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Neuromodulatory Targets for Neuroprotection: Bridging Acetylcholinesterase Inhibition and Neuronal Health

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ABSTRACT

Neurodegenerative diseases such as Alzheimer's, Parkinson's, and Huntington's are marked by progressive neuronal loss and impaired synaptic function, often exacerbated by oxidative stress, excitotoxicity, and neurotransmitter imbalances. Among the promising therapeutic strategies, modulation of acetylcholinesterase (AChE) activity has garnered significant attention not only for its symptomatic relief through enhanced cholinergic transmission but also for its emerging role in broader neuroprotective pathways. This review delineates the dual role of AChE as both an enzymatic regulator of synaptic acetylcholine and a non-catalytic modulator involved in apoptosis, neurite outgrowth, and synaptic remodeling. Furthermore, we explore the interconnected signaling cascades involving neurotrophic factors, inflammatory mediators, and oxidative stress modulators that intersect with AChE regulation. Natural and synthetic AChE inhibitors, such as donepezil, galantamine, huperzine A, and novel multitarget compounds, are examined for their efficacy, blood-brain barrier permeability, and off-target effects. Finally, we propose a systems pharmacology approach integrating AChE inhibition with secondary neuromodulatory targets, such as NMDA receptors, nicotinic receptors, and neurotrophin signaling, to enhance therapeutic precision. This integrative model offers a conceptual bridge between symptomatic management and disease-modifying interventions in neurodegeneration.

Keywords: Acetylcholinesterase inhibition; Neurodegeneration; Synaptic plasticity; Neuroinflammation; Multitarget therapy

INTRODUCTION

Neurodegenerative disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD) are characterized by progressive neuronal loss, synaptic dysfunction, and accumulation of misfolded proteins [1]. These diseases contribute significantly to morbidity and mortality in aging populations worldwide. Central to the pathology of many of these conditions is the disruption of neurotransmitter systems, particularly the cholinergic system, which plays a pivotal role in cognition, learning, and memory [2]. Acetylcholine (ACh), a key neurotransmitter in this system, is rapidly hydrolyzed by the enzyme acetylcholinesterase (AChE), making the regulation of AChE activity crucial for maintaining cholinergic balance [3]. Acetylcholinesterase inhibitors (AChEIs) have been widely employed in the symptomatic treatment of AD, primarily to enhance cholinergic neurotransmission [4]. However, recent studies have revealed broader roles of AChE beyond neurotransmitter hydrolysis, implicating it in neurodevelopment, synaptic plasticity, and neurodegenerative processes. This broader functional spectrum of AChE suggests that its inhibition may yield not only symptomatic relief but also direct neuroprotective benefits [3]. As the focus of neurodegeneration research shifts toward multifactorial interventions, AChE has emerged as a promising neuromodulatory target that bridges neurotransmitter regulation and neuronal

survival [4]. This review explores the evolving understanding of AChE in neuronal health, its neuromodulatory influence beyond enzymatic activity, and the mechanistic basis by which AChEIs contribute to neuroprotection.

Acetylcholinesterase: Beyond Neurotransmitter Hydrolysis

Acetylcholinesterase is a serine hydrolase enzyme localized primarily at cholinergic synapses, where it catalyzes the rapid degradation of acetylcholine into acetate and choline [3]. This enzymatic action is essential for terminating synaptic transmission and preventing overstimulation of postsynaptic receptors. However, research over the past two decades has uncovered several non-classical, non-enzymatic functions of AChE that are critical to neural physiology and pathology [5]. These functions include roles in cell adhesion, neurite outgrowth, apoptosis, and synaptic remodeling. AChE exists in multiple molecular isoforms, including the synaptic globular tetrameric (G4) form, the monomeric (G1) form, and the readthrough variant (AChE-R). These isoforms are differentially expressed in response to physiological cues and pathological stressors [6]. The AChE-R isoform, for example, has been shown to increase in the brain following injury and stress, suggesting a potential role in neuronal repair or degeneration [7]. Notably, in neurodegenerative conditions such as AD, AChE expression is often dysregulated [8]. Increased AChE activity has been associated with enhanced deposition of β-amyloid plaques and tau hyperphosphorylation, hallmarks of AD pathology [9]. Furthermore, AChE is known to interact with amyloid precursor protein (APP) and may facilitate the formation of toxic Aβ aggregates [10]. AChE also interacts with cytoskeletal and membrane proteins, influencing axonal growth and synapse formation [11]. Through these actions, AChE is positioned not just as an enzymatic regulator but as a multifunctional protein intricately involved in maintaining or disrupting neuronal architecture and function.

