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

RESEARCH INVENTION JOURNAL OF RESEARCH IN MEDICAL SCIENCES 4(3):103-108, 2025

ONLINE ISSN: 1115- 6198

Print ISSN: 1597-3107

https://doi.org/10.59298/RIJRMS/2025/43103108

Acetylcholinesterase in Neuromodulation: Dual Roles in Synaptic Plasticity and Neurotoxicity

Kirabo Nansubuga K.

Faculty of Science and Technology Kampala International University Uganda

ABSTRACT

Acetylcholinesterase (AChE), traditionally known for its role in hydrolyzing acetylcholine at cholinergic synapses, has emerged as a multifunctional enzyme with critical neuromodulatory functions in the central and peripheral nervous systems. Beyond terminating cholinergic transmission, AChE plays paradoxical roles in regulating synaptic plasticity, neurite outgrowth, and neurodegeneration. This review explores the dualistic functions of AChE, analyzing its physiological contributions to neuronal health and learning, as well as its pathological involvement in neurotoxic cascades, including oxidative stress, excitotoxicity, and apoptotic signaling. We discuss how dysregulation of AChE expression and activity contributes to neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease. Furthermore, we examine therapeutic strategies targeting AChE and highlight recent advances in modulating its activity for neuroprotection and synaptic repair. A clearer understanding of AChE's dual roles could unlock novel strategies for balancing neuromodulation and mitigating neurotoxicity in neurological disorders.

Keywords: Acetylcholinesterase, Neuromodulation, Synaptic Plasticity, Neurotoxicity, Neurodegeneration

INTRODUCTION

Acetylcholinesterase (AChE; EC 3.1.1.7) is a serine hydrolase best known for its classical role in catalyzing the breakdown of acetylcholine (ACh) at cholinergic synapses, thereby terminating neurotransmission [1]. For decades, its function was viewed narrowly through the lens of cholinergic signaling, particularly in neuromuscular junctions and central cholinergic circuits. However, a growing body of evidence reveals that AChE is much more than a terminator of synaptic signals; it is a complex neuromodulator with significant influence on neurodevelopment, plasticity, and pathophysiological processes [2] The dualistic role of AChE encompasses both neuroprotective and neurotoxic dimensions. On one hand, it contributes to synaptic stability, promotes neurite extension, and supports learning and memory through cholinergic tone regulation [3]. On the other, AChE is implicated in cell death pathways, oxidative stress, and neuroinflammation, particularly under conditions of overexpression or exposure to environmental and endogenous toxins [4]. Its non-classical roles, including interactions with amyloid-β, cell adhesion molecules, and structural scaffolds, further complicate its neurobiological impact [5] Given these contrasting effects, understanding the regulatory mechanisms that modulate AChE activity and expression is crucial for developing therapies that harness its beneficial roles while minimizing its neurotoxic potential. This review explores the molecular underpinnings of AChE's involvement in synaptic plasticity and neurotoxicity, emphasizing its relevance to neurodegenerative and neurodevelopmental disorders.

Acetylcholinesterase in Synaptic Plasticity and Neurodevelopment

Synaptic plasticity is the capacity of synapses to strengthen or weaken over time, is fundamental to learning and memory [6]. AChE contributes to this process by modulating cholinergic tone, which in turn influences long-term potentiation (LTP), neuronal excitability, and cognitive performance [7]. Experimental studies have shown that

regulated AChE activity ensures proper synaptic spacing, neurotransmitter turnover, and oscillatory rhythm generation, particularly in the hippocampus and basal forebrain [8]. Moreover, AChE plays a significant role in neurodevelopmental processes, including neurite outgrowth, synaptogenesis, and axonal guidance [9]. These effects are partly mediated through the non-enzymatic N-terminal peptides derived from AChE mRNA splice variants (e.g., AChE-R, AChE-S), which influence cell adhesion, neuronal migration, and intracellular calcium dynamics [10]. AChE also interacts with neurotrophin receptors such as TrkA, modulating the responsiveness of neurons to growth factors like nerve growth factor (NGF) [11]. The role of AChE in synaptic architecture is further supported by its localization in growth cones, dendritic spines, and glial cells, where it participates in cell-cell communication and cytoskeletal remodeling [12]. These findings collectively underscore AChE's pivotal function in establishing and refining neural circuits essential for behavioral flexibility and cognitive integrity.

