REVIEW ARTICLE

CONTENTS

Emerging therapeutic targets beyond amyloid and tau in Alzheimer's Disease: Implications for lifestyle, metabolism and preventive medicine

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ABSTRACT

Alzheimer's disease (AD) is the leading cause of dementia and remains a major global health challenge. Although current disease-modifying therapies primarily target amyloid-β and tau pathology, their clinical efficacy is limited. Increasing evidence indicates that AD is a multifactorial disorder involving neuroinflammation, mitochondrial dysfunction, impaired autophagy-lysosomal pathways, and dysregulated lipid metabolism. These interconnected mechanisms contribute to disease progression and represent promising therapeutic targets. This narrative review summarizes current evidence on emerging treatment strategies beyond the classical amyloid and tau paradigm, with particular emphasis on microglial activation, mitochondrial function, autophagy, and lipid homeostasis. Additionally, the translational potential of lifestyle-based interventions, including physical activity and metabolic regulation, is discussed. A broader understanding of AD pathogenesis may support the development of integrated therapeutic approaches combining pharmacological and non-pharmacological strategies to improve clinical outcomes.

KEYWORDS: Alzheimer's disease, neuroinflammation, microglia, metabolism, physical activity, prevention

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INTRODUCTION

Alzheimer's disease (AD) is one of the most prevalent neurodegenerative disorders. The underlying pathological process is characterized by a progressive and irreversible disruption of cellular homeostasis, leading to gradual neuronal dysfunction and death. These changes are associated with the accumulation of amyloid-β deposits, the formation of neurofibrillary tangles composed of hyperphosphorylated tau protein, and disturbances in calcium (Ca^{2+}) homeostasis. Neuronal loss is further promoted by neuroinflammatory mechanisms, including phagocytic activity and the release of inflammatory mediators such as cytokines, reactive oxygen species, and nitric oxide.

The persistent activation of microglia and astrocytes contributes to neuronal apoptosis and impairment of the blood–brain barrier integrity. Consequently, these alterations facilitate the infiltration of peripheral immune cells into the central nervous system, enhancing and sustaining the local inflammatory response. Dysregulation of inflammatory control mechanisms ultimately contributes to impaired brain function and widespread neurodegeneration [1].

Despite extensive research efforts, therapeutic strategies targeting the classical pathological hallmarks of AD have demonstrated limited clinical efficacy [2]. Recent comprehensive studies indicate that AD pathogenesis involves a complex network of interacting mechanisms extending beyond amyloid and tau pathology [3]. Therefore, AD is increasingly recognized as a multifactorial and systemic disorder involving the interplay of neuroinflammation, metabolic disturbances, mitochondrial dysfunction, and lipid metabolism abnormalities [4-6].

AIM

The aim of this review is to analyze emerging therapeutic targets in Alzheimer's disease beyond the classical amyloid and tau paradigm, with particular emphasis on their translational relevance and potential integration with lifestyle-based and preventive strategies.

MATERIALS AND METHODS

A narrative literature review was conducted using the PubMed, Scopus, Web of Science, and Google Scholar databases. Articles published between 2008 and 2024 were considered, with priority given to systematic reviews, meta-analyses, and high-impact original research studies.

The search strategy included the following keywords and terms: Alzheimer's disease, neuroinflammation, microglia, mitochondrial dysfunction, autophagy, lipid metabolism, and emerging therapies. Only articles published in English were included.

The review was performed in accordance with established methodological principles for narrative literature reviews.

REVIEW

ALZHEIMER'S DISEASE AS A NETWORK DISORDER

Although amyloid-β (Aβ) and tau pathology remain central components of the classical model of Alzheimer's disease (AD), these mechanisms alone do not fully explain disease progression or the limited efficacy of current therapeutic approaches [2,7]. Increasing evidence supports the concept of AD as a network disorder involving multiple interacting biological systems and pathological pathways [4-6].

AD may be considered not solely as a disease of the brain, but as a progressive system-level disorder associated with chronic network stress and disruption of homeostatic mechanisms. Such disturbances may arise from various endogenous and exogenous factors, including chronic inflammatory states, infections, vascular dysfunction, traumatic brain injury, environmental toxicity, and immune dysregulation. Regardless of whether the initiating factors originate within the central nervous system (CNS) or in peripheral tissues, chronic stress, inflammation, and toxic stimuli can be transmitted to the CNS through humoral and neural pathways. These processes may preferentially affect highly interconnected regulatory regions and neuronal circuits, eventually contributing to the development of neurodegenerative changes [8].