Mechanisms of AChE Inhibitor-Induced Neuroprotection

While the primary function of AChE inhibitors is to elevate synaptic acetylcholine levels and improve cholinergic transmission, accumulating evidence suggests that these agents exert a broad range of neuroprotective effects [12]. These include antioxidative actions, anti-inflammatory responses, anti-apoptotic effects, and enhancement of neurotrophic signaling. By increasing ACh availability, AChEIs indirectly stimulate muscarinic and nicotinic receptors, which in turn activate intracellular pathways such as PI3K/Akt and MAPK/ERK [13]. These signaling cascades promote neuronal survival, synaptic plasticity, and long-term potentiation. Galantamine, for instance, not only inhibits AChE but also acts as an allosteric potentiator of nicotinic acetylcholine receptors (nAChRs), amplifying neuroprotective signaling [14]. Moreover, AChEIs reduce oxidative stress by preserving mitochondrial function and scavenging reactive oxygen species, particularly in the case of natural inhibitors like huperzine A [15]. They also suppress the release of pro-inflammatory cytokines such as TNF-α and IL-1β through activation of the cholinergic anti-inflammatory pathway mediated by α7-nAChRs on microglia [16].

In apoptotic regulation, AChEIs have been shown to modulate the balance between pro- and anti-apoptotic proteins, downregulating Bax and caspase-3 while upregulating Bcl-2 [17]. Additionally, by enhancing cholinergic tone, these inhibitors promote the expression of brain-derived neurotrophic factor (BDNF), supporting synaptic health and regeneration. In sum, AChEIs represent more than symptomatic agents—they engage a network of neuroprotective pathways that justify their inclusion in multimodal strategies for managing neurodegenerative diseases.

Secondary Neuromodulatory Targets and Crosstalk with AChE

While acetylcholinesterase (AChE) inhibition enhances cholinergic transmission, it also initiates crosstalk with several other crucial neuromodulatory systems that collectively influence neuronal survival and plasticity [18]. Effective neuroprotection increasingly requires a multi-target approach, recognizing that neurodegeneration is rarely driven by a single pathogenic mechanism. AChE inhibition influences several key targets indirectly, creating synergistic neuroprotective effects. First, the glutamatergic system, particularly N-methyl-D-aspartate (NMDA) receptors, is affected. Overactivation of NMDA receptors results in excitotoxicity, a hallmark of many neurodegenerative diseases [19]. Some studies have demonstrated that AChE inhibitors, by modulating neuronal excitability and reducing oxidative stress, can indirectly regulate NMDA receptor activity [20]. This effect can protect neurons from calcium overload and apoptosis.Second, nicotinic acetylcholine receptors (nAChRs), especially the α7 subtype, are directly influenced by elevated acetylcholine levels [21]. Activation of α7-nAChRs enhances synaptic plasticity, modulates neurotransmitter release, and stimulates the release of neurotrophic factors like brain-derived neurotrophic factor (BDNF) [22]. Galantamine, in particular, not only inhibits AChE but also acts as an allosteric potentiator of nAChRs, reinforcing these beneficial effects [23].Third, the modulation of neuroinflammatory pathways plays a significant role. AChE inhibition activates the "cholinergic anti-inflammatory

pathway," resulting in the downregulation of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β) in microglial cells [24]. By reducing chronic inflammation, a major contributor to neuronal damage, AChE inhibitors promote a neuroprotective environment. Finally, enhanced cholinergic signaling upregulates neurotrophin signaling cascades, notably the BDNF-TrkB pathway, fostering neuronal survival, dendritic branching, and synaptic strength [25]. These complex interactions highlight that targeting AChE alone can impact multiple systems critical for maintaining neuronal health, supporting the rationale for developing multitarget-directed therapeutic strategies.

