https://rijournals.com/research-in-medical-sciences/

RESEARCH INVENTION JOURNAL OF RESEARCH IN MEDICAL SCIENCES 4(3):33-37, 2025

ONLINE ISSN: 1115- 6198

Print ISSN: 1597-3107

https://doi.org/10.59298/RIJRMS/2025/433337

A Review of AChE Inhibitors as Therapeutic Neuromodulators in Neurodegenerative and Neuroinflammatory Conditions

Okello Abura L.

Faculty of Medicine Kampala International University Uganda

ABSTRACT

Acetylcholinesterase inhibitors (AChEIs) have long been used as symptomatic treatments in neurodegenerative disorders, particularly Alzheimer's disease. However, emerging evidence highlights their broader therapeutic potential beyond cholinergic enhancement, extending into neuroprotection, anti-inflammatory modulation, and neuronal repair. This review explores the multifaceted mechanisms by which AChEIs act as therapeutic neuromodulators in both neurodegenerative and neuroinflammatory contexts. We discuss the classical and non-classical roles of acetylcholinesterase (AChE), the current landscape of AChEI pharmacotherapy, and novel approaches aiming to develop multitarget-directed ligands (MTDLs). Challenges, including blood-brain barrier penetration, adverse effects, and disease heterogeneity, are addressed alongside future perspectives emphasizing personalized medicine and combinatorial strategies. Harnessing the full neuromodulatory potential of AChE inhibition could lead to more comprehensive therapies for a range of neurological diseases.

Keywords: Acetylcholinesterase inhibitors; Neurodegeneration; Neuroinflammation; Neuromodulation; Multitarget therapy

INTRODUCTION

Neurodegenerative and neuroinflammatory disorders are among the leading causes of disability and death worldwide, posing significant socio-economic and healthcare challenges [1]. Conditions such as Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), and amyotrophic lateral sclerosis (ALS) are characterized by progressive neuronal loss, synaptic dysfunction, and chronic neuroinflammation [2]. Despite their diverse clinical presentations, these disorders share common underlying pathophysiological features, including oxidative stress, mitochondrial dysfunction, excitotoxicity, and impaired neurotransmission, particularly within the cholinergic system. The cholinergic hypothesis, proposed in the 1970s, highlighted the critical role of acetylcholine (ACh) depletion in cognitive decline observed in AD [3]. This led to the development and approval of acetylcholinesterase inhibitors (AChEIs) as one of the first symptomatic treatments for neurodegenerative disease. AChEIs act by inhibiting acetylcholinesterase (AChE), the enzyme responsible for hydrolyzing ACh in the synaptic cleft, thereby enhancing cholinergic neurotransmission and temporarily improving cognition and functional abilities [4] However, the therapeutic significance of AChEIs extends far beyond symptomatic cognitive enhancement. Recent discoveries have revealed that AChEIs modulate a wide array of cellular processes, including neuroinflammation, oxidative stress responses, neuronal survival, and synaptic plasticity [5]. Moreover, the non-classical roles of AChE in cell signaling, apoptosis, and neuroimmune regulation have sparked renewed interest in targeting this enzyme for broader neuroprotective strategies [6].

Given the multifactorial nature of neurodegenerative and neuroinflammatory diseases, a multitarget therapeutic approach is increasingly considered necessary for effective intervention. In this context, AChEIs emerge not just as cholinergic enhancers but also as potential neuromodulators capable of altering disease progression through diverse mechanisms [4]. This review aims to provide a comprehensive synthesis of the evolving roles of AChEIs in neurodegenerative and neuroinflammatory conditions, examining their mechanisms of action, clinical applications, and future therapeutic potential. Understanding the expanded capabilities of AChE inhibition will enable the design of next-generation therapeutic agents that move beyond symptomatic relief toward true disease modification, addressing the complex interplay of pathogenic processes that drive neuronal damage and loss.

