or DBH (-/-) single mutant mice were augmented in DBH (-/-)/APP/PS1 double mutant mice and were independent of Aβ accumulation [11]. Globally, these results suggest that the LC neuronal loss contributes to distinct aspects of AD; while loss of NE itself impairs synaptic plasticity and cognitive performance, LC neuron degeneration worsens AD neuropathology. Importantly, the addition of LC lesion on top of mutant APP expression in mice seems to recapitulate more closely the neuropathological and cognitive features of clinical AD, giving further credit to the role of LC and noradrenergic brain system in AD [7].

## ADRENERGIC RECEPTORS IN AD

The effects of NE are mediated by the modulation of AR in brain, with both α- and β-AR playing an important role in brain neurotransmission. The ARs belong to the superfamily of the seven membrane-spanning, G-protein-coupled receptors (GPCR) and they are divided into two main groups, α and β, all highly expresses in brain, where they regulate synaptic transmission. In particular, β-ARs are distributed widely in different regions, such as the cerebral cortex, nucleus accumbens and striatum. At lower density, they are also present in amygdala, hippocampus and cerebellum [12].

Despite responding to the same ligands (norepinephrine and epinephrine), ARs differ significantly in the types of cellular responses they mediate. Agonist binding to ARs catalyzes the exchange of GTP for GDP on the Gα-subunit of the cognate G proteins, resulting in the dissociation of the heterotrimer into active Gα- and Gβγ-subunits, which can activate independent signaling pathways. The activated Gα-subunit dissociates from the G protein complex and stimulates (Gs) or inhibits (Gi) adenylyl cyclase, and therefore modulates the intracellular amount of cyclic AMP. The dissociation of the Gβγ subunit facilitates the juxtaposition of AR and G-protein receptor kinases (GRKs), which ultimately mediate the phosphorylation of AR [13]. GRK-mediated phosphorylation results in agonist-dependent desensitization (homologous desensitization) of the ARs and promotes the binding of the cytosolic proteins arrestins. Once bound to the receptor, arrestins interdict further G-protein coupling and target the activated receptor for endocytosis (downregulation) [14-16].

Several lines of evidence suggest that an association exists between AR signaling and AD. Aβ binds to β2-AR, and the extracellular N terminus of β2-AR is critical for the binding. This induces G-protein/cAMP/protein kinase A (PKA) signaling for glutamatergic regulation of synaptic activities [17]. Moreover, in brains of mice expressing human familial mutant presenilin 1 and amyloid precursor protein genes, the levels of β2-AR are drastically reduced. Aβ also induces internalization of β2-AR and prolonged Aβ treatment causes β2-AR degradation; the Aβ-induced β2-AR internalization requires phosphorylation of β2-AR by GRKs and arrestins and results in the impairment of adrenergic and glutamatergic activities [18]. Ligand binding studies in post-mortem human brains have demonstrated that, compared with the controls, total concentrations of β-ARs are significantly reduced in the thalamus of AD brains. In particular, β1-AR concentrations are significantly reduced in the hippocampus, and increased in the nucleus basalis of Meynert and cerebellum, whereas β2-AR concentrations were significantly reduced in the thalamus, nucleus basalis of Meynert, and cerebellum and increased in the hippocampus and putamen of AD brains, suggesting that in patients with AD there are significant changes in AR subtypes in different brain regions [19]. Also, in lymphocytes of patients with AD lower β2-AR levels and lower levels ofβ2-adrenergic-stimulated cAMP have been found, when compared to controls [20]. Similarly, the β-adrenergic-stimulated increase in cAMP was reduced approximately 80% in fibroblasts from Alzheimer's disease compared with age-matched controls [21]. Our group has previously demonstrated that GRK2 mRNA and protein expression in the lymphocytes of AD patients were higher compared to controls. Furthermore, lymphocyte GRK2 levels were significantly correlated to the degree of cognitive decline [22]. Karczewski *et al*. demonstrated the presence of agonistic autoantibodies directed at the α1-ARs and the β2-ARs in the circulation of patients with mild-to-moderate Alzheimer's and vascular dementia [23]. In addition to that, it has been shown that patients with AD have a larger number of β1- and β2-AR in the hippocampus and also an increased number of β2-AR in cerebral microvessels [24, 25].