Neurotoxicity Mediated by Acetylcholinesterase Dysregulation

While tightly regulated AChE activity supports neuronal function, its dysregulation is a hallmark of neurotoxicity. Elevated AChE expression has been observed in conditions of acute and chronic neurodegeneration, including Alzheimer's disease (AD), Parkinson's disease (PD), epilepsy, and traumatic brain injury (TBI) [10]. In these contexts, AChE contributes to neurotoxicity through both catalytic and non-catalytic mechanisms. Catalytically, hyperactive AChE results in rapid acetylcholine hydrolysis, impairing cholinergic neurotransmission and disrupting memory circuits [13]. Non-catalytically, AChE interacts with amyloid precursor protein (APP) and amyloid-β (Aβ) to promote plaque formation and aggregation, thereby accelerating the pathogenesis of Alzheimer's disease [14]. Additionally, AChE augments oxidative stress by enhancing mitochondrial dysfunction and free radical generation, sensitizing neurons to excitotoxic insults [15]. Moreover, AChE is a downstream effector of apoptotic pathways. Under toxic stress, AChE translocates to the nucleus and facilitates chromatin condensation and caspase activation, hastening neuronal death [16]. Its interaction with pro-apoptotic proteins such as Bax and cytochrome c underscores its integral role in programmed cell death cascades [17]. Environmental neurotoxins—such as organophosphates, heavy metals, and pesticides—also exploit AChE's catalytic site to disrupt synaptic homeostasis [18]. While acute inhibition of AChE leads to cholinergic crisis, chronic exposure results in compensatory overexpression, synaptic dysfunction, and long-term cognitive impairment.

Acetylcholinesterase in Synaptic Plasticity and Neurodevelopment

Acetylcholinesterase (AChE) plays a vital role in maintaining synaptic fidelity through the rapid hydrolysis of acetylcholine (ACh), thereby ensuring precise signal termination at cholinergic synapses [1]. However, contemporary neuroscience recognizes that AChE's influence extends far beyond neurotransmitter breakdown. Accumulating evidence suggests that AChE contributes actively to neuronal development, circuit refinement, and synaptic plasticity—key components of cognitive function and learning [7]. In the central nervous system (CNS), ACh acts as a modulatory neurotransmitter, particularly in the hippocampus, amygdala, and cortex—regions implicated in memory and attention [1]. By regulating the local concentration of ACh in synaptic clefts, AChE indirectly influences the activation of muscarinic and nicotinic receptors, both of which are critical for long-term potentiation (LTP), a cellular correlate of memory [7]. Thus, the enzymatic action of AChE, when optimally regulated, supports cognitive performance by modulating receptor signaling thresholds and maintaining cholinergic tone. More intriguingly, AChE exhibits non-enzymatic functions mediated by alternative splicing and expression of different isoforms, notably AChE-S (synaptic), AChE-R (readthrough), and AChE-E (erythrocytic) [19]. These isoforms exhibit distinct cellular localizations and roles. AChE-R, for instance, is induced under stress and injury and has been associated with enhanced neuroplasticity and neuroprotection in some models [19]. These variants produce functional peptides and fragments that interact with cell surface receptors and intracellular proteins, influencing neuronal morphology and differentiation.

In the developing brain, AChE is expressed prior to the establishment of functional synapses, suggesting a morphogenic role [1]. Studies in rodent models have demonstrated that AChE enhances neurite outgrowth, regulates growth cone dynamics, and promotes synaptogenesis [20]. These developmental processes are mediated through non-classical mechanisms involving interactions with laminin, integrins, and heparan sulfate proteoglycans. Additionally, AChE participates in the formation of growth cones, facilitating axonal pathfinding and proper network formation [21]. At the synaptic level, AChE has been implicated in dendritic spine maturation and plasticity [22]. AChE-containing complexes have been detected at synapse-associated membranes, where they appear to regulate actin cytoskeletal dynamics and modulate calcium signaling cascades [23]. These interactions suggest that AChE not only contributes to maintaining cholinergic balance but also structurally organizes the synaptic microenvironment.

A particularly novel aspect of AChE's role in plasticity lies in its modulation of glial-neuronal communication. Astrocytes, microglia, and oligodendrocytes express AChE under specific conditions and influence the release of neurotrophic factors, inflammatory mediators, and extracellular matrix components [24]. This broader expression profile implies that AChE may serve as a hub connecting neurotransmission with neuroimmune regulation and homeostasis. Together, these findings underscore AChE's critical role as a multifunctional protein in the nervous system. Its involvement in neurodevelopment, synaptic remodeling, and plasticity reveals a spectrum of biological functions that challenge its narrow categorization as merely a cholinergic enzyme. Understanding how to harness or modulate these diverse functions represents a promising therapeutic frontier in neurobiology.