Acetylcholinesterase Function and Dysregulation in Disease

Acetylcholinesterase (AChE) is a critical enzyme primarily responsible for the termination of cholinergic signaling in the central and peripheral nervous systems [4]. By hydrolyzing acetylcholine into acetate and choline, AChE ensures the rapid and precise cessation of neurotransmission, allowing neurons to reset and respond to subsequent stimuli [7]. This enzymatic function is essential for normal cognition, muscle contraction, autonomic regulation, and behavioral responses [4]. Beyond its classical role, AChE exhibits a range of non-catalytic functions that are particularly relevant in the context of neurological health and disease [9]. AChE participates in cellular adhesion, synaptic organization, neurite outgrowth, and apoptosis regulation. These functions are mediated through its interaction with extracellular matrix proteins, cytoskeletal components, and cell surface receptors [8]. Importantly, alternative splicing of the AChE gene produces distinct isoforms, such as the synaptic (AChE-S) and readthrough (AChE-R) variants, each exhibiting unique roles in neural physiology and response to injury [10].

In neurodegenerative diseases, dysregulation of AChE expression and function is a consistent finding. For example, in Alzheimer's disease, elevated AChE activity has been detected in association with amyloid-beta plaques [11]. It has been shown that AChE can interact directly with amyloid precursor protein (APP), promoting amyloid aggregation and accelerating plaque formation, thus exacerbating neurotoxicity [12]. Furthermore, increased AChE activity is associated with enhanced oxidative stress, mitochondrial dysfunction, and activation of apoptotic pathways, all of which contribute to progressive neuronal degeneration [13]. Similarly, in neuroinflammatory conditions like multiple sclerosis, altered cholinergic signaling due to changes in AChE activity affects the balance between pro-inflammatory and anti-inflammatory cytokine production [14]. Reduced acetylcholine levels resulting from excessive AChE activity dampen the activation of α7 nicotinic acetylcholine receptors (α7nAChRs) on immune cells, thereby limiting the cholinergic anti-inflammatory response and promoting a pro-inflammatory environment within the central nervous system [15]. The emerging recognition of AChE as a regulator of not only synaptic activity but also neuroinflammatory and neurodegenerative pathways has broadened its appeal as a therapeutic target. Inhibiting AChE not only enhances neurotransmission but may also disrupt pathogenic cascades that underlie disease progression, making AChEIs attractive candidates for a new generation of neuroprotective interventions.

Mechanisms of AChE Inhibitor-Mediated Neuroprotection and Immunomodulation

Acetylcholinesterase inhibitors (AChEIs) extend their benefits beyond cholinergic enhancement to provide neuroprotection and immunomodulation through multiple, interlinked mechanisms [16]. These effects are especially valuable in neurodegenerative and neuroinflammatory disorders, where oxidative damage, excitotoxicity, apoptosis, and chronic inflammation converge to promote neuronal injury. A key mechanism involves the antioxidative properties of certain AChEIs [17]. Natural compounds like huperzine A and synthetic agents such as rivastigmine have been shown to reduce oxidative stress by scavenging reactive oxygen species (ROS) and preserving mitochondrial membrane potential [18]. By mitigating oxidative damage, these agents help maintain neuronal integrity and prevent energy failure, both critical to slowing neurodegeneration.

AChE inhibition also attenuates excitotoxicity, a process where excessive glutamate release leads to calcium overload and neuronal death [19]. Increased acetylcholine availability indirectly modulates glutamatergic neurotransmission, reducing NMDA receptor overactivation [20]. Donepezil, for example, has been associated with decreased glutamate-induced neurotoxicity in experimental models, suggesting an additional protective role through excitotoxicity suppression [19]. Furthermore, AChEIs enhance neurotrophic support. Elevated cholinergic tone stimulates muscarinic and nicotinic receptors, which activate intracellular signaling pathways like PI3K/Akt and MAPK/ERK [21]. These pathways promote the expression of neurotrophins, particularly brain-derived neurotrophic factor (BDNF), crucial for neuronal survival, synaptic maintenance, and plasticity. Galantamine uniquely acts as an allosteric potentiator of α7 nicotinic acetylcholine receptors (α7nAChRs), reinforcing

neurotrophic and anti-apoptotic signaling [22]. In the context of inflammation, AChEIs modulate the "cholinergic anti-inflammatory pathway [23]." Acetylcholine, acting on α7nAChRs present on immune cells like microglia and macrophages, inhibits the nuclear factor kappa B (NF-κB) signaling cascade, leading to reduced production of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6. By sustaining higher acetylcholine levels [24], AChEIs dampen neuroinflammation, a major contributor to progressive neuronal damage [25]. Finally, AChEIs influence apoptotic pathways by regulating the expression of apoptosis-related proteins. They downregulate pro-apoptotic proteins like Bax and caspase-3 and upregulate anti-apoptotic proteins such as Bcl-2, shifting the balance toward neuronal survival [26]. Together, these multifaceted mechanisms establish AChEIs as promising multitarget agents in combating the complex pathology of neurodegenerative and neuroinflammatory diseases.