In addition to that, genetic studies have shown a correlation between AR polymorphisms and AD. Yu *et al.* evaluated the association of two polymorphisms in the β2-AR gene (Gly16Arg and Gln27Glu) with the risk of late onset AD in a Chinese population, demonstrating that both β2-AR gene variants were associated with an increased risk of late onset AD. Interestingly, they also showed a significant correlation with the apolipoprotein E ε4 allele, suggesting that the Gly16 and Gln27 variants are associated with the development of AD, and might also interact with apolipoprotein E ε4 status [26]. Bullido and colleagues analyzed the allelic frequencies of two functional single-nucleotide polymorphisms (SNPs) in the β1-AR (ADRB1) and the G protein β3 subunit (GNB3) genes, in a case-control sample of AD. They found that the GNB3 T allele produces a significant risk for AD in individuals homozygous for the ADRB1 C allele, suggesting that the combined effect of both polymorphisms influences AD susceptibility. Furthermore, the co-expression of these alleles in cellular models increased APP expression [27]. In a Greek population of sporadic AD patients, MCI cases and controls, a significant difference in the frequency of an ADRA2B genetic variation among the three groups was observed. Specifically, this common SNP of the ADRA2B, resulting in a deletion of three glutamic acids on the third intracellular loop of the protein, is more prevalent in controls than in AD and MCI patients, demonstrating a possible protective role of the deletion variant against the disease development [28].

In the light of these evidences, the idea that the adrenergic system might play a significant role in AD pathophysiology is strongly supported. However, whether

adrenergic stimulation or blocking can be beneficial in AD is still debated. In the following section we have summarized data from studies evaluating both hypotheses (Table **2**).

## ADRENERGIC AGONISM IN AD

Recent studies have provided insight into the mechanisms linking LC degeneration, NE loss and AD pathogenesis. In particular, it has been demonstrated that NE is a key regulator of microglial function, promoting the production of anti-inflammatory cytokines and suppressing pro-inflammatory molecules, such as TNF-α and IL-1β [7]. In this vein, LC degeneration with consequent NE deficiency might contribute to the initiation and progression of AD. Thus, studies aiming at increasing NE levels in brain with subsequent increased AR stimulation, have shown favorable effects in AD. However, recent data indicate the neuroprotective effects of NE might be AR-independent. Indeed, it has been shown that NE dose-dependently protects primary cortical and LC neurons from amyloid-β toxicity, through the activation of the tropomyosin-related kinase B (TrkB) and these effects not mimicked by adrenergic agonists [29].

Doze *et al.* have observed an enhancement in cognitive functions both in mice with a constitutively active mutant form of alpha 1a-AR and in mice treated with a selective alpha 1a-AR agonist (cirazoline) compared to controls, with improvement in synaptic plasticity, mood and also longevity [30]. A recent report has shown that the exposure to an enriched environment facilitates signaling in the hippocampus in mice and a key feature of the enriched environment effect was activation of β2 and downstream G-protein/cAMP/protein kinase A signaling. This pathway prevented LTP inhibition by soluble oligomers of Aβ, which was also beneficially activated by prolonged oral administration of the β-AR agonist isoproterenol [31]. Other data indicate that formoterol, a long-acting β2 agonist, is able to improve cognitive function and restore synaptic plasticity in a mouse model of Down syndrome, which shows similar brain amyloid pathology to that observed in AD. Formoterol seems to act through the Fibroblast Growth Factor 2 (FGF2), a trophic factor synthesized by hippocampal cells that can enhance the proliferative activity of glial and neuronal precursor cells [32]. Interestingly, exercise is known to activate the LC and to increase brain norepinephrine release; based on this hypothesis, Segal *et al.* have demonstrated that both in mild cognitive impairment (MCI) and cognitively normal elderly individuals post-learning, acute exercise activates the NE system, significantly enhancing memory in both groups and facilitating memory consolidation. These data suggest that acute exercise, activating the noradrenergic system, may serve as a beneficial therapeutic intervention for cognitive decline [33]. In addition to that, it is known thatβ3-AR are expressed in brain and that β3-AR agonists have been shown to enhance $^{18}$Fluordeoxyglucose uptake in brown adipose tissue *in vivo*. Thus, their role is of potential interest not only in obesity and diabetes, but also in AD. Intracranial

