

Neurometabolic Reprogramming in Alzheimer's Disease: Emerging Insights into Metabolic Dysfunction and Therapeutic Opportunities

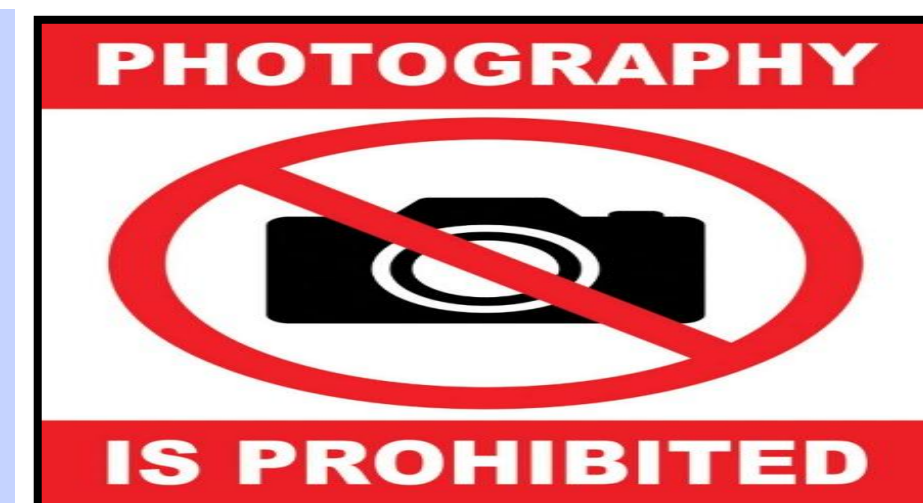
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Take Home Message

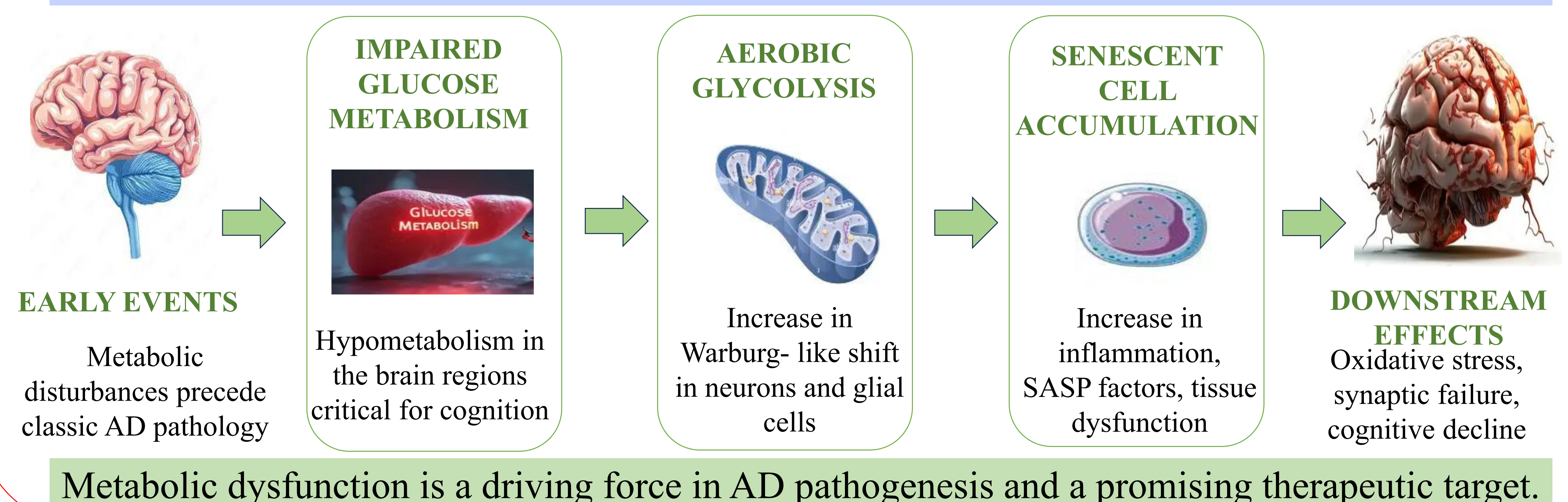
Targeting metabolic dysfunction early, alongside established amyloid- centered approaches, may open a new window for slowing or modifying Alzheimer's disease progression.



INTRODUCTION

- Neurometabolic reprogramming offers a powerful framework for understanding Alzheimer's disease (AD), positioning metabolic dysfunction as a fundamental driver of pathogenesis.
- Disruptions in cerebral glucose metabolism and accumulation of senescent cells emerge early in AD, potentially laying the groundwork for classical amyloid pathology.
- These findings highlight the importance of metabolic disturbances as both early biomarkers and promising therapeutic targets.

NEUROMETABOLIC DYSFUNCTION IN ALZHEIMER'S DISEASE



METHODS

- Synthesized current evidence on metabolic dysregulation in AD, focusing on impaired glucose metabolism, aerobic glycolysis, and cellular senescence.
- Reviewed clinical and experimental studies covering oxidative stress, the microbiota-gut-brain axis, metal ion dysregulation, and aberrant autophagy across AD progression.
- Explored therapeutic strategies targeting metabolic imbalances, including dietary interventions and pharmacological modulation, grounded in contemporary research findings.

RESULTS

- Neurometabolic dysfunction in AD involves impaired glucose utilization, oxidative stress, gut-brain axis disruption, and altered cellular pathways, contributing to neuronal decline.
- Early metabolic alterations before amyloid- β deposition provide potential targets for therapeutic intervention.

TABLE:1. THERAPEUTIC OPPORTUNITIES

STRATEGY	ACTION/ROLE IN AD	REFERENCE
INSULIN SENSITIZERS	Restore glucose metabolism and improve neuronal energy balance	Song, M., et al. (2023). Systemic metabolism and mitochondria in the mechanism and treatment of Alzheimer's disease. International Journal of Molecular Sciences, 24(9), 8398.
KETONE-BASED THERAPY	Provides alternative brain fuel and supports mitochondrial function	Neth, B.J, et al. (2024). Consuming a modified mediterranean ketogenic diet alters the plasma lipidome in Alzheimer's disease. Communications Medicine, 4, Article 67
MITOCHONDRIAL ANTIOXIDANTS	Reduce oxidative stress, mitochondrial dysfunction and neuronal damage	Sousa, T., et al. (2023). Current advances in mitochondrial targeted interventions in Alzheimer's disease. Antioxidants, 12(6), 1250
ANTI- INFLAMMATORY THERAPY	Control microglial activation and neuroinflammation	Jurcău, M. C., et al. (2022). The link between oxidative stress, mitochondrial dysfunction and neuroinflammation in Alzheimer's disease. Antioxidants, 11(11), 2167
LIFESTYLE MODIFICATION	Improves metabolic health and slow cognitive decline	Nagpal, D., et al. (2025). Management and prevention of neurodegenerative disorders. Antioxidants, 14(9),1078

CONCLUSION

Neurometabolic reprogramming highlights metabolic dysfunction as an early feature of AD. Targeting metabolic pathways offers promising therapeutic strategies to slow disease progression and improve outcomes.

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