Clinical Applications and Emerging Therapies

Clinically, AChEIs have been primarily utilized in managing cognitive symptoms associated with mild to moderate Alzheimer's disease. Donepezil, rivastigmine, and galantamine are the three major FDA-approved AChEIs currently in use [27]. These drugs improve cognition, daily function, and quality of life, albeit temporarily and modestly, without significantly altering the underlying disease course. Donepezil is a reversible AChEI with high selectivity for brain AChE and is approved for all stages of AD [28]. Rivastigmine inhibits both AChE and butyrylcholinesterase (BuChE), offering broader cholinergic enhancement, and is also approved for Parkinson's disease dementia [29]. Galantamine not only inhibits AChE but also positively modulates nicotinic receptors, providing an additional mechanism for enhancing cholinergic neurotransmission and neurotrophic support [30].

Emerging therapies are moving toward the development of multitarget-directed ligands (MTDLs) designed to simultaneously modulate multiple pathological pathways. Compounds such as ladostigil, combining AChE and monoamine oxidase (MAO) inhibition, aim to address both cholinergic deficits and oxidative stress [31]. Similarly, ASS234 integrates AChE inhibition with anti-amyloid and antioxidant activities, reflecting a systems pharmacology approach to therapy [32]. Natural products, notably huperzine A, are also being explored for broader applications beyond AD, including vascular dementia and traumatic brain injury, owing to their antioxidant, anti-apoptotic, and anti-inflammatory properties. Additionally, nanoparticle-based drug delivery systems are being developed to enhance blood-brain barrier (BBB) penetration and improve central nervous system (CNS) targeting, potentially maximizing the efficacy of AChEI-based therapies [33].

Challenges and Future Directions

Despite these advances, several challenges hinder the optimization and broader application of AChEIs in neurodegenerative and neuroinflammatory diseases. A major obstacle is effective delivery across the blood-brain barrier (BBB). Although agents like donepezil achieve reasonable CNS penetration, many experimental compounds exhibit poor BBB permeability, limiting their clinical utility. Long-term use of AChEIs can be associated with adverse effects, including gastrointestinal disturbances, bradycardia, muscle cramps, and insomnia, due to peripheral cholinergic overstimulation. Developing CNS-selective AChEIs that minimize peripheral side effects remains an important goal. Furthermore, the clinical efficacy of AChEIs is highly variable among patients, reflecting disease heterogeneity. Differences in genetic backgrounds, disease stages, and individual neuroinflammatory profiles suggest that a personalized approach—tailoring AChEI therapy based on biomarkers of cholinergic dysfunction and inflammation—may be required for optimal outcomes. Tolerance development, where patients gradually lose responsiveness to AChEIs over time, is another significant concern. Strategies to overcome tolerance, such as combination therapy with anti-inflammatory agents, NMDA antagonists, or antioxidants, are being actively investigated. Future directions involve designing hybrid compounds that combine AChE inhibition with antioxidant, anti-apoptotic, and anti-amyloid actions. Advances in artificial intelligence (AI) and structure-based drug design are accelerating the identification of novel multitarget molecules. Additionally, innovative drug delivery technologies, including liposomal and nanoparticle carriers, offer new opportunities for enhancing CNS-specific targeting. Overall, transforming AChEIs from symptomatic agents into truly disease-modifying therapies requires addressing these challenges through multidisciplinary approaches that integrate pharmacology, molecular biology, biomarker science, and nanotechnology.

CONCLUSION

Acetylcholinesterase inhibitors offer more than symptomatic relief; they act as neuromodulators influencing neuroprotection, anti-inflammatory pathways, and synaptic health. By targeting multiple mechanisms underlying neurodegenerative and neuroinflammatory diseases, AChEIs represent a promising therapeutic strategy. Future

advancements in multitarget drug design and personalized approaches will be essential to unlock their full disease-modifying potential.

