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Opinion Article

OPINION ARTICLE

Towards Astroglia-based Noradrenergic Hypothesis of Alzheimer's Disease

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Alzheimer disease (AD) is the most common form of dementia, affecting in 2021 6.2 million people in the USA, and 72% are >75 yr. AD and other dementia related healthcare and associated costs in the USA alone are projected to increase from $355 billion in 2021 to $1.1 trillion by 2050 (https://www.alz.org/alzheimers-dementia/facts-figures). Prevalence and incidence are similar in the EU.

While some symptomatic treatments with limited efficacy are currently available, it has been only in the summer of 2021 that aducanumab (Aduhelm™, Biogen), a therapeutic antibody, was conditionally approved to treat early stages of AD in the US, but not in the EU. The mechanism of action of aducanumab is to target the β-amyloid extracellular deposits (one of the hallmarks of AD). Medicare in the US initially negated the reimbursement of aducanumab based on the excessive costs and the severe adverse reactions (brain swelling or brain bleeding). However, as requested by the FDA, the coverage is now available for patients in the ongoing clinical trials. While a similar anti-β-amyloid antibody (*lecanemab*, Eisai, Biogen) is being tested with a bit more promising interim results (September 28th, 2022; https://www.medtechdive.com/news/eisai-biogen-alzheimers-lecanemab-trial-results-positive/632834/?utm_source=Sailthru&utm_medium=email&utm_campaign=Issue:%202022-09-28%20MedTech%20Dive%20%5Bissue:44856%5D&utm_term=MedTech%20Dive), AD remains an important unmet medical need, affecting millions of people worldwide.

The pathophysiology of AD is poorly understood. There are many lead hypotheses underlying the AD pathogenesis, including amyloid cascade, neurovascular, tau propagation, mitochondrial, and the cholinergic (ACh) one, being the oldest theory, positing the demise of ACh neurons of the nucleus basalis of Meynert (NBM) as a crucial event.[1] The nature of ACh neuron loss in AD is presently unknown, but it has been linked to insufficient levels of the nerve growth factor (NGF), which in part depends on astrocyte regulation of plasmin, an enzyme involved in the processing of NGF.[2]

Astrocytes, key homeostasis-providing cells in the central nervous system (CNS),[3] are also involved in AD through the neurodegeneration of locus coeruleus (LC) neurons,[4] the prime source of noradrenaline (NA) in the CNS, playing a fundamental role in many functions, including attention, arousal, sleep/wakefulness, consciousness as well as in learning and memory.[5] Why LC neurons degenerate is unclear, but they are uniquely susceptible to oxidative stress, possibly due to their relatively high energetic needs, and their localization near the fourth ventricle exposes them to harmful environmental factors.[4]

The demise of the noradrenergic system has been discussed for several years to be a possible causative factor in AD,[5] being present often decades prior to the appearance of clinical symptoms[6] and providing an important contribution to the loss of neural reserve in AD.[7]

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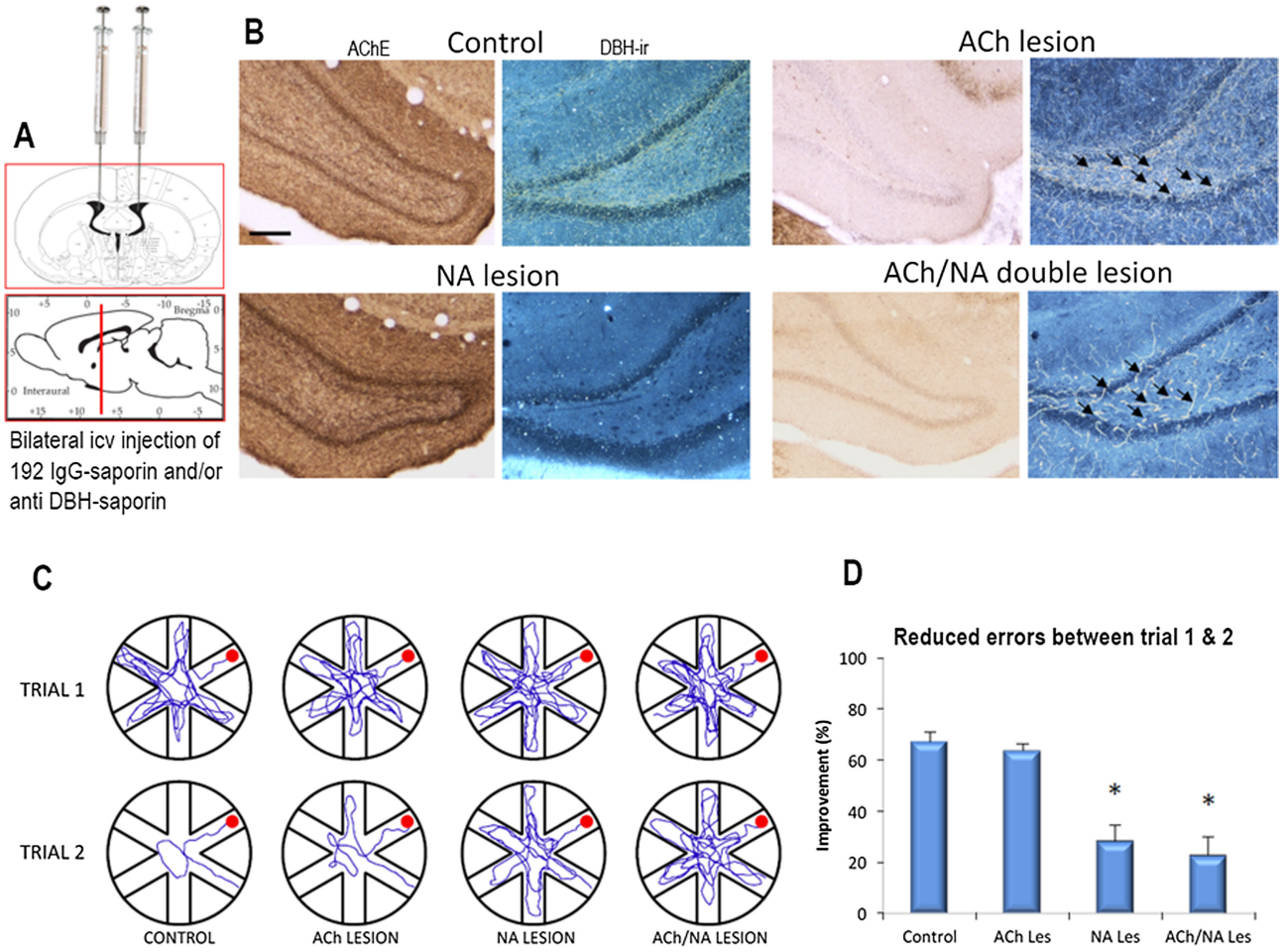

