Metabolism and Translational Medicine

MINI REVIEW

Metabolic biomarkers for Alzheimer's disease: A mini review

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ABSTRACT

Alzheimer's disease (AD) is the most common neurodegenerative disorder and a leading cause of dementia worldwide, which characterized by progressive cognitive decline, memory impairment, and changes in behavior and personality. The prevalence of AD is expected to rise significantly in the coming decades due to the aging population, making it a major public health concern. Mounting evidence suggests that metabolic dysregulation plays a critical role in the pathogenesis of AD. In this mini review, we provide an overview of the current understanding of the interplay between metabolism and AD. Specifically, we explore the dysregulation of glucose metabolism, lipid metabolism, amino acid metabolism, and nitrogen oxide synthesis pathways in AD. These metabolic alterations have been identified as potential biomarkers for early diagnosis and prognosis of AD. Additionally, we discuss the current status of research in this field, including the advancements in metabolomics and imaging techniques that have allowed for the identification and validation of metabolic biomarkers.

Key words: Alzheimer's disease, glucose metabolism, lipid metabolism, amino metabolism, metabolic biomarkers

INTRODUCTION

Alzheimer's disease (AD) is a devastating neurodegenerative disorder characterized by progressive cognitive decline and memory impairment. It is the most common cause of dementia, affecting millions of people worldwide.[1] The etiology of AD is complex and multifactorial, involving a combination of genetic, environmental, and lifestyle factors. While the amyloid-beta (Aβ) plaques and neurofibrillary tangles composed of tau protein are well-known pathological hallmarks of AD, emerging evidence suggests that metabolic dysregulation plays a crucial role in the disease progression.[2,3] Growing research indicates that disturbances in metabolism, including glucose metabolism, lipid metabolism, amino acid metabolism, and nitrogen oxide synthesis pathways, contribute to the pathophysiology of AD. Understanding the metabolic alterations associated with AD provides valuable insights into disease mechanisms and potential therapeutic targets. Metabolic biomarkers hold promise for early detection, diagnosis, and monitoring of AD progression. Advances in metabolomics and imaging techniques have enabled the identification and validation of specific metabolic signatures associated with AD. Furthermore, targeting metabolic pathways may offer novel strategies for disease-modifying treatments. In this mini review, we will explore the current understanding of the relationship between metabolism and AD and discuss the potential implications for diagnosis and treatment.

CURRENT STATUS

In recent years, there has been growing interest in exploring the link between metabolism and AD. Numerous studies have shed light on the alterations in

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Received: 12 July 2023; Revised: 18 September 2023; Accepted: 25 September 2023; Published: 27 October 2023
https://doi.org/10.54844/mtm.2023.0409

various metabolic pathways observed in individuals with AD, highlighting their potential role in disease progression. Herein, we provide an overview of the current status of research on metabolism in AD.

One of the prominent metabolic dysregulations observed in AD is the impairment of glucose metabolism. Positron emission tomography (PET) imaging studies consistently demonstrate reduced glucose uptake and metabolism in specific brain regions of AD patients, indicating compromised energy utilization. The dysfunction of glucose metabolism is believed to arise from insulin resistance and deficiencies in insulin signaling pathways within the brain. Insulin resistance hampers the neurons' ability to effectively utilize glucose, resulting in energy deficits and impaired neuronal function. Moreover, abnormal glucose metabolism plays a critical role in the pathophysiological changes of AD by inducing various pathogenic factors, such as oxidative stress and mitochondrial dysfunction. These cascading effects contribute to neuronal degeneration and cognitive impairment in individuals with AD.[4,5]

Extensive research has revealed the multifaceted interplay between lipid metabolism and key pathological mechanisms underlying AD, including amyloidosis, bioenergetic deficits, oxidative stress, neuroinflammation, and myelin dysfunction. Dysregulation of lipid metabolism has been implicated in AD pathology, manifesting in alterations in cholesterol metabolism, fatty acid metabolism, and lipid transport. Accumulation of cholesterol and lipid metabolites, such as ceramides and sphingolipids, has been associated with neurotoxicity and the formation of Aβ plaques. Additionally, lipids play a crucial role in maintaining the integrity and fluidity of cell membranes, and disruptions in lipid metabolism can impact neuronal function and survival.[6] The apolipoprotein E (APOE) ε4 allele remains the strongest genetic risk factor for sporadic AD, whereas the APOE ε2 allele confers the strongest genetic protective effect. Our understanding of the pathogenic mechanisms involving APOE has expanded beyond the Aβ peptide-centric mechanisms to include tau neurofibrillary degeneration, microglial and astrocytic responses, and disruption of the blood-brain barrier. These findings highlight the intricate involvement of lipid metabolism and APOE in AD pathogenesis, shedding light on novel therapeutic targets and strategies for disease intervention.[7]

