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Research Article

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Therapeutic Potential of Cell-Type-Specific Upregulation of the NMD Pathway in Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is a neurodegenerative disease characterized by the accumulation of amyloid plaques and neurofibrillary tangles. AD is rapidly growing, impacts millions worldwide, and is only expected to get worse in the coming years. Current research finds that neurodegenerative diseases, including AD, have selective neuronal vulnerability, meaning specific neurons are much more affected than others. In AD, this is the case for both cholinergic and glutamatergic neurons, with defects contributing to impaired cognition and behavior. Additionally, research has found that the upregulation of the nonsense-mediated mRNA decay (NMD) pathway has been shown to exert neuroprotective effects. Despite this understanding, current research in neurodegeneration has been entirely panneuronal, which may have unknown negative consequences or prove less effective than cell-type-specific approaches. Therefore, this article outlines the therapeutic impact of upregulating the NMD pathway in cell-type-specific cholinergic and glutamatergic neurons of AD, to showcase that cell-type-specific approaches to neurodegeneration may yield positive results compared to current panneuronal approaches. Ultimately, current research should establish whether a cell-type-specific approach to AD neurodegeneration outweighs the current panneuronal approach. If results are favorable, future research should expand this targeted avenue to other neurodegenerative diseases.

Keywords: Alzheimer's Disease, Cholinergic, Cell-Type-Specific, Glutamatergic, Neurodegeneration, Nonsense-Mediated mRNA Decay, Panneuronal, Selective Neuronal Vulnerability

1. Background

1.1. Alzheimer's Disease

Alzheimer's disease (AD) is the most common cause of dementia and is the biological process that begins with the appearance of a buildup of proteins in the form of amyloid plaques and neurofibrillary tangles in the brain [1]. Early symptoms of AD include forgetting recent events or conversations. However, over time, AD is much more serious, causing memory loss and affecting a person's ability to do everyday tasks. Additionally, there is no cure for AD, and in advanced stages, loss of brain function can cause dehydration, poor nutrition, or infection, potentially resulting in death. This neurodegenerative disease is also rapidly growing every year. Most notably, the incidence of AD and other dementias increased by 147.95% from 1990 to 2019 [2]. The U.S. alone has 6.9 million people aged 65 and older living with AD, and there are around 50 million AD patients worldwide, with this number projected to double every 5 years to reach 152 million by 2050. Overall, this burden affects individuals, their families, and the economy, with estimated global costs of US$1 trillion annually [3].

1.2. AD's Effect on Neurons

Neurons are constantly in touch with neighboring brain cells [4]. When a neuron receives signals from other neurons, it generates an electrical charge that travels down the length of its axon and releases neurotransmitter chemicals across a tiny gap called a synapse. In fact, scientists estimate that in the brain's communications network, one neuron may have as many as 7,000 synaptic connections with other neurons. The early loss of synaptic connections is a primary hallmark of cognitive decline associated with Alzheimer's disease. Alzheimer's damages the connections among neurons in parts of the brain involved in memory, including the entorhinal cortex and hippocampus. It later affects areas in the cerebral cortex responsible for language, reasoning, and social

behavior. This information indicates that AD differentially and specifically affects brain regions and neuronal cell types in a predictable pattern, suggesting that AD does not affect the entire brain [5].

More specifically, AD has a large impact on cholinergic and glutamatergic neurons. Basal forebrain cholinergic neurons constitute a major neuromodulatory system implicated in normal cognition and neurodegenerative dementias. Cholinergic projections densely innervate the neocortex, releasing acetylcholine to regulate arousal, attention, and learning. The severity of cognitive impairment in AD is correlated with the extent of deterioration of basal forebrain cholinergic neurons. Deficits in the cholinergic transmission can potentially influence all aspects of cognition and behavior, including cortical and hippocampal processing of information [6]. Disruption of cholinergic inputs to the cortex can impair attention and the use of instructive cues needed for decision-making related to ongoing behavior. Similar to cholinergic neurons, glutamatergic neurons are heavily affected by AD. Glutamate is the primary excitatory neurotransmitter acting on both ionotropic and metabotropic receptors [7]. It is at the crossroad between multiple metabolic pathways and plays an important role in the functions of learning and memory. The activity of glutamatergic neurons is compromised in AD due to the destruction of synapses and neuronal death, and their deficit can influence cortical and hippocampal processing.