**Table 2. Major findings from studies evaluating the effects of adrenergic stimulation or blockade in AD.**

| Authors | Adrenergic modulator | Major findings | Reference |
|---|---|---|---|
| Doze VA, *et al.* | Cirazoline, agonist | Enhancement in cognitive functions in mice, with improvement in synaptic plasticity, mood and also longevity | [30] |
| Li S, *et al.* | Isoproterenol, agonist | Prevented LTP inhibition by soluble oligomers of Aβ | [31] |
| Dang V, *et al.* | Formoterol, agonist | Improvement in cognitive function and restorement of synaptic plasticity in a mouse model of Down syndrome | [32] |
| Mirbolooki MR, *et al.* | Mirabegron, agonist | This β3-AR selective agonist induced a dose-dependent increase in frontal cortex 18F-FDG uptake in rat brain | [35] |
| Scullion GA, *et al.* | Fluparoxan, antagonist | Chronic treatment with thisα2-AR antagonist can prevent the onset of AD-like pathology and memory deficits in APP/PS1 transgenic mice, reducing amyloid deposition and astrocytosis and preventing spatial working memory deficits | [36] |
| Dobarro M, *et al.* | Propranolol, antagonist | Able to attenuate cognitive impairment and to counteract the increases in hippocampal levels of Aβ in mice. Tau hyperphosphorylation was decreased in the hippocampus of propranolol-treated mice | [40] |
| Wang J, *et al.* | Carvedilol, antagonist | Significant attenuation of brain amyloid content and cognitive deterioration in two AD mouse models, significantly improved neuronal transmission | [42] |
| Wang J, *et al.* | Nebivolol, antagonist | Nebivolol is bioavailable in brain and results in a significant reduction of amyloid pathology in brain | [43] |
| Ni Y, *et al.* | ICI-118,551, antagonist | This β2-AR–selective antagonist ameliorates amyloid plaque pathology in mouse models of AD | [45] |
| Katsouri L, *et al.* | Prazosin, antagonist | This α1-AR antagonist was able to reduce the generation of amyloid β in neuroblastomacells in vitro and to prevent memory deficits in transgenic AD mice | [48] |

administration of β3-AR antagonists induces amnesia in chicks, while memory loss is rescued by β3-AR antagonists [34]. Mirbolooki *et al.* have demonstrated that mirabegron, a β3-adrenoceptor selective agonist that shows some permeability across the blood-brain barrier, exhibited a dose-dependent increase in frontal cortex 18Fluorodeoxyglucose uptake in rat brain [35].

Apart from direct agonist stimulation, other studies have focused on enhancing NE release through the administration of antagonist to the inhibitory α2-adrenoceptor or through the administration of NE transporter inhibitors. Scullion *et al.* have demonstrated that chronic treatment with the α2-adrenoceptor antagonist fluparoxan can prevent the onset of AD-like pathology and memory deficits in APP/PS1 transgenic mice. Fluparoxan was able to reduce amyloid deposition and astrocytosis and prevented spatial working memory deficits in mice [36].

In a clinical placebo-controlled study in patients with major depressive disorder, the role of NE on memory was evaluated by administering clonidine, anα2-AR agonist, which globally suppresses the noradrenergic output. Clonidine impaired memory consolidation in depressed patients and controls, suggesting that reducing noradrenergic activity had a specific effect on memory consolidation in patients with depression and healthy controls [37].