REFERENCES

1. Ayeni EA, Aldossary AM, Ayejoto DA, Gbadegesin LA, Alshehri AA, Alfassam HA, et al. Neurodegenerative diseases: implications of environmental and climatic influences on neurotransmitters and neuronal hormones activities. International Journal of Environmental Research and Public Health. 2022;19(19):12495. doi:10.3390/ijerph191912495
2. Gadhave DG, Sugandhi VV, Jha SK, Nangare SN, Gupta G, Singh SK, et al. Neurodegenerative disorders: Mechanisms of degeneration and therapeutic approaches with their clinical relevance. Ageing Research Reviews. 2024;99:102357. doi:10.1016/j.arr.2024.102357
3. Chen ZR, Huang JB, Yang SL, Hong FF. Role of cholinergic signaling in Alzheimer's disease. Molecules. 2022;27(6):1816. doi:10.3390/molecules27061816
4. Trang A, Khandhar PB. Physiology, acetylcholinesterase. StatPearls – NCBI Bookshelf. 2023.
5. Egba, S.I., Ademola C F and Omoruyi L E (2021) Bucholzia coriacea seed extract attenuates mercury induced cerebral and cerebellar oxidative neurotoxicity via NO signalling and suppression of oxidative stress, adenosine deaminase and acetylcholinesterase activities in rats. Avicenna J Phytomed. 2022 Jan-Feb;12(1):42-53. doi: 10.22038/AJP.2021.18262. PMID: 35145894; PMCID: PMC8801217.
6. Zhang XJ, Greenberg DS. Acetylcholinesterase involvement in apoptosis. Frontiers in Molecular Neuroscience. 2012;5. doi:10.3389/fnmol.2012.00040
7. Johnson EA. CLOSTRIDIUM | Clostridium botulinum. In: Elsevier eBooks. 1999;458–63. doi:10.1006/rwfm.1999.0395
8. Juliano RL. Signal transduction by cell adhesion receptors and the cytoskeleton: functions of integrins, cadherins, selectins, and Immunoglobulin-Superfamily members. Annual Review of Pharmacology and Toxicology. 2002;42(1):283–323. doi:10.1146/annurev.pharmtox.42.090401.151133
9. Zimmermann M. Neuronal AChE splice variants and their non-hydrolytic functions: redefining a target of AChE inhibitors? British Journal of Pharmacology. 2013;170(5):953–67. doi:10.1111/bph.12359
10. Nijholt I, Farchi N, Kye M, Sklan EH, Shoham S, Verbeure B, et al. Stress-induced alternative splicing of acetylcholinesterase results in enhanced fear memory and long-term potentiation. Molecular Psychiatry. 2003;9(2):174–83. doi:10.1038/sj.mp.4001446
11. Carvajal FJ, Inestrosa NC. Interactions of AChE with Aβ aggregates in Alzheimer's brain: therapeutic relevance of IDN 5706. Frontiers in Molecular Neuroscience. 2011;4. doi:10.3389/fnmol.2011.00019
12. Rajmohan R, Reddy PH. Amyloid-Beta and phosphorylated Tau accumulations cause abnormalities at synapses of Alzheimer's disease neurons. Journal of Alzheimer's Disease. 2016;57(4):975–99. doi:10.3233/jad-160612
13. Luo H, Wei S, Fu S, Han L. Role of Achyranthes aspera in neurodegenerative diseases: current evidence and future directions. Frontiers in Pharmacology. 2025;16. doi:10.3389/fphar.2025.1511011
14. Gatta V, Mengod G, Reale M, Tata AM. Possible correlation between cholinergic system alterations and neuro/inflammation in multiple sclerosis. Biomedicines. 2020;8(6):153. doi:10.3390/biomedicines8060153
15. Liu H, Zhang X, Shi P, Yuan J, Jia Q, Pi C, et al. α7 Nicotinic acetylcholine receptor: a key receptor in the cholinergic anti-inflammatory pathway exerting an antidepressant effect. Journal of Neuroinflammation. 2023;20(1). doi:10.1186/s12974-023-02768-z
16. Walczak-Nowicka ŁJ, Herbet M. Acetylcholinesterase inhibitors in the treatment of neurodegenerative diseases and the role of acetylcholinesterase in their pathogenesis. International Journal of Molecular Sciences. 2021;22(17):9290. doi:10.3390/ijms22179290
17. Da Silva Mendes JW, Camilo CJ, De Carvalho NKG, De Fatima Alves Nonato C, De Lima RDP, Alves DR, et al. In vitro antioxidant and acetylcholinesterase inhibitory properties of the alkaloid fraction of Cissampelos sympodialis Eichler. South African Journal of Botany. 2021;141:99–104. doi:10.1016/j.sajb.2021.04.027
18. Chen X, Drew J, Berney W, Lei W. Neuroprotective natural products for Alzheimer's disease. Cells. 2021;10(6):1309. doi:10.3390/cells10061309