Therapeutic Agents Targeting AChE and Neuroprotective Pathways

Current pharmacotherapies for neurodegenerative diseases largely focus on symptomatic relief, with AChE inhibitors being the mainstay for cognitive symptoms in Alzheimer's disease. Drugs like donepezil, rivastigmine, and galantamine have shown consistent, albeit modest, benefits in improving cognitive function and daily living activities [26]. Beyond these, a growing body of research aims to develop agents that not only inhibit AChE but also provide broader neuroprotective effects.

Natural compounds such as huperzine A have demonstrated dual functionality: potent AChE inhibition and direct antioxidant activity [27]. Huperzine A, derived from Huperzia serrata, effectively crosses the blood-brain barrier and exhibits properties that reduce oxidative stress, protect mitochondria, and inhibit apoptosis [28]. These additional actions make it an attractive candidate for disease-modifying interventions. Synthetic multitarget-directed ligands (MTDLs) represent an emerging class of compounds designed to simultaneously modulate AChE activity and other pathogenic pathways [29]. For example, ladostigil combines AChE and monoamine oxidase (MAO) inhibition, targeting both cholinergic and dopaminergic systems along with antioxidant effects [30]. Similarly, compounds like ASS234 inhibit both AChE and β-amyloid aggregation while offering antioxidant protection [31]. These multifunctional agents are particularly promising because they address the multifactorial nature of neurodegenerative diseases, potentially slowing disease progression rather than merely alleviating symptoms. The ongoing refinement of such compounds, focusing on improving blood-brain barrier permeability, metabolic stability, and minimizing side effects, is critical for future clinical success.

Challenges and Future Directions

Despite promising advances, significant challenges remain in translating AChE-based neuroprotective strategies into effective, disease-modifying therapies. One major limitation is the blood-brain barrier (BBB), which restricts the entry of many potential therapeutic agents into the central nervous system [32]. Even among agents that do cross the BBB, achieving sufficient concentrations without inducing systemic toxicity remains a delicate balance [33]. Moreover, long-term use of current AChE inhibitors can be associated with adverse effects, including gastrointestinal disturbances, bradycardia, and, in some cases, tolerance development where efficacy diminishes over time [34]. Designing drugs with selective targeting of neuronal AChE, while sparing peripheral tissues, remains a critical goal.

Another challenge is the heterogeneity of neurodegenerative diseases themselves. Alzheimer's disease, for example, displays diverse pathophysiological profiles across individuals, suggesting that "one-size-fits-all" treatments are unlikely to be universally effective. Future strategies should emphasize personalized medicine approaches, utilizing biomarkers to tailor AChE-targeted therapies based on individual disease phenotypes.

Emerging technologies offer solutions. Nanocarrier-based delivery systems are being explored to enhance CNS targeting while minimizing systemic side effects. Artificial intelligence and machine learning tools are being leveraged to design more potent multitarget compounds and predict drug behavior in biological systems. Furthermore, combination therapies that integrate AChE inhibition with antioxidants, anti-inflammatory agents, or amyloid-targeting drugs could provide synergistic benefits. Advancing the role of AChE inhibitors from symptomatic agents to components of comprehensive neuroprotective regimens requires a paradigm shift. Integrating molecular insights, precision targeting, and combination strategies holds promise for future interventions aimed at halting or reversing neurodegenerative processes.

