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Exploring How Acetylcholinesterase Influences Neural Signaling Beyond Neurotransmitter Hydrolysis and Its Paradoxical Role in Neurodegeneration

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ABSTRACT

Acetylcholinesterase (AChE) is traditionally known for its catalytic role in hydrolyzing acetylcholine at synaptic junctions, thereby terminating cholinergic signaling. However, emerging evidence suggests that AChE also participates in non-classical roles extending far beyond neurotransmitter clearance. These roles encompass cell adhesion, apoptosis modulation, neurite outgrowth, and participation in neuroinflammatory processes. Intriguingly, AChE displays paradoxical behavior in neurodegenerative diseases such as Alzheimer's and Parkinson's, where its overexpression and aberrant splicing variants contribute to neuronal damage despite the concurrent loss of cholinergic tone. This review explores the dualistic and complex role of AChE in the central nervous system (CNS), shedding light on its signaling roles beyond catalysis, the molecular basis of its neurotoxic versus neuroprotective profiles, and its therapeutic implications in managing neurodegeneration.

Keywords: Acetylcholinesterase, Non-classical signaling, Neurodegeneration, Synaptic plasticity, Cholinergic dysfunction

INTRODUCTION

Acetylcholinesterase (AChE) has long been established as a key enzymatic regulator of cholinergic neurotransmission through its role in catalyzing the hydrolysis of acetylcholine (ACh) [1]. This enzymatic activity ensures the rapid termination of synaptic transmission, thereby maintaining the temporal precision of cholinergic signaling within both central and peripheral nervous systems. However, recent research has dramatically expanded our understanding of AChE's functional repertoire [2]. It is now recognized that, beyond neurotransmitter degradation, AChE exerts non-classical, non-enzymatic roles that are crucial in neurodevelopment, cellular adhesion, synaptic plasticity, and the modulation of neuroinflammatory responses [1]. This expanded view has significant implications for our understanding of neurological diseases, particularly neurodegenerative disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS) [3].

AChE's non-classical roles are mediated by its ability to interact with a diverse array of molecular partners, including structural proteins, cell surface receptors, and signaling molecules [4]. These interactions allow AChE to function as a morphogenic factor during brain development and as a regulator of neurogenesis. Furthermore, AChE's non-catalytic activities are implicated in apoptosis regulation, stress responses, and glial-neuronal communication [5]. Notably, the expression of AChE can be dramatically upregulated in response to physiological stress, injury, and neuroinflammatory stimuli—contexts in which its role may shift from neuroprotection to neurotoxicity [6].

The dual role of AChE is acting as both a protector and a promoter of neural damage, has spurred considerable interest in its paradoxical function in neurodegenerative diseases. For instance, while inhibition of AChE enzymatic activity remains a mainstay in treating cognitive decline in AD, accumulating evidence suggests that certain AChE isoforms may accelerate pathological processes independently of their enzymatic role [1]. Consequently, a comprehensive understanding of both the classical and non-classical functions of AChE is vital to fully grasp its role in brain health and disease.

Molecular Isoforms and Localization of AChE

A key to understanding the multifunctionality of AChE lies in its isoforms, which arise from alternative mRNA splicing and differential post-translational modifications. The ACHE gene, located on chromosome 7q22, encodes several structurally and functionally distinct isoforms, the most well-characterized of which are AChE-S (synaptic), AChE-E (erythrocytic), and AChE-R (readthrough) [7]. These isoforms differ not only in their amino acid sequences and structural motifs but also in their cellular localization and physiological roles. The AChE-S isoform is predominant in the central nervous system and is tethered to the synaptic cleft via a proline-rich membrane anchor (PRiMA) [8]. This isoform is essential for the rapid clearance of ACh from the synaptic cleft and is tightly regulated to ensure signal fidelity in cholinergic transmission [8]. AChE-E, the erythrocytic form, lacks a membrane anchor and circulates freely, serving functions outside the nervous system, including roles in hematopoiesis and possibly peripheral immune modulation [9].