Neurotoxicity Mediated by Acetylcholinesterase Dysregulation

While acetylcholinesterase is essential for neural homeostasis, its dysregulation is strongly implicated in the pathogenesis of various neurological disorders. Both the overexpression and abnormal activity of AChE have been associated with mechanisms of neurotoxicity, including excitotoxicity, oxidative stress, inflammation, and apoptosis [10]. These effects are particularly evident in the context of neurodegenerative diseases, such as Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and Huntington's disease [10,25]. One of the principal mechanisms through which AChE contributes to neurotoxicity is excessive hydrolysis of acetylcholine, which disrupts cholinergic neurotransmission [26]. In AD, reduced cholinergic tone is a hallmark feature, resulting in cognitive deficits and memory impairment [13]. Although AChE inhibitors are used therapeutically to restore ACh levels, the paradox lies in the observation that AChE itself is often overexpressed in AD brains [27]. This paradox is explained by the presence of AChE splice variants, such as AChE-S, which exhibit increased aggregation-promoting properties and can associate with amyloid-β (Aβ) plaques [27].

Importantly, non-catalytic roles of AChE are also deeply implicated in neurodegeneration. AChE can directly bind to Aβ peptides, promoting their fibrillization and deposition [28]. The AChE-Aβ complexes have been shown to be more neurotoxic than Aβ alone, contributing to synaptic loss and neuronal death [29]. This interaction is mediated via a peripheral anionic site (PAS) on the AChE molecule, which represents a novel target for anti-amyloid therapies aimed at disrupting these pathological complexes [28]. AChE also plays a role in apoptotic signaling. During cellular stress, AChE is upregulated and translocated to the nucleus, where it facilitates chromatin condensation and activates caspase cascades [30]. This nuclear translocation has been observed in response to excitotoxic glutamate exposure, oxidative stress, and mitochondrial dysfunction [30]. Additionally, AChE modulates the expression and activity of apoptosis-related proteins such as Bax, Bcl-2, and cytochrome c, influencing intrinsic pathways of programmed cell death [31].

Oxidative stress and inflammation represent other pathways through which AChE mediates neurotoxicity. AChE activity enhances reactive oxygen species (ROS) generation by impairing mitochondrial function and activating NADPH oxidase [32]. Inflammatory responses are also heightened, with AChE overexpression linked to increased microglial activation and cytokine release, further exacerbating neuronal injury [33]. Environmental neurotoxins, particularly organophosphate and carbamate compounds, exploit AChE as their primary target. Acute poisoning with these agents leads to AChE inhibition and cholinergic crisis [34]. Paradoxically, chronic low-level exposure often triggers a compensatory overexpression of AChE, leading to long-term synaptic dysregulation, behavioral deficits, and increased vulnerability to neurodegeneration [10].

In sum, AChE's role in neurotoxicity is multifaceted and context-dependent. The enzyme's overactivity and aberrant interactions with pathological proteins and intracellular signaling cascades can initiate and amplify neuronal damage. Therapeutic strategies aimed at modulating both the catalytic and non-catalytic functions of AChE must therefore be carefully tailored to mitigate neurotoxicity without impairing essential neuromodulatory functions.

Therapeutic Implications: Targeting AChE for Neuroprotection

The central role of acetylcholinesterase (AChE) in both physiological neuromodulation and pathological neurotoxicity positions it as a strategic therapeutic target for various neurological disorders. The clinical utility of AChE inhibitors (AChEIs), such as donepezil, rivastigmine, and galantamine, has been well established in Alzheimer's disease (AD) [35]. These agents prolong cholinergic signaling by inhibiting AChE's enzymatic activity, thereby enhancing cognitive function in early to moderate stages of the disease. However, their effects are symptomatic and do not halt disease progression.

Emerging strategies are shifting toward selective targeting of AChE variants and non-catalytic domains, particularly the peripheral anionic site (PAS), which mediates interactions with amyloid-β (Aβ). PAS-targeted

ligands aim to disrupt AChE-Aβ complex formation, thus attenuating amyloid plaque aggregation and reducing neurotoxicity [36].

Natural compounds and plant-derived bioactives have shown promise as dual-function agents, offering mild AChE inhibition along with antioxidant, anti-inflammatory, and neurotrophic properties. Polyphenols such as curcumin, resveratrol, and berberine not only modulate AChE activity but also improve mitochondrial function and synaptic plasticity [37].