Atomoxetine, an NE transporter inhibitor approved for the treatment of children and adults with attention-deficit hyperactive disorder, has been evaluated in a trial in mild-moderate AD patients. Despite being generally well tolerated, 6-month atomoxetine administration was not able to significantly improve cognitive function. However, the study did not investigate the potential neuroprotective role of NE pharmacotherapy [38].

## ADRENERGIC ANTAGONISM IN AD

While there are evidences in favor of the adrenergic system stimulation in AD, there is probably an equal amount supporting the opposite hypothesis, i.e. adrenergic blockade in AD. Indeed, preclinical and clinical data have demonstrated that blocking AR might have beneficial effects in AD pathogenesis. In rat astrocytes, AR stimulation with NE resulted in amiloyd precursor protein overexpression, which was inhibited by the β-AR antagonist propranolol [39]. The possible efficacy of propranolol on cognition and AD-related markers has also been studied in transgenic mouse models of AD, showing that propranolol, at a lower dose than that used as antihypertensive, was able to attenuate cognitive impairment and to counteract the increases in hippocampal levels of Aβ in mice. Moreover, Tau hyper-phosphorylation was also decreased in the hippocampus of propranolol-treated mice [40]. Recently, propranolol has also been shown to improve performance during cognitive flexibility tasks in rodents [41]. Wang *et al.* have demonstrated that chronic oral administration of carvedilol, a nonselective β-blocker, significantly attenuates brain amyloid content and cognitive deterioration in two AD mouse models, significantly improving neuronal transmission [42]. The same authors also evaluated the effects of nebivolol, a selective β1 adrenergic receptor antagonist with vasodilatory properties, on the modulation of amyloid neuropathology in a mouse model of AD. They found that nebivolol is bioavailable in brain and that three weeks of treatment resulted in a significant reduction of amyloid pathology in brain, although it failed to improve cognitive function [43].

Igbavboa *et al.* found a link between ApoE homeostasis and AR in AD, showing that stimulation of β-AR increased cAMP levels consequently resulting in ApoE abundance; this increase was abolished by β-AR selective antagonists, with the greatest inhibition observed with the β2-AR antagonist. Other data have proven further insight on the important role of β-AR in amyloid formation [44]. Ni and colleagues demonstrated that β2-AR stimulation increases Aβ production *in vitro* and amyloid plaque formation *in vivo* by enhancing γ-secretase activity. They propose that β2-AR associates with presenilin-1 and undergoes agonist-induced endocytosis. Moreover, chronic treatment with β2-AR agonists increased cerebral amyloid plaques formation, while the β2-AR–selective antagonist ICI-118,551 ameliorated amyloid plaque pathology in mouse models of AD, indicating that abnormal β2-AR activation might contribute to Aβ accumulation in AD pathogenesis [45]. In a model of acute restraint stress, the administration of the β2-AR selective agonist clenbuterol increased the stress-induced Aβ production, while the β2-AR antagonist ICI 118,551 reduced it [46]. Moreover, it has been demonstrated that in primary cortical neurons Aβ is able to bind to β2AR and induce receptors internalization and degradation, and pretreatment with β-AR antagonist timolol is able to prevent this effect [18]. Interestingly, it has been recently demonstrated that β2-adrenergic receptor might mediate amyloid-induced tau pathology in AD. Wang *et al.* have shown that in the prefrontal cortex AD transgenic mice with human familial mutant genes of presenilin 1 and amyloid precursor protein, the deletion of β2AR gene greatly decreases the phosphorylation of tau at Ser-214 Ser-262 and Thr-181 as well as the phosphorylation of other associated kinases. In addition to that, the density of dendritic spines and synapses, which is decreased in the prefrontal cortex of PS1/APP mice, is ameliorated by β2AR gene deletion [47].