1.3. AD's Effect on the Nonsense-Mediated mRNA Decay Pathway

Nonsense-mediated mRNA decay (NMD) is a translation-dependent mRNA surveillance mechanism in eukaryotes that helps to maintain the quality of gene expression [8]. NMD accelerates the degradation of aberrant mRNAs harboring a premature termination codon (PTC) and, in this capacity, is estimated to downregulate one-third of disease-causing mRNAs. Additionally, a 2022 study found that transgenic expression of disease-associated mutant human tau and wild-type human tau causes an overall deficit in NMD, and NMD-sensitive transcripts that evade clearance can be translated into protein, suggesting that tau-induced deficits in NMD are causally associated with neurodegeneration [9]. The same study also noted that there have been similar reports in yeast, rodent, fly, and human models of amyotrophic lateral sclerosis and frontotemporal dementia (ALS-FTD), suggesting an overlapping pathophysiology of tauopathies and ALS, a motor neuron disease involving RNA dysregulation.

2. Methodology

Articles from PubMed on AD and the NMD pathway were reviewed and summarized to ensure relevance and accuracy of this article.

3. Data

No data associated with this article.

4. Present Research

Neurodegenerative diseases, including AD, are prone to selective neuronal vulnerability, meaning only specific subsets of neurons are affected by the disease [10]. The selective loss of vulnerable neurons in early AD is more closely linked to tau pathology. Neurons that are vulnerable to the accumulation of pathological forms of tau and that are lost early in the disease mainly include large pyramidal neurons in layer II of the entorhinal cortex (EC), the subiculum, the CA1 region of the hippocampus, corticopetal cholinergic neurons in the basal forebrain, and noradrenergic neurons in the locus coeruleus. There are currently methods of distinguishing cell types, including single-cell RNA-seq and single-nuclei RNA-seq techniques, which have been successfully applied to identify microglia and to distinguish between different subtypes of excitatory and inhibitory neurons in human postmortem brain tissues based on their unique transcriptomics. However, the current ability to discriminate between neuronal subtypes is rudimentary. Despite limited approaches to identifying neuronal subtypes, research highlights the necessity of addressing cell-type-specific vulnerabilities in relation to neurodegenerative disease. Building on this idea, a recent study (2024) utilized mRNA expression levels that were subject to gray matter (GM) voxels in the standardized MNI brain space to estimate multiple canonical cell types using the Brain Cell type-Specific Gene Expression Analysis software (neuroimaging to map spatial distributions of brain cell types) [11]. The study demonstrated that cell-type spatial distributions can extensively predict tissue damage in AD alongside other neurodegenerative diseases. Although this line of research has increased our understanding of neuronal involvement in neurodegeneration, no studies have compared the therapeutic value of targeting neurons versus implementing panneuronal interventions.

Moreover, a major limitation in AD- and NMD-related research is the focus on panneuronal upregulation. A 2022 study found that mutant and wild-type forms of human tau limit NMD in the *Drosophila* brain, that genetic manipulation of NMD modifies tau-induced neuronal death, and that tau-induced deficits in NMD are amenable to pharmacological intervention [9]. Specifically, the study used the drug tranilast, a well-tolerated and low-toxicity drug that penetrates the blood-brain barrier, activates NMD, and suppresses tau-induced neurotoxicity in *Drosophila.* However, the mechanism of tranilast-induced NMD activation is unclear. Importantly, the study used the panneuronal driver *elav-Gal4* to activate *tau-UAS* (AD). However, research indicates that AD is selective, meaning research on targeted approaches to mitigating the effects of neurodegeneration is needed. Furthermore, the pharmacological use of tranilast in this study resulted in panneuronal NMD upregulation as indicated by the *elav-Gal4* crossed with the *UTR-UAS* (NMD reporter on the X chromosome). Additionally, a 2025 study used advanced imaging techniques and personalized brain simulations in mice to investigate how targeted brain interventions, such as lesions or temporary silencing of certain regions, reshape global brain connectivity [12]. It was found that local manipulations disrupted the brain's ability to sustain network-wide activity, leading to global functional connectivity (FC) reconfigurations. These results indicate that region-specific interventions can create unpredictable outcomes