The most intriguing isoform in the context of neurodegeneration is AChE-R, a soluble, stress-inducible variant generated by readthrough of the stop codon in the ACHE gene. AChE-R is upregulated in response to oxidative stress, excitotoxicity, and injury, and has been implicated in promoting apoptosis and inflammation [6]. Unlike AChE-S, which localizes predominantly at the synapse, AChE-R can be found in the cytoplasm, nucleus, and extracellular space, suggesting broad functionality [1]. Subcellular localization of these isoforms is functionally significant. For instance, membrane-bound AChE variants may participate in synaptic remodeling, while soluble forms may act as paracrine or autocrine signaling agents [10]. The dynamic regulation of AChE isoform expression, particularly under stress or pathological conditions, underscores their potential roles in shaping the cellular response to injury and degeneration. This molecular diversity not only reflects the enzyme's evolutionary complexity but also poses challenges for therapeutic targeting, as inhibition of one isoform might exacerbate the harmful effects mediated by another.

AChE in Synaptic Plasticity and Neural Development

Beyond neurotransmitter hydrolysis, AChE plays critical roles in neuronal development, synaptogenesis, and plasticity processes fundamental to learning, memory, and repair [11]. These functions are largely independent of its catalytic activity and are instead mediated through protein-protein interactions and structural domains outside the active site. During embryogenesis and early postnatal brain development, AChE expression is temporally and spatially regulated to coordinate key neurodevelopmental events such as neural tube closure, cell migration, and the establishment of synaptic circuits [12]. It has been demonstrated that AChE promotes neurite outgrowth and axonal elongation through interactions with cell adhesion molecules and extracellular matrix proteins, such as laminins and heparan sulfates [13]. These interactions are thought to provide guidance cues and structural support for growing neurites.

Furthermore, AChE modulates sensitivity to neurotrophic factors such as nerve growth factor (NGF) [14]. It can influence NGF signaling pathways through non-catalytic binding to membrane receptors, thereby affecting neuronal survival and differentiation. AChE has also been shown to regulate intracellular calcium flux and cytoskeletal dynamics, processes integral to synaptic plasticity [15]. Studies using knock-in and knock-out models reveal that both overexpression and absence of AChE disrupt long-term potentiation (LTP) and long-term depression (LTD), synaptic phenomena that underlie memory consolidation and cognitive flexibility [16]. In adult brains, AChE continues to be involved in the fine-tuning of synaptic strength, particularly in cholinoceptive areas such as the hippocampus and prefrontal cortex [1]. Dysregulation of AChE in these regions has been implicated in age-related cognitive decline and neurodegenerative disease. Notably, alterations in AChE expression correlate with impairments in synaptic density and plasticity in Alzheimer's disease models, further highlighting the enzyme's central role in maintaining neural circuit integrity [17]. The developmental and plasticity-related roles of AChE present opportunities for regenerative therapies. Harnessing its neuritogenic and synaptogenic properties, without triggering its pro-apoptotic or inflammatory effects, could yield novel treatments for neurodevelopmental disorders and post-injury neural repair.

Paradoxical Role of AChE in Neurodegeneration

The role of acetylcholinesterase (AChE) in neurodegeneration presents a fascinating paradox. While its enzymatic function as degrading acetylcholine is essential for neuronal signaling, excessive or aberrant expression of AChE has been linked to neuronal dysfunction and degeneration, especially in conditions such as Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD) [18]. In these contexts, AChE does not merely exacerbate cholinergic deficits; it appears to directly participate in the pathogenesis of disease. In Alzheimer's disease, for instance, AChE has been shown to co-localize with amyloid-beta (Aβ) plaques, forming stable AChE-Aβ complexes that accelerate Aβ fibrillogenesis and promote neurotoxicity [19]. These hybrid complexes are more toxic than Aβ alone and enhance the oxidative stress and mitochondrial dysfunction that contribute to neuronal death [20]. This pathological interaction is facilitated by the peripheral anionic site of AChE, which binds to Aβ and other

hydrophobic molecules. Notably, this function is independent of AChE's catalytic site, underscoring the significance of its non-enzymatic actions in disease progression [20]. Moreover, the stress-inducible AChE-R isoform is upregulated in response to neurotoxic stimuli such as inflammation, oxidative damage, and ischemia [21]. This variant lacks the membrane anchor, allowing it to diffuse into different cellular compartments where it may exert pro-apoptotic effects. For example, AChE-R has been implicated in mitochondrial destabilization and the activation of intrinsic apoptotic pathways through interactions with cytochrome c and caspases [22]. Elevated AChE-R expression has been detected in degenerating neurons in both human brain samples and animal models of neurodegeneration, supporting its role as a marker and mediator of neuronal injury [6].