Not only β-AR, but also α-AR manipulation might play an important role in AD pathophysiology. Katsouri *et al.* tested the effect of various agonists and antagonists for adrenergic receptors on amyloid precursor protein processing. They found that prazosin, an α1 antagonist, was able to reduce the generation of amyloid β in neuroblastoma cells *in vitro*. Moreover, treatment of transgenic AD mice with prazosin prevented memory deficits, induced astrocytic proliferation and increased the release of anti-inflammatory cytokines, although it was not able to influence amyloid plaque load [48].

Further data on the potential role of adrenergic blockers came from clinical studies examining the association of cardiovascular medication use and AD incidence. Data from the Dementia Progression Study of the Cache County Study indicate that the use of statins and β-blockers was associated with a slower annual rate of functional decline in this AD population, while other cardiovascular drugs did not affect the functional decline [49]. Interestingly, the Honolulu-Asia

Aging Study, a prospective, community-based cohort study of Japanese American men, has demonstrated that, among anti-hypertensive medications, β-blockers were the only associated with a lower risk of developing cognitive impairment, even after adjusting for pulse pressure, heart rate, baseline and mid-life systolic blood pressure and mid-life antihypertensive treatment [50]. However, data on prevention of cognitive decline and dementia with blood pressure lowering treatments have shown inconsistent results, and it is not clear yet which category of antihypertensive drugs is the most effective in reducing the risk of cognitive decline [51].

## CONCLUSION

In conclusion, it is well established that a correlation between LC neurodegeneration, impaired adrenergic neurotransmission and AD pathogenesis exists. LC is affected early in the stages of AD by the formation of neurofibrillary tangles and its dysfunction correlates with cognitive decline [7]. However, whether AR stimulation or inhibition might be beneficial in AD therapeutics is still unclear. Evidence support both hypothesis, making the picture not easy to delineate. This might be partly due to the diverse effects elicited by stimulation/blocking of different AR subtypes and also by the cellular subset expressing the specific receptor. As an example, while stimulation of β-AR on glial cells might reduce neuroinflammation, β-AR blockade on brain endothelial cells might prevent microvascular damage. Moreover, some of the effects of NE as a neurotransmitter in brain are AR-independent. This dual favorable and harmful effect of AR modulation in AD might also be related to the fact that LC degeneration is accompanied by compensatory sprouting which might create a microenvironment where NE neurotransmission is decreased in some regions and enhanced in others. Whatever is the prevalent role of AR system in AD, it is certain that further studies are needed, aiming at investigating both hypotheses comprehensively.

## LIST OF ABBREVIATIONS

AD = Alzheimer's Dementia

APOE = Apolipoprotein E

APP = Amyloid Precursor Protein

Aβ = Amyloid Beta

cAMP = Cyclic Adenosine MonoPhosphate

DBH = Dopamine Beta Hydroxylase

GPCR = G-Protein-Coupled Receptors

GRK = G-Protein Kinase Receptors

IL-1β = Interleukin 1 Beta

LC = Locus Coeruleus

LTP = Long Term Potentiation

MCI = Mild Cognitive Impairment

MRI = Magnetic Resonance Imaging

NE = Norepinephrine

PET = Positron Emission Tomography

SNP = Single-Nucleotide Polymorphisms

TNF = Tumor Necrosis Factor

TrkB = Tropomyosin-Related Kinase B

B-AR = Beta-Adrenergic Receptor

## CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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## REFERENCES

[1] Nelson AR, Kolasa K, McMahon LL. Noradrenergic sympathetic sprouting and cholinergic reinnervation maintains non-amyloidogenic processing of AbetaPP. J Alzheimer's Dis 2014; 38(4): 867-79.

[2] Sara SJ. The locus coeruleus and noradrenergic modulation of cognition. Nat Rev Neurosci 2009; 10(3): 211-23.

[3] Coull JT, Buchel C, Friston KJ, Frith CD. Noradrenergically mediated plasticity in a human attentional neuronal network. Neuroimage 1999; 10(6): 705-15.