Amino acid metabolism has emerged as a key contributor to the pathogenesis of AD. Dysregulation of amino acid metabolism can profoundly impact neurotransmitter synthesis, oxidative stress, and protein homeostasis, all of which play crucial roles in the development of AD. The dysfunction of N-methyl-D-aspartate receptors (NMDARs), responsible for maintaining neuronal excitability and preventing neurotoxicity, has been strongly linked to AD. Memantine, a widely used NMDAR antagonist in AD treatment, modulates NMDAR activity to reduce glutamate-mediated neurotoxicity and improve AD symptoms.[8] Additionally, elevated levels of d-serine, an atypical amino acid, have been observed in the serum of AD patients, suggesting its potential involvement in AD pathogenesis and neurodegenerative processes. Branched-chain amino acids (BCAAs) play critical roles in normal brain function, particularly in signal transduction, nitrogen homeostasis, and neurotransmitter cycling. Disruption of BCAA metabolism in astrocytes has been implicated in neurotransmitter and energy imbalances in the AD brain.[9] Furthermore, studies have revealed close associations between tryptophan, iron metabolism, carbon metabolism, ribonucleic acid (RNA) metabolism, and AD (Table 1).[10–13]

The current status of research indicates a strong association between metabolic dysregulation and AD. Glucose metabolism dysfunction, lipid metabolism alterations, amino acid imbalances, and disturbances in other metabolism have all been implicated in AD pathogenesis. However, further research is needed to unravel the complex interplay between metabolism and AD and to identify potential therapeutic targets. Understanding the metabolic changes in AD may provide valuable insights into disease mechanisms and pave the way for the development of novel diagnostic and therapeutic strategies.

FUTURE DIRECTIONS

The field of metabolic research in AD is advancing rapidly, opening up promising avenues for further investigation. To deepen our understanding of metabolic alterations in AD and their therapeutic implications, several future directions deserve attention. Firstly, longitudinal studies are crucial to unravel the temporal sequence of metabolic changes in AD. By observing how these alterations evolve over time and their correlation with disease progression, researchers can gain valuable insights into the early stages of AD and potentially identify metabolic markers for early diagnosis. Secondly, examining the interconnectedness of different metabolic pathways is vital. Metabolism forms a complex network, where changes in one pathway can impact others. Integrated omics approaches, such as metabolomics and proteomics, hold promise in uncovering these interconnected pathways and identifying key molecular targets. Thirdly, elucidating the mechanisms underlying metabolic alterations is pivotal for developing targeted therapeutic

Table 1: Overview of metabolic pathways implicated in Alzheimer's disease

Metabolic pathway	Relationship with Alzheimer's disease
Glucose metabolism	Impaired brain glucose utilization, insulin resistance, energy deficits, oxidative stress
Lipid metabolism	Dysregulated cholesterol metabolism, altered fatty acid metabolism, impaired lipid transport
Amino acid metabolism	Disrupted glutamate metabolism, elevated D-serine, impaired BCAA metabolism
Other metabolism	Disrupted iron metabolism, altered carbon metabolism, impaired RNA metabolism, reduced NOS activity

BCAA: branched-chain amino acids; RNA: ribonucleic acid; NOS: nitric oxide synthase.

strategies. Modulating key metabolic pathways, such as enhancing glucose utilization, restoring lipid homeostasis, and regulating amino acid metabolism, may offer potential interventions. Exploring how lifestyle factors, including diet and exercise, modulate metabolism and their impact on AD risk and progression, is an important area for future investigation. Finally, non-invasive biomarkers that reliably measure metabolic alterations in AD are essential for early diagnosis and treatment monitoring. Imaging techniques like PET and magnet resonance imaging (MRI), combined with advanced metabolomic profiling, show promise in identifying metabolic signatures associated with AD. These biomarkers can aid in early detection, disease progression monitoring, and evaluating therapeutic efficacy.

In conclusion, future research in the field of metabolic alterations in AD should prioritize longitudinal studies, understanding the interplay between metabolic pathways, elucidating underlying mechanisms, developing targeted therapies, and identifying non-invasive biomarkers. These efforts will contribute to a better understanding of AD pathogenesis, enable early diagnosis, and facilitate the development of effective treatments to mitigate the impact of metabolic dysregulation in AD.

CONCLUSION

In conclusion, the relationship between metabolic alterations and AD is a complex and dynamic field of research. These metabolic changes not only impact energy production and neuronal function but also contribute to neuroinflammation and the accumulation of Aβ and tau proteins. While our understanding of the metabolic alterations in AD has significantly advanced, there is still much to uncover. Further research is needed to elucidate the underlying mechanisms, identify early diagnostic markers, and develop targeted therapeutic interventions. Longitudinal studies, integrated omics approaches, and the exploration of lifestyle factors hold promise in deepening our knowledge of metabolic dysregulation in AD. Additionally, the development of non-invasive biomarkers will be crucial for early detection and monitoring of disease progression.

Overall, a comprehensive understanding of metabolic alterations in AD will provide valuable insights into disease mechanisms, facilitate early diagnosis, and guide the development of effective treatments. By targeting metabolic pathways, we may ultimately be able to slow down or prevent the progression of AD and improve the quality of life for individuals affected by this devastating neurodegenerative disorder.

DECLARATIONS

Author contributions

Bai CB: Conceptualization, Data curation, Methodology, Software, Validation, Formal analysis, Investigation, Writing—Original draft, Writing—Review and Editing. Yuan JL: Conceptualization, Writing—Review and Editing, Visualization, Supervision, Project administration, and Funding acquisition. All authors have read and approve the final manuscript.

Source of funding

This study was supported by the National Natural Science Foundation of China (No. 82071552).

Ethical approval

Not applicable.

Conflict of interest

The author has no conflicts of interest to declare.

Data sharing

No additional data.

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