Figure 1. Dominant role of ascending LC noradrenergic, vs. basal forebrain ACh projections in the regulation of spatial learning and memory. A: to selectively lesion the ACh neurons in the basal forebrain and the noradrenergic (NA) neurons in the LC, the immunotoxins 192 IgG-saporin or anti-dopamine-ß-hydroxylase(DBH)-saporin were injected either alone or in combination into the lateral ventricles (coronal plane) of 4–8 d-old rat pups as schematically represented. B: representative examples of Acetylcholinesterase (AChE) histochemistry and of DBH-ir immunohistochemistry in the hippocampal dentate gyrus illustrating, on the coronal plane, the effects of the lesion protocols. Note the pattern of ACh (ie AChE-positive) or noradrenergic (ie DBH-immunoreactive) innervation in controls and its loss in animals with single and double lesions. Note also that in the specimens from the single ACh-lesioned and the ACh/NA double lesioned animals, there are thick and coarse DBH-immunoreactive fibers (arrows) outgrowing from the superior cervical ganglia in response to the ACh loss. These fibers, however, do not seem to provide any functional contribution to the behavioral readout. C: representative swim paths taken by rats in the various treatment groups while searching for the hidden platform in the Radial Arm Water Maze (RAWM) task. Note the rapid improvements of control and single ACh-lesioned animals, which markedly reduce the latency and the errors (ie entering a wrong arm) between the first and second trial, and the dramatic impairments of the animals in the single NA-lesion and the ACh/NA double-lesion groups, which show no improvements. D: group performances plotted as the average % improvement (savings) ± SEM between trials 1 and 2 for the error measure [calculated as: (errors in trial 1–errors in trial 2)/errors in trial 1*100]. Note the marked improvement of control and single ACh-lesioned rats as opposed to the poor performance exhibited by the rats in the single NA-lesion and ACh/NA double-lesion groups. Scale bar in (B): 100 μM. Asterisks in (D) indicate significant difference from the control and single ACh lesion groups at $P < 0.01$ (modified from de Leo et al., brain communications, in press).

Strategies to increase the NA levels in the CNS, by either attenuating its degradation via inhibitors of monoamine oxidase (MOA), or inhibiting the uptake from the synaptic/extracellular space via membrane transporters, failed to be very effective clinically.[5] While the LC-NA dysfunction in AD is unclear, it likely involves impairments of mechanisms that are activated by different adrenergic receptors on various neural cell types. Astrocytes exhibit a particularly high density of β-adrenergic receptors, which regulate aerobic glycolysis with the end product lactate in astrocytes, a fuel transported to neurons for energy, a concept known as the astrocyte to neuron lactate shuttle (ANLS).[8] The release of NA from LC neurons was shown to stimulate lactate production in astrocytes, and the consequential release of lactate from astrocytes may further stimulate astroglial lactate production through a yet unknown receptor-like mechanism.[9] It is likely that NA reduction in AD and the impaired lactate production in astrocytes are concurrently linked to the hypometabolic state of the brain, commonly observed in AD patients.[6]

As both the ACh and noradrenergic systems share the anatomical characteristic of providing diffuse innervation to the CNS and mediate functions related to aspects of learning and memory, the question arises, as to which of these systems degenerates first in AD. Due to their peculiar metabolic demand, LC neurons are more likely to be prone to degenerate rapidly, leading to the secondary ACh neuron loss. However, we lack definitive experimental evidence to show how selective lesion of NA and/or ACh neurons affect various aspects of cognitive readouts, related to AD. The recent experiments where immunotoxins specific for NA and ACh neurons were used revealed that acetylcholine and NA differentially regulate hippocampus-dependent spatial learning and memory in rats. Specifically, the

lesion of NA- or ACh-neurons failed to affect reference memory, whereas the combined lesion did. Moreover, the selective lesion of only LC resulted in impairment of working memory, which was not further exacerbated by concomitant lesion of ACh neurons (Figure 1; de Leo et al., brain comm in press). These results indicate a prominent role of NA-neurons vs. the ACh ones in the impairments of working memory, relevant for AD, and are consistent with an astrocyte-specific metabolic impairment in a mouse model of intellectual disability.[10]

In summary, while both the ACh and the noradrenergic systems involve astrocytes in their function related to AD, it is likely that targeting LC-NA-dependent mechanisms of astroglial function, involved in the early stages of AD, may hold promises for novel drug developments.

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Conflict of interest

RZ holds the position of Editorial Board Member for Function and is blinded from reviewing or making decisions for the manuscript. No other conflicts to be declared by the authors.

Data availability

Data will be provided upon reasonable request.

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