19. Egba, S Ikechukwu, Okonkwo C Onyinye, Ogbodo J Onyebuchi and Ezeh V Nzubechukwu Neuroprotective Potentials of *Alstonia boonei* extracts on Biochemical Markers of Brain Integrity in Experimental Rats, Trop J Nat Prod Res, 2021; 5(6): 1106-1109. doi.org/10.26538/tjnpr/v5i6.21
20. Stone TW. Relationships and interactions between ionotropic glutamate receptors and nicotinic receptors in the CNS. Neuroscience. 2021;468:321–65. doi:10.1016/j.neuroscience.2021.06.007
21. Carlson AB, Kraus GP. Physiology, cholinergic receptors. StatPearls – NCBI Bookshelf. 2023.
22. Texidó L, Ros E, Martín-Satué M, López S, Aleu J, Marsal J, et al. Effect of galantamine on the human α7 neuronal nicotinic acetylcholine receptor, the Torpedo nicotinic acetylcholine receptor and spontaneous cholinergic synaptic activity. British Journal of Pharmacology. 2005;145(5):672–8. doi:10.1038/sj.bjp.0706221
23. Wang W, Xu H, Lin H, Molnar M, Ren H. The role of the cholinergic anti-inflammatory pathway in septic cardiomyopathy. International Immunopharmacology. 2020;90:107160. doi:10.1016/j.intimp.2020.107160
24. Mizrachi T, Vaknin-Dembinsky A, Brenner T, Treinin M. Neuroinflammation modulation via α7 nicotinic acetylcholine receptor and its chaperone, RIC-3. Molecules. 2021;26(20):6139. doi:10.3390/molecules26206139
25. Adamu A, Li S, Gao F, Xue G. The role of neuroinflammation in neurodegenerative diseases: current understanding and future therapeutic targets. Frontiers in Aging Neuroscience. 2024;16. doi:10.3389/fnagi.2024.1347987
26. Singh R, Letai A, Sarosiek K. Regulation of apoptosis in health and disease: the balancing act of BCL-2 family proteins. Nature Reviews Molecular Cell Biology. 2019;20(3):175–93. doi:10.1038/s41580-018-0089-8
27. Marucci G, Buccioni M, Ben DD, Lambertucci C, Volpini R, Amenta F. Efficacy of acetylcholinesterase inhibitors in Alzheimer's disease. Neuropharmacology. 2020;190:108352. doi:10.1016/j.neuropharm.2020.108352
28. Kumar A, Gupta V, Sharma S. Donepezil. StatPearls – NCBI Bookshelf. 2023.
29. Patel PH, Gupta V. Rivastigmine. StatPearls – NCBI Bookshelf. 2023.
30. Rathi V. Galantamine. In: Elsevier eBooks. 2020;83–92. doi:10.1016/B978-0-12-819212-2.00006-2
31. Weinreb O, Amit T, Bar-Am O, Youdim MBH. Ladostigil: A novel multimodal neuroprotective drug with cholinesterase and brain-selective monoamine oxidase inhibitory activities for Alzheimer's disease treatment. Current Drug Targets. 2012;13(4):483–94. doi:10.2174/138945012799499794
32. Marco-Contelles J, Unzeta M, Bolea I, Esteban G, Ramsay RR, Romero A, et al. ASS234, as a new multi-target directed propargylamine for Alzheimer's disease therapy. Frontiers in Neuroscience. 2016;10. doi:10.3389/fnins.2016.00294
33. Wilar G, Suhandi C, Wathoni N, Fukunaga K, Kawahata I. Nanoparticle-based drug delivery systems enhance treatment of cognitive defects. International Journal of Nanomedicine. 2024;19:11357–78. doi:10.2147/IJN.S484838

CITE AS: Okello Abura L. (2025). A Review of AChE Inhibitors as Therapeutic Neuromodulators in Neurodegenerative and Neuroinflammatory Conditions. RESEARCH INVENTION JOURNAL OF RESEARCH IN MEDICAL SCIENCES 4(3):33-37. https://doi.org/10.59298/RIJRMS/2025/433337