The paradox deepens when one considers that therapeutic AChE inhibitors, such as donepezil and rivastigmine, are used to treat symptoms of AD by prolonging acetylcholine availability. However, these drugs target the catalytic function of AChE and may have little to no impact, or could even exacerbate, the enzyme's non-catalytic, deleterious activities. Some studies suggest that chronic AChE inhibition may lead to compensatory upregulation of AChE expression, including the harmful AChE-R isoform [23]. This observation underscores the need for alternative therapeutic strategies that target the specific isoforms or domains of AChE responsible for neurotoxicity. Thus, the paradoxical role of AChE in neurodegeneration lies in its dualistic nature: it is both a vital enzyme for cholinergic signaling and a potential facilitator of neuronal injury through non-classical mechanisms. A deeper understanding of these dual roles is critical for designing next-generation therapies that can mitigate cognitive decline without promoting neurodegenerative processes.

AChE and Neuroinflammation: Linking Cholinergic Deficit to Immune Dysregulation

Neuroinflammation is a central component of neurodegenerative disease pathology, and recent research has identified acetylcholinesterase as a key player in modulating the neuroimmune environment [24]. While AChE is classically associated with neurons, its expression in glial cells, particularly microglia and astrocytes, has opened new avenues for understanding its role in immune regulation within the central nervous system [25]. Acetylcholine plays a significant anti-inflammatory role through its interaction with α7 nicotinic acetylcholine receptors (α7nAChRs) expressed on immune cells, including glial populations [26]. Activation of these receptors inhibits the release of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6), thus contributing to the "cholinergic anti-inflammatory pathway [27]." When AChE activity is upregulated, acetylcholine is rapidly degraded, resulting in decreased activation of α7nAChRs and a breakdown of this anti-inflammatory mechanism [1].

In neurodegenerative disorders, elevated AChE expression has been observed in regions of inflammation and gliosis. For example, reactive astrocytes in AD show increased levels of AChE, which correlate with higher levels of inflammatory markers and oxidative damage [28]. Similarly, in multiple sclerosis (MS), AChE levels rise during active demyelination, and experimental inhibition of AChE in animal models has been shown to reduce disease severity by dampening neuroinflammatory responses [29]. Moreover, AChE's role in neuroinflammation extends to its influence on blood-brain barrier (BBB) integrity. Chronic inflammation mediated by glial AChE overexpression can disrupt BBB function, allowing peripheral immune cells and cytokines to infiltrate the brain parenchyma [30]. This breach further exacerbates neural injury and propagates the cycle of inflammation and degeneration.

Interestingly, non-neuronal AChE is also found in circulating immune cells such as monocytes and lymphocytes [31]. These cells may act as peripheral amplifiers of neuroinflammation through altered ACh metabolism. AChE activity in these cells has been proposed as a biomarker for systemic inflammatory responses in neurodegenerative diseases, suggesting potential diagnostic and prognostic utility [31]. Collectively, these findings highlight that AChE is more than a neurotransmitter-degrading enzyme, it is a significant modulator of neuroimmune dynamics. Its overactivity contributes to the loss of cholinergic anti-inflammatory tone, promoting sustained microglial activation, cytokine overproduction, and neuronal damage. Therapeutic strategies that modulate AChE activity in immune cells or enhance cholinergic signaling may hold promise in mitigating neuroinflammation in chronic CNS disorders.

Therapeutic Implications and Future Perspectives

The therapeutic landscape for managing neurodegenerative diseases remains dominated by acetylcholinesterase inhibitors, which temporarily alleviate symptoms by increasing synaptic acetylcholine levels. However, these agents-donepezil, galantamine, and rivastigmine—do not address the multifaceted, non-enzymatic roles of AChE that contribute to neurodegeneration. As our understanding of AChE's paradoxical role deepens, it becomes evident that traditional enzyme inhibition is an incomplete approach. Future therapies must go beyond merely blocking the catalytic activity of AChE. One promising direction is the development of isoform-specific inhibitors that selectively target the deleterious AChE-R variant without affecting the physiological functions of AChE-S. Small molecules,

antisense oligonucleotides, or CRISPR-based gene editing tools could be employed to selectively suppress AChE-R expression or its pathological interactions, particularly with Aβ or pro-apoptotic proteins.