[4] Tronel S, Feenstra MG, Sara SJ. Noradrenergic action in prefrontal cortex in the late stage of memory consolidation. Learn Memory 2004; 11(4): 453-8.

[5] Sterpenich V, D'Argembeau A, Desseilles M, *et al.* The locus ceruleus is involved in the successful retrieval of emotional memories in humans. J Neurosci 2006; 26(28): 7416-23.

[6] Bekar LK, Wei HS, Nedergaard M. The locus coeruleus-norepinephrine network optimizes coupling of cerebral blood volume with oxygen demand. J Cereb Blood Flow Metab 2012; 32(12): 2135-45.

[7] Chalermpalanupap T, Kinkead B, Hu WT, *et al.* Targeting norepinephrine in mild cognitive impairment and Alzheimer's disease. Alzheimer's Res Ther 2013; 5(2): 21.

[8] Heneka MT, Ramanathan M, Jacobs AH, *et al.* Locus ceruleus degeneration promotes Alzheimer pathogenesis in amyloid precursor protein 23 transgenic mice. J Neurosci 2006; 26(5): 1343-54.

[9] Jardanhazi-Kurutz D, Kummer MP, Terwel D, Vogel K, Thiele A, Heneka MT. Distinct adrenergic system changes and neuroinflammation in response to induced locus ceruleus degeneration in APP/PS1 transgenic mice. Neuroscience 2011; 176: 396-407.

[10] Rey NL, Jardanhazi-Kurutz D, Terwel D, *et al.* Locus coeruleus degeneration exacerbates olfactory deficits in APP/PS1 transgenic mice. Neurobiol Aging 2012; 33(2): 426 e1-11.

[11] Hammerschmidt T, Kummer MP, Terwel D, *et al.* Selective loss of noradrenaline exacerbates early cognitive dysfunction and synaptic deficits in APP/PS1 mice. Biol Psychiatry 2013; 73(5): 454-63.

[12] Femminella GD, Rengo G, Pagano G, *et al.* beta-adrenergic receptors and G protein-coupled receptor kinase-2 in Alzheimer's disease: a new paradigm for prognosis and therapy? J Alzheimer's Dis 2013; 34(2): 341-7.

[13] Rengo G, Lymperopoulos A, Koch WJ. Future g protein-coupled receptor targets for treatment of heart failure. Curr Treatment Options Cardiovasc Med 2009; 11(4): 328-38.

[14] Femminella GD, Rengo G, Komici K, *et al.* Autonomic dysfunction in Alzheimer's disease: tools for assessment and review of the literature. J Alzheimer's Dis 2014; 42(2): 369-77.

[15] Corbi G, Conti V, Russomanno G, *et al.* Adrenergic signaling and oxidative stress: a role for sirtuins? Front Physiol 2013; 4: 324.

[16] Lymperopoulos A, Rengo G, Koch WJ. GRK2 inhibition in heart failure: something old, something new. Curr Pharm Des 2012; 18(2): 186-91.

[17] Wang D, Govindaiah G, Liu R, De Arcangelis V, Cox CL, Xiang YK. Binding of amyloid beta peptide to beta2 adrenergic receptor induces PKA-dependent AMPA receptor hyperactivity. FASEB J 2010; 24(9): 3511-21.

[18] Wang D, Yuen EY, Zhou Y, Yan Z, Xiang YK. Amyloid beta peptide-(1-42) induces internalization and degradation of beta2 adrenergic receptors in prefrontal cortical neurons. J Biol Chem 2011; 286(36): 31852-63.

[19] Shimohama S, Taniguchi T, Fujiwara M, Kameyama M. Changes in beta-adrenergic receptor subtypes in Alzheimer-type dementia. J Neurochem 1987; 48(4): 1215-21.

[20] Oppenheim G, Mintzer J, Halperin Y, Eliakim R, Stessman J, Ebstein RP. Acute desensitization of lymphocyte beta-adrenergic-stimulated adenylate cyclase in old age and Alzheimer's disease. Life Sci 1984; 35(17): 1795-802.