CONCLUSION

Acetylcholinesterase inhibition remains a cornerstone of symptomatic treatment for neurodegenerative diseases. However, its broader role in neuromodulation opens the door to comprehensive neuroprotective strategies. Bridging the enzymatic and non-enzymatic functions of AChE with co-targeted neuromodulatory pathways offers a robust platform for therapeutic innovation. A systems biology approach, combined with next-generation multitarget drug

design, may ultimately transform AChE-targeted interventions into disease-modifying therapies capable of halting or reversing neurodegenerative processes.

REFERENCES

1. Jellinger KA. Basic mechanisms of neurodegeneration: a critical update. Journal of Cellular and Molecular Medicine. 2010;14(3):457–87. doi:10.1111/j.1582-4934.2010.01010.x
2. 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
3. Gajendra K, Pratap GK, Poornima DV, Shantaram M, Ranjita G. Natural acetylcholinesterase inhibitors: A multi-targeted therapeutic potential in Alzheimer's disease. European Journal of Medicinal Chemistry Reports. 2024;11:100154. doi:10.1016/j.ejmcr.2024.100154
4. Cao B, Xu Q, Shi Y, Zhao R, Li H, Zheng J, et al. Pathology of pain and its implications for therapeutic interventions. Signal Transduction and Targeted Therapy. 2024;9(1). doi:10.1038/s41392-024-01845-w
5. Luo X, Lauwers M, Layer PG, Wen C. Non-neuronal role of acetylcholinesterase in bone development and degeneration. Frontiers in Cell and Developmental Biology. 2021;8. doi:10.3389/fcell.2020.620543
6. Nazim M, Masuda A, Rahman MA, Nasrin F, Takeda JI, Ohe K, et al. Competitive regulation of alternative splicing and alternative polyadenylation by hnRNP H and CstF64 determines acetylcholinesterase isoforms. Nucleic Acids Research. 2016;gkw823. doi:10.1093/nar/gkw823
7. Karve IP, Taylor JM, Crack PJ. The contribution of astrocytes and microglia to traumatic brain injury. British Journal of Pharmacology. 2015;173(4):692–702. doi:10.1111/bph.13125
8. 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
9. Gajendra K, Pratap GK, Poornima DV, Shantaram M, Ranjita G. Natural acetylcholinesterase inhibitors: A multi-targeted therapeutic potential in Alzheimer's disease. European Journal of Medicinal Chemistry Reports. 2024;11:100154. doi:10.1016/j.ejmcr.2024.100154
10. Nalivaeva NN, Turner AJ. AChE and the amyloid precursor protein (APP) – Cross-talk in Alzheimer's disease. Chemico-Biological Interactions. 2016;259:301–6. doi:10.1016/j.cbi.2016.04.009
11. Kiyoshi C, Tedeschi A. Axon growth and synaptic function: A balancing act for axonal regeneration and neuronal circuit formation in CNS trauma and disease. Developmental Neurobiology. 2020;80(7–8):277–301. doi:10.1002/dneu.22780
12. Colovic MB, Krstic DZ, Lazarevic-Pasti TD, Bondzic AM, Vasic VM. Acetylcholinesterase inhibitors: Pharmacology and toxicology. Current Neuropharmacology. 2013;11(3):315–35. doi:10.2174/1570159x11311030006
13. Sam C, Bordoni B. Physiology, acetylcholine. StatPearls – NCBI Bookshelf. 2023. doi: (NCBI Bookshelf entry)
14. Egba SI, Famurewa AC, Omoruyi LE. *Buchholzia coriacea* seed extract attenuates mercury-induced cerebral and cerebellar oxidative neurotoxicity via NO signaling 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.
15. Simunkova M, Alwasel SH, Alhazza IM, Jomova K, Kollar V, Rusko M, et al. Management of oxidative stress and other pathologies in Alzheimer's disease. Archives of Toxicology. 2019;93(9):2491–513. doi:10.1007/s00204-019-02538-y
16. 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
17. Choi HS, Baek KH. Pro-apoptotic and anti-apoptotic regulation mediated by deubiquitinating enzymes. Cellular and Molecular Life Sciences. 2022;79(2). doi:10.1007/s00018-022-04132-5
18. Trang A, Khandhar PB. Physiology, acetylcholinesterase. StatPearls – NCBI Bookshelf. 2023. doi: (NCBI Bookshelf entry)
19. Liu J, Chang L, Song Y, Li H, Wu Y. The role of NMDA receptors in Alzheimer's disease. Frontiers in Neuroscience. 2019;13. doi:10.3389/fnins.2019.00043