Another therapeutic avenue involves modulating AChE's non-enzymatic interactions, especially those involved in neurite outgrowth, cell adhesion, and inflammation. This may include designing peptides or synthetic ligands that competitively inhibit AChE's peripheral anionic site, thereby preventing its binding to Aβ and other pathological ligands. These compounds would ideally preserve ACh hydrolysis while neutralizing AChE's role in fibril formation and apoptosis. Additionally, immunotherapeutic strategies such as monoclonal antibodies against AChE isoforms or epitopes associated with neurotoxicity are under exploration. These agents could potentially neutralize the harmful forms of AChE in the brain and modulate disease progression more directly than enzyme inhibitors. Beyond pharmacological interventions, gene therapy and neuroprotective strategies aimed at enhancing cholinergic tone without over activating AChE may offer long-term benefits. For instance, increasing acetylcholine synthesis or stabilizing postsynaptic receptor activity might reduce the need for high AChE inhibition and lower the risk of adverse compensatory responses.

Ultimately, personalized medicine approaches incorporating biomarkers for AChE isoform expression, cholinergic tone, and inflammatory status will be essential in tailoring therapies. The future of AChE-targeted therapy lies in precision modulation-preserving its indispensable physiological roles while silencing its pathological expressions. As we refine our molecular understanding of AChE, it is likely to evolve from a symptom-relief target to a strategic node in neurodegenerative disease modification.

CONCLUSION

Acetylcholinesterase is no longer viewed merely as a neurotransmitter terminator but rather as a multifaceted modulator of neural architecture and health. Its influence on neural signaling extends beyond hydrolytic activity, embracing roles in neurodevelopment, inflammation, and neurodegeneration. Understanding the conditions under which AChE transitions from neuroprotective to neurotoxic is crucial in devising targeted interventions for neurodegenerative diseases.

REFERENCES

1. Trang A, Khandhar PB. Physiology, acetylcholinesterase. StatPearls – NCBI Bookshelf. 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK539735/
2. Zimmerman G, Soreq H. Termination and beyond: acetylcholinesterase as a modulator of synaptic transmission. Cell and Tissue Research. 2006;326(2):655–69. doi:10.1007/s00441-006-0239-8
3. De Tommaso M, Arendt-Nielsen L, Defrin R, Kunz M, Pickering G, Valeriani M. Pain in neurodegenerative disease: current knowledge and future perspectives. Behavioural Neurology. 2016;2016:1–14. doi:10.1155/2016/7576292
4. Silman I, Sussman JL. Acetylcholinesterase: 'classical' and 'non-classical' functions and pharmacology. Current Opinion in Pharmacology. 2005;5(3):293–302. doi:10.1016/j.coph.2005.01.014
5. Zhang XJ, Greenberg DS. Acetylcholinesterase involvement in apoptosis. Frontiers in Molecular Neuroscience. 2012;5:40. doi:10.3389/fnmol.2012.00040
6. 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
7. Xi H, Wu R, Liu J, Zhang L, Li Z. Role of acetylcholinesterase in lung cancer. Thoracic Cancer. 2015;6(4):390–8. doi:10.1111/1759-7714.12249
8. Xie HQ, Leung KW, Chen VP, Chan GKL, Xu SL, Guo AJY, et al. PRiMA directs a restricted localization of tetrameric AChE at synapses. Chemico-Biological Interactions. 2010;187(1–3):78–83. doi:10.1016/j.cbi.2010.02.018
9. Saldanha C. Human erythrocyte acetylcholinesterase in health and disease. Molecules. 2017;22(9):1499. doi:10.3390/molecules22091499
10. Grisaru D, Sternfeld M, Eldor A, Glick D, Soreq H. Structural roles of acetylcholinesterase variants in biology and pathology. European Journal of Biochemistry. 1999;264(3):672–86. doi:10.1046/j.1432-1327.1999.00693.x
11. 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
12. Silbereis JC, Pochareddy S, Zhu Y, Li M, Sestan N. The cellular and molecular landscapes of the developing human central nervous system. Neuron. 2016;89(2):248–68. doi:10.1016/j.neuron.2015.12.008
13. Paraoanu LE, Layer PG. Acetylcholinesterase in cell adhesion, neurite growth and network formation. FEBS Journal. 2008;275(4):618–24. doi:10.1111/j.1742-4658.2007.06237.x