[21] Huang HM, Gibson GE. Altered beta-adrenergic receptor-stimulated cAMP formation in cultured skin fibroblasts from Alzheimer donors. J Biol Chem 1993; 268(20): 14616-21.

[22] Leosco D, Fortunato F, Rengo G, *et al.* Lymphocyte G-protein-coupled receptor kinase-2 is upregulated in patients with Alzheimer's disease. Neurosci Lett 2007; 415(3): 279-82.

[23] Karczewski P, Hempel P, Kunze R, Bimmler M. Agonistic autoantibodies to the alpha(1) -adrenergic receptor and the beta(2) -adrenergic receptor in Alzheimer's and vascular dementia. Scandinav J Immunol 2012; 75(5): 524-30.

[24] Kalaria RN, Andorn AC, Harik SI. Alterations in adrenergic receptors of frontal cortex and cerebral microvessels in Alzheimer's disease and aging. Prog Clin Biol Res 1989; 317: 367-74.

[25] Kalaria RN, Andorn AC, Tabaton M, Whitehouse PJ, Harik SI, Unnerstall JR. Adrenergic receptors in aging and Alzheimer's disease: increased beta 2-receptors in prefrontal cortex and hippocampus. J Neurochem 1989; 53(6): 1772-81.

[26] Yu JT, Tan L, Ou JR, *et al.* Polymorphisms at the beta2-adrenergic receptor gene influence Alzheimer's disease susceptibility. Brain Res 2008; 1210: 216-22.

[27] Bullido MJ, Ramos MC, Ruiz-Gomez A, *et al.* Polymorphism in genes involved in adrenergic signaling associated with Alzheimer's. Neurobiol Aging 2004; 25(7): 853-9.

[28] Koutroumani M, Daniilidou M, Giannakouros T, *et al.* The deletion variant of alpha2b-adrenergic receptor is associated with decreased risk in Alzheimer's disease and mild cognitive impairment. J Neurol Sci 2013; 328(1-2): 19-23.

[29] Liu X, Ye K, Weinshenker D. Norepinephrine Protects against Amyloid-beta Toxicity via TrkB. J Alzheimer's Dis 2015; 44(1): 251-60.

[30] Doze VA, Papay RS, Goldenstein BL, *et al.* Long-term alpha1A-adrenergic receptor stimulation improves synaptic plasticity, cognitive function, mood, and longevity. Mol Pharmacol 2011; 80(4): 747-58.

[31] Li S, Jin M, Zhang D, *et al.* Environmental novelty activates beta2-adrenergic signaling to prevent the impairment of hippocampal LTP by Abeta oligomers. Neuron 2013; 77(5): 929-41.

[32] Dang V, Medina B, Das D, *et al.* Formoterol, a long-acting beta2 adrenergic agonist, improves cognitive function and promotes dendritic complexity in a mouse model of Down syndrome. Biol Psychiatry 2014; 75(3): 179-88.

[33] Segal SK, Cotman CW, Cahill LF. Exercise-induced noradrenergic activation enhances memory consolidation in both normal aging and patients with amnestic mild cognitive impairment. J Alzheimer's Dis 2012; 32(4): 1011-8.

[34] Mirbolooki MR, Constantinescu CC, Pan ML, Mukherjee J. Quantitative assessment of brown adipose tissue metabolic activity and volume using 18F-FDG PET/CT and 3-adrenergic receptor activation. EJNMMI Res 2011; 1(1): 30.

[35] Mirbolooki MR, Schade KN, Constantinescu CC, Pan ML, Mukherjee J. Enhancement of 18F-fluorodeoxyglucose metabolism in rat brain frontal cortex using a beta3 adrenoceptor agonist. Synapse 2015; 69(2): 96-8.

[36] Scullion GA, Kendall DA, Marsden CA, Sunter D, Pardon MC. Chronic treatment with the alpha2-adrenoceptor antagonist fluparoxan prevents age-related deficits in spatial working memory in APPxPS1 transgenic mice without altering beta-amyloid plaque load or astrocytosis. Neuropharmacology 2011; 60(2-3): 223-34.

