

RNA-Based Modification–Driven Synaptic Failure as an Early, Reversible Event in Alzheimer's Disease

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BACKGROUND

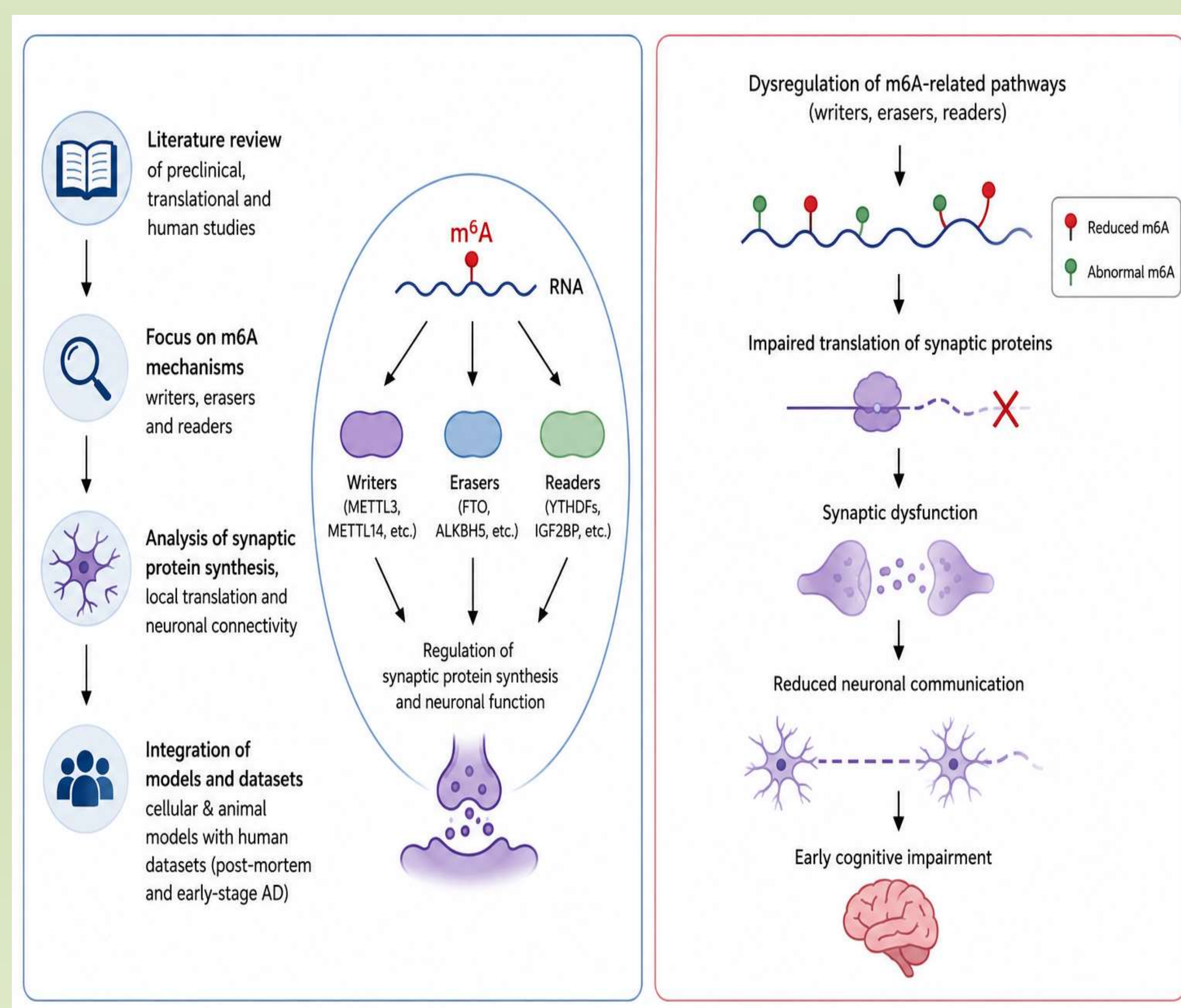
Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by synaptic dysfunction, cognitive decline, and neuronal loss. Emerging evidence indicates that synaptic impairment occurs before significant amyloid- β plaque deposition and tau pathology, making it a promising target for early therapeutic intervention. Recent advances in epitranscriptomics have identified RNA modifications, particularly N6-methyladenosine (m6A), as key regulators of neuronal development, synaptic plasticity, and local protein translation. Dysregulation of these RNA modifications may contribute to early synaptic dysfunction and cognitive impairment in AD. This review explores the role of RNA modification-mediated synaptic failure as an early and potentially reversible mechanism in Alzheimer's disease.

METHODS

A comprehensive literature review was conducted using peer-reviewed articles published in PubMed, Scopus, Web of Science, and Google Scholar. Studies investigating RNA epitranscriptomic modifications, particularly m6A methylation, in Alzheimer's disease were included. Experimental evidence from cellular and transgenic animal models, as well as human post-mortem brain tissues, was systematically analysed. Special emphasis was placed on the roles of RNA methyltransferases (METTL3/METTL14), demethylases (FTO and ALKBH5), and m6A reader proteins (YTHDF family) in regulating synaptic protein synthesis, dendritic spine maintenance, neuronal communication, and cognitive function.

RESULTS AND CONCLUSION

The collected evidence consistently demonstrates that dysregulation of m6A RNA modification pathways contributes significantly to early synaptic dysfunction in Alzheimer's disease. Altered expression of RNA methylation regulators disrupts activity-dependent protein translation, impairs dendritic spine formation, reduces synaptic plasticity, and weakens neuronal connectivity before extensive neuronal degeneration occurs. Several experimental studies reported that restoration of normal m6A signaling through genetic or pharmacological modulation partially rescued synaptic protein expression, improved synaptic integrity, and enhanced cognitive performance in preclinical AD models. These findings suggest that RNA modification abnormalities represent an early, reversible pathological event preceding irreversible neurodegeneration.



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