14. Tanaka T, Okuda H, Isonishi A, Terada Y, Kitabatake M, Shinjo T, et al. Dermal macrophages set pain sensitivity by modulating the amount of tissue NGF through an SNX25–Nrf2 pathway. Nature Immunology. 2023;24(3):439–51. doi:10.1038/s41590-022-01418-5
15. Song Q, E S, Zhang Z, Liang Y. Neuroplasticity in the transition from acute to chronic pain. Neurotherapeutics. 2024;e00464. doi:10.1016/j.neurot.2024.e00464
16. Escobar ML, Derrick B. Long-term potentiation and depression as putative mechanisms for memory formation. Neural Plasticity and Memory – NCBI Bookshelf. 2007. Available from: https://www.ncbi.nlm.nih.gov/books/NBK3912/
17. Henstridge CM, Hyman BT, Spires-Jones TL. Beyond the neuron–cellular interactions early in Alzheimer disease pathogenesis. Nature Reviews Neuroscience. 2019;20(2):94–108. doi:10.1038/s41583-018-0113-1
18. 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;16:1347987. doi:10.3389/fnagi.2024.1347987
19. Carvajal FJ, Inestrosa NC. Interactions of AChE with Aβ aggregates in Alzheimer's brain: therapeutic relevance of IDN 5706. Frontiers in Molecular Neuroscience. 2011;4:19. doi:10.3389/fnmol.2011.00019
20. Chen JX, Du Yan S. Amyloid-β-induced mitochondrial dysfunction. Journal of Alzheimer's Disease. 2007;12(2):177–84. doi:10.3233/JAD-2007-12208
21. Fischer R, Maier O. Interrelation of oxidative stress and inflammation in neurodegenerative disease: role of TNF. Oxidative Medicine and Cellular Longevity. 2015;2015:610813. doi:10.1155/2015/610813
22. Cai J, Yang J, Jones Dean P. Mitochondrial control of apoptosis: the role of cytochrome c. Biochimica et Biophysica Acta (BBA) – Bioenergetics. 1998;1366(1–2):139–49. doi:10.1016/S0005-2728(98)00109-1
23. Singh R, Sadiq NM. Cholinesterase inhibitors. StatPearls – NCBI Bookshelf. 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK544336/
24. 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
25. Dash UC, Bhol NK, Swain SK, Samal RR, Nayak PK, Raina V, et al. Oxidative stress and inflammation in the pathogenesis of neurological disorders: mechanisms and implications. Acta Pharmaceutica Sinica B. 2024;15(1):15–34. doi:10.1016/j.apsb.2024.10.004
26. Keever KR, Yakubenko VP, Hoover DB. Neuroimmune nexus in the pathophysiology and therapy of inflammatory disorders: role of α7 nicotinic acetylcholine receptors. Pharmacological Research. 2023;191:106758. doi:10.1016/j.phrs.2023.106758
27. Chen L, Deng H, Cui H, Fang J, Zuo Z, Deng J, et al. Inflammatory responses and inflammation-associated diseases in organs. Oncotarget. 2017;9(6):7204–18. doi:10.18632/oncotarget.23208
28. Di Benedetto G, Burgaletto C, Bellanca CM, Munafò A, Bernardini R, Cantarella G. Role of microglia and astrocytes in Alzheimer's disease: from neuroinflammation to Ca^{2+} homeostasis dysregulation. Cells. 2022;11(17):2728. doi:10.3390/cells11172728
29. Procaccini C, De Rosa V, Pucino V, Formisano L, Matarese G. Animal models of multiple sclerosis. European Journal of Pharmacology. 2015;759:182–91. doi:10.1016/j.ejphar.2015.03.042
30. Mukhtar I. Inflammatory and immune mechanisms underlying epileptogenesis and epilepsy: from pathogenesis to treatment target. Seizure. 2020;82:65–79. doi:10.1016/j.seizure.2020.09.015
31. Fujii T, Mashimo M, Moriwaki Y, Misawa H, Ono S, Horiguchi K, et al. Physiological functions of the cholinergic system in immune cells. Journal of Pharmacological Sciences. 2017;134(1):1–21. doi:10.1016/j.jphs.2017.05.002

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