Recent innovations include antisense oligonucleotides (ASOs) and RNA interference techniques designed to downregulate AChE gene expression selectively, potentially offering precision-based neuroprotection in models of epilepsy, trauma, and neurodegeneration [38]. Furthermore, peptide-based inhibitors and monoclonal antibodies are under investigation to block toxic interactions while preserving beneficial enzymatic functions.

The future of AChE-targeted therapy lies in fine-tuning modulation, leveraging its protective roles in synaptic maintenance while inhibiting its pathological contributions to neuronal injury and degeneration.

CONCLUSION

Acetylcholinesterase serves as both a guardian and a threat within the nervous system, facilitating synaptic precision while contributing to neurodegeneration when dysregulated. Its dual roles in neuromodulation and neurotoxicity highlight the complexity of targeting this enzyme therapeutically. Advancing our understanding of AChE's catalytic and non-catalytic functions will enable the development of precision interventions that restore neuronal balance, enhance plasticity, and mitigate neurodegenerative progression. AChE remains a pivotal, yet nuanced, target in the quest for neurological health and cognitive resilience.

REFERENCES

1. Trang A, Khandhar PB. Physiology, acetylcholinesterase. StatPearls – NCBI Bookshelf. 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK539735/
2. Bazzari A, Parri H. Neuromodulators and long-term synaptic plasticity in learning and memory: a steered-glutamatergic perspective. Brain Sciences. 2019;9(11):300. doi:10.3390/brainsci9110300
3. Olivera S, Rodriguez-Ithurralde D, Henley JM. Acetylcholinesterase promotes neurite elongation, synapse formation, and surface expression of AMPA receptors in hippocampal neurones. Molecular and Cellular Neuroscience. 2003;23(1):96–106. doi:10.1016/S1044-7431(03)00021-6
4. Zhang Y, Xie J. Ferroptosis implication in environmental-induced neurotoxicity. The Science of the Total Environment. 2024;934:172618. doi:10.1016/j.scitotenv.2024.172618
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
6. Weishaupt N. Cortical plasticity in response to injury and disease. In: Elsevier eBooks. 2017. p. 37–56. doi:10.1016/B978-0-12-801942-9.00002-1
7. Picciotto MR, Higley MJ, Mineur YS. Acetylcholine as a neuromodulator: cholinergic signaling shapes nervous system function and behavior. Neuron. 2012;76(1):116–29. doi:10.1016/j.neuron.2012.08.036
8. Huang Q, Liao C, Ge F, Ao J, Liu T. Acetylcholine bidirectionally regulates learning and memory. Journal of Neurorestoratology. 2022;10(2):100002. doi:10.1016/j.jnrt.2022.100002
9. Batool S, Raza H, Zaidi J, Riaz S, Hasan S, Syed NI. Synapse formation: from cellular and molecular mechanisms to neurodevelopmental and neurodegenerative disorders. Journal of Neurophysiology. 2019;121(4):1381–97. doi:10.1152/jn.00833.2018
10. 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
11. Huang EJ, Reichardt LF. Neurotrophins: roles in neuronal development and function. Annual Review of Neuroscience. 2001;24(1):677–736. doi:10.1146/annurev.neuro.24.1.677
12. 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
13. 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