comparable to those of whole-brain interventions. Collectively, this evidence suggests that current panneuronal approaches may produce unintended consequences, and future research should prioritize cell-type-specific approaches to neurodegeneration.

Pharmacological intervention in AD has also been widely investigated; however, similar to prior studies of NMD modulation, these approaches predominantly employ panneuronal therapeutic strategies. For example, cholinesterase inhibitors and memantine (donepezil, rivastigmine, galantamine, and memantine) increase neurotransmitter levels broadly across the brain, without distinguishing between healthy and selectively vulnerable neuronal populations [13]. Likewise, small-molecule interventions such as phenserine and memogain act on acetylcholinesterase-containing neurons throughout the brain rather than targeting specific affected regions or cell types implicated in AD pathology [14]. Additionally, nilvadipine, a calcium channel blocker administered orally, enters systemic circulation and subsequently reaches the brain globally, further reflecting a non-selective therapeutic approach [15]. Overall, these findings illustrate that current research has not established an effective therapeutic intervention that focuses on targeted approaches to mitigating the effects of AD, including targeted approaches to NMD upregulation [16-18].

5. Discussion

Current research highlights that the upregulation of the NMD pathway can reduce neurodegenerative effects. Additionally, research has used pharmacological activation (e.g., tranilast), which has been shown to improve NMD function. Despite these findings, no study has upregulated the NMD pathway in cell-type-specific neurons, including cholinergic and glutamatergic neurons, which are significantly degenerated in neurodegenerative diseases such as AD. Previous research has explored whole-brain prevention of AD and NMD regulation; however, cell-specific approaches to AD may slow down the progression of AD, minimizing its effect more significantly than current approaches. Additionally, due to the lack of understanding between panneuronal and cell-type-specific approaches, it is unclear whether current panneuronal interventions create unintended negative consequences. Moreover, since the neurophysiology of many neurodegenerative diseases is similar to that of AD, such as FTD or ALS, if future research shows that cell-type-specific approaches to AD are greater than panneuronal approaches, research should then move on to analyzing neurodegeneration through cell-type-specific interventions as a whole. Ultimately, upregulating the NMD pathway in cell-type-specific neurons could minimize the neurodegenerative effects of AD more than current panneuronal approaches, meaning future research should pursue cell-specific approaches to neurodegeneration. Future research should also investigate specific molecular components of the NMD pathway that mediate neuroprotective effects, and explore cell-type-specific delivery systems (genetic or viral), while also establishing potential risks to this approach. Overall, this potential avenue of neurodegeneration, from a clinical standpoint, may enhance therapeutic efficacy and reduce neurodegenerative progression.

Statement of Novelty

To the best of my knowledge, this is the first report on the therapeutic potential of cell-type-specific upregulation of the NMD pathway in AD and the importance of cell-type-specific approaches in neurodegeneration. This potential avenue for future research is derived from an analysis of the relationship between Alzheimer's disease and the NMD pathway, and how cell-type-specific upregulation could minimize the progression of AD far more effectively than current panneuronal approaches.

Credit Authorship Contribution Statement

Jacob Hoppa: Conceptualization, Methodology, Formal Analysis, Writing - Original Draft Preparation, Writing - Review and Editing.

Declaration of Competing Interest

The author declares that there were no competing interests that might have affected the work in this paper.

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