20. Bendix I, Serdar M, Herz J, Von Haefen C, Nasser F, Rohrer B, et al. Inhibition of acetylcholinesterase modulates NMDA receptor antagonist mediated alterations in the developing brain. International Journal of Molecular Sciences. 2014;15(3):3784–98. doi:10.3390/ijms15033784
21. Letsinger AC, Gu Z, Yakel JL. α7 nicotinic acetylcholine receptors in the hippocampal circuit: taming complexity. Trends in Neurosciences. 2021;45(2):145–57. doi:10.1016/j.tins.2021.11.006
22. Maurer SV, Williams CL. The Cholinergic System Modulates Memory and Hippocampal Plasticity via Its Interactions with Non-Neuronal Cells. Frontiers in Immunology. 2017;8. doi:10.3389/fimmu.2017.01489
23. 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
24. Reale M, Costantini E. Cholinergic modulation of the immune system in neuroinflammatory diseases. Diseases. 2021;9(2):29. doi:10.3390/diseases9020029
25. Ibrahim AM, Chauhan L, Bhardwaj A, Sharma A, Fayaz F, Kumar B, et al. Brain-Derived neurotropic factor in neurodegenerative disorders. Biomedicines. 2022;10(5):1143. doi:10.3390/biomedicines10051143
26. Battle CE, Abdul-Rahim AH, Shenkin SD, Hewitt J, Quinn TJ. Cholinesterase inhibitors for vascular dementia and other vascular cognitive impairments: a network meta-analysis. Cochrane Library. 2021;2021(2). doi:10.1002/14651858.cd013306.pub2
27. Herzon S, Tun MKM. The pharmacology and therapeutic potential of (-)-huperzine A. Journal of Experimental Pharmacology. 2012;113. doi:10.2147/jep.s27084
28. Yadav A, Yadav SS, Singh S, Dabur R. Natural products: Potential therapeutic agents to prevent skeletal muscle atrophy. European Journal of Pharmacology. 2022;925:174995. doi:10.1016/j.ejphar.2022.174995
29. Minarini A, Milelli A, Tumiatti V, Rosini M, Simoni E, Bolognesi ML, et al. Cystamine-tacrine dimer: A new multi-target-directed ligand as potential therapeutic agent for Alzheimer's disease treatment. Neuropharmacology. 2011;62(2):997–1003. doi:10.1016/j.neuropharm.2011.10.007
30. Weinreb O, Amit T, Bar-Am O, Youdim MBH. A novel anti-Alzheimer's disease drug, ladostigil. International Review of Neurobiology. 2011;191–215. doi:10.1016/b978-0-12-386467-3.00010-8
31. 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
32. Wu D, Chen Q, Chen X, Han F, Chen Z, Wang Y. The blood–brain barrier: Structure, regulation and drug delivery. Signal Transduction and Targeted Therapy. 2023;8(1). doi:10.1038/s41392-023-01481-w
33. Hersh DS, Wadajkar AS, Roberts NB, Perez JG, Connolly NP, Frenkel V, et al. Evolving drug delivery strategies to overcome the blood brain barrier. Current Pharmaceutical Design. 2016;22(9):1177–93. doi:10.2174/1381612822666151221150733
34. Young S, Chung E, Chen MA. Cardiovascular Complications of Acetylcholinesterase Inhibitors in Patients with Alzheimer's Disease: A Narrative Review. Annals of Geriatric Medicine and Research. 2021;25(3):170–7. doi:10.4235/agmr.21.0079

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