14. 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
15. Depp C, Bas-Orth C, Schroeder L, Hellwig A, Bading H. Synaptic activity protects neurons against calcium-mediated oxidation and contraction of mitochondria during excitotoxicity. Antioxidants and Redox Signaling. 2017;29(12):1109–24. doi:10.1089/ars.2017.7092
16. Kopeina GS, Prokhorova EA, Lavrik IN, Zhivotovsky B. Alterations in the nucleocytoplasmic transport in apoptosis: caspases lead the way. Cell Proliferation. 2018;51(5):e12467. doi:10.1111/cpr.12467
17. Korsmeyer SJ, Wei MC, Saito M, Weiler S, Oh KJ, Schlesinger P. Pro-apoptotic cascade activates BID, which oligomerizes BAK or BAX into pores that result in the release of cytochrome c. Cell Death and Differentiation. 2000;7(12):1166–73. doi:10.1038/sj.cdd.4400783
18. 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
19. Jiang H, Zhang X. Acetylcholinesterase and apoptosis. FEBS Journal. 2008;275(4):612–7. doi:10.1111/j.1742-4658.2007.06236.x
20. Meldolesi J. Neurite outgrowth: this process, first discovered by Santiago Ramon y Cajal, is sustained by the exocytosis of two distinct types of vesicles. Brain Research Reviews. 2010;66(1–2):246–55. doi:10.1016/j.brainresrev.2010.06.004
21. Liu Z, Pan C, Huang H. The role of axon guidance molecules in the pathogenesis of epilepsy. Neural Regeneration Research. 2024;20(5):1244–57. doi:10.4103/nrr.nrr-d-23-01620
22. Stratton HJ, Khanna R. Sculpting dendritic spines during initiation and maintenance of neuropathic pain. Journal of Neuroscience. 2020;40(40):7578–89. doi:10.1523/JNEUROSCI.1664-20.2020
23. Bazan NG, Stark DT, Petasis NA. Lipid mediators. In: Elsevier eBooks. 2012. p. 643–62. doi:10.1016/B978-0-12-374947-5.00036-5
24. Rahman MdM, Islam MdR, Yamin Md, Islam MdM, Sarker MdT, Meem AFK, et al. Emerging role of neuron-glia in neurological disorders: at a glance. Oxidative Medicine and Cellular Longevity. 2022;2022:3201644. doi:10.1155/2022/3201644
25. 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
26. Colović MB, Krstić DZ, Lazarević-Pasti TD, Bondzić AM, Vasić VM. Acetylcholinesterase inhibitors: pharmacology and toxicology. Current Neuropharmacology. 2013;11(3):315–35. doi:10.2174/1570159X11311030006
27. Mushtaq G, Greig NN, Khan J, Kamal M. Status of acetylcholinesterase and butyrylcholinesterase in Alzheimer's disease and type 2 diabetes mellitus. CNS & Neurological Disorders – Drug Targets. 2014;13(8):1432–9. doi:10.2174/1871527313666141023141545
28. Atali S, Dorandish S, Devos J, Williams A, Price D, Taylor J, et al. Interaction of amyloid beta with humanin and acetylcholinesterase is modulated by ATP. FEBS Open Bio. 2020;10(12):2805–23. doi:10.1002/2211-5463.13023
29. Neto DCF, De Almeida JSFD, Guimarães SJA, Santos EMD, Nascimento MDDSB, De Azevedo-Santos APS, et al. Guanylhydrazone and semicarbazone derivatives as potential prototypes for the design of cholinesterase inhibitors against Alzheimer's disease: biological evaluation and molecular modeling studies. Chemico-Biological Interactions. 2025;111515. doi:10.1016/j.cbi.2025.111515
30. Fulda S, Gorman AM, Hori O, Samali A. Cellular stress responses: cell survival and cell death. International Journal of Cell Biology. 2010;2010:214074. doi:10.1155/2010/214074
31. BAX BCL2 associated X, apoptosis regulator [Homo sapiens (human)] – Gene – NCBI. Available from: https://www.ncbi.nlm.nih.gov/gene/581
32. Olufunmilayo EO, Gerke-Duncan MB, Holsinger RMD. Oxidative stress and antioxidants in neurodegenerative disorders. Antioxidants. 2023;12(2):517. doi:10.3390/antiox12020517

33. Kim ME, Lee JS. Mechanisms and emerging regulators of neuroinflammation: exploring new therapeutic strategies for neurological disorders. Current Issues in Molecular Biology. 2024;47(1):8. doi:10.3390/cimb47010008
34. Robb EL, Regina AC, Baker MB. Organophosphate toxicity. StatPearls – NCBI Bookshelf. 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470430/
35. 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
36. 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
37. Grabarczyk M, Justyńska W, Czpakowska J, Smolińska E, Bielenin A, Glabiński A, et al. Role of plant phytochemicals: resveratrol, curcumin, luteolin and quercetin in demyelination, neurodegeneration, and epilepsy. Antioxidants. 2024;13(11):1364. doi:10.3390/antiox13111364
38. Lim DW, Lee JE, Lee C, Kim YT. Natural products and their neuroprotective effects in degenerative brain diseases: a comprehensive review. International Journal of Molecular Sciences. 2024;25(20):11223. doi:10.3390/ijms252011223

CITE AS: Kirabo Nansubuga K. (2025). Acetylcholinesterase in Neuromodulation: Dual Roles in Synaptic Plasticity and Neurotoxicity. RESEARCH INVENTION JOURNAL OF RESEARCH IN MEDICAL SCIENCES 4(3):103-108. https://doi.org/10.59298/RIJRMS/2025/43103108