[37] Kuffel A, Eikelmann S, Terfehr K, *et al.* Noradrenergic blockade and memory in patients with major depression and healthy participants. Psychoneuroendocrinology 2014; 40: 86-90.

[38] Mohs RC, Shiovitz TM, Tariot PN, Porsteinsson AP, Baker KD, Feldman PD. Atomoxetine augmentation of cholinesterase inhibitor therapy in patients with Alzheimer disease: 6-month, randomized, double-blind, placebo-controlled, parallel-trial study. Am J Geriatric Psychiatry 2009; 17(9): 752-9.

[39] Lee RK, Araki W, Wurtman RJ. Stimulation of amyloid precursor protein synthesis by adrenergic receptors coupled to cAMP formation. Proc Natl Acad Sci USA 1997; 94(10): 5422-6.

[40] Dobarro M, Gerenu G, Ramirez MJ. Propranolol reduces cognitive deficits, amyloid and tau pathology in Alzheimer's transgenic mice. Int J Neuropsychopharmacol 2013; 16(10): 2245-57.

[41] Hecht PM, Will MJ, Schachtman TR, Welby LM, Beversdorf DQ. Beta-adrenergic antagonist effects on a novel cognitive flexibility task in rodents. Behav Brain Res 2014; 260: 148-54.

[42] Wang J, Ono K, Dickstein DL, *et al.* Carvedilol as a potential novel agent for the treatment of Alzheimer's disease. Neurobiol Aging 2011; 32(12): 2321e1-12.

[43] Wang J, Wright HM, Vempati P, *et al.* Investigation of nebivolol as a novel therapeutic agent for the treatment of Alzheimer's disease. J Alzheimer's Dis 2013; 33(4): 1147-56.

[44] Igbavboa U, Johnson-Anuna LN, Rossello X, Butterick TA, Sun GY, Wood WG. Amyloid beta-protein1-42 increases cAMP and apolipoprotein E levels which are inhibited by beta1 and beta2-adrenergic receptor antagonists in mouse primary astrocytes. Neuroscience 2006; 142(3): 655-60.

[45] Ni Y, Zhao X, Bao G, *et al.* Activation of beta2-adrenergic receptor stimulates gamma-secretase activity and accelerates amyloid plaque formation. Nat Med 2006; 12(12): 1390-6.

[46] Yu NN, Wang XX, Yu JT, *et al.* Blocking beta2-adrenergic receptor attenuates acute stress-induced amyloid beta peptides production. Brain Res 2010; 1317: 305-10.

[47] Wang D, Fu Q, Zhou Y, *et al.* beta2 adrenergic receptor, protein kinase A (PKA) and c-Jun N-terminal kinase (JNK) signaling pathways mediate tau pathology in Alzheimer disease models. J Biol Chem 2013; 288(15): 10298-307.

[48] Katsouri L, Vizcaychipi MP, McArthur S, *et al.* Prazosin, an alpha(1)-adrenoceptor antagonist, prevents memory deterioration in the APP23 transgenic mouse model of Alzheimer's disease. Neurobiol Aging 2013; 34(4): 1105-15.

[49] Rosenberg PB, Mielke MM, Tschanz J, *et al.* Effects of cardiovascular medications on rate of functional decline in Alzheimer disease. Am J Geriatr Psychiatry 2008; 16(11): 883-92.

[50] Gelber RP, Ross GW, Petrovitch H, Masaki KH, Launer LJ, White LR. Antihypertensive medication use and risk of cognitive impairment: the Honolulu-Asia Aging Study. Neurology 2013; 81(10): 888-95.

[51] Levi Marpillat N, Macquin-Mavier I, Tropeano AI, Bachoud-Levi AC, Maison P. Antihypertensive classes, cognitive decline and incidence of dementia: a network meta-analysis. J Hypertension 2013; 31(6): 1073-82.