NEUROINFLAMMATION AND MICROGLIAL DYSFUNCTION

According to the hypothesis proposed by Krstic and Knuesel [9], neuroinflammation may represent a primary mechanism underlying AD pathogenesis, resulting from excessive activation of astrocytes and microglia. Supporting evidence for this concept has been provided by epidemiological studies suggesting a potential protective effect of non-steroidal anti-inflammatory drugs (NSAIDs) [10]. However, this hypothesis has not been confirmed in randomized clinical trials, meta-analyses, or clinical studies involving AD patients. Nevertheless, ibuprofen, a cyclooxygenase inhibitor and peroxisome proliferator-activated receptor gamma (PPAR-γ) agonist, is currently being investigated in combination with cromolyn, an anti-allergic agent that inhibits mast cell degranulation [11].

Chronic inflammation, metabolic disturbances, hormonal alterations, and immune dysregulation are common features of numerous chronic diseases affecting the CNS, including AD. Recent studies indicate that chronic inflammation, whether originating centrally or peripherally, may act both as a cause and a consequence of progressive disturbances in homeostatic regulation and physiological processes underlying complex diseases [12-15].

Neuroinflammation is considered a major contributor to AD pathogenesis. Microglia exhibit both neuroprotective and neurotoxic properties depending on their activation state and the surrounding microenvironment [16,17]. Genetic studies have identified triggering receptor expressed on myeloid cells 2 (TREM2) and CD33 as important regulators of microglial function and AD susceptibility [18,19]. These discoveries have stimulated the development of therapeutic strategies aimed at modifying microglial activity and restoring immune balance rather than completely inhibiting inflammatory responses [20]. Consequently, neuroinflammation, particularly microglial dysregulation, remains one of the most important mechanisms contributing to disease progression [21].

MITOCHONDRIAL DYSFUNCTION AND METABOLIC ALTERATIONS

Mitochondria are essential cellular organelles involved in ATP production, regulation of apoptosis, calcium homeostasis, and iron metabolism. Due to their high energy requirements and limited regenerative capacity, neurons are particularly dependent on efficient mitochondrial function.

Numerous studies have demonstrated that mitochondrial dysfunction represents an important pathological feature of AD. Metabolic impairment appears early during disease development and contributes to increased neuronal vulnerability [22,23]. Mitochondrial abnormalities result in decreased energy production, impaired cellular metabolism, and enhanced oxidative stress [22]. Furthermore, accumulating evidence indicates bidirectional interactions between mitochondrial dysfunction and pathological protein aggregation.

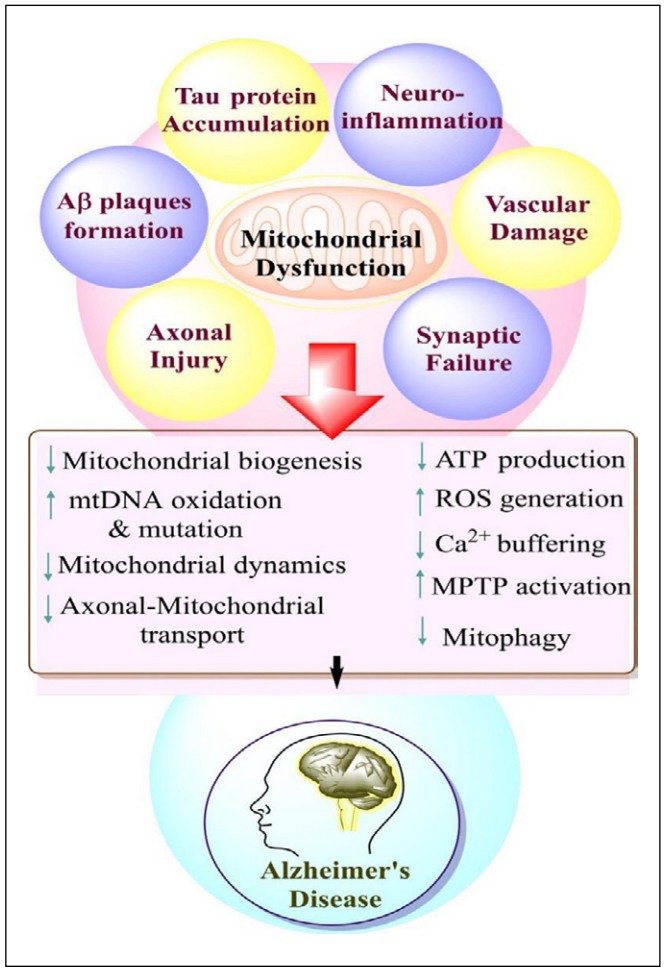

Figure 1. Bhatia S, Rawal R, Sharma P, Singh T, Singh M, Singh V. Mitochondrial Dysfunction in Alzheimer's Disease: Opportunities for Drug Development. Current neuropharmacology, 2022;20(4):675–692. https://pubmed.ncbi.nlm.nih.gov/33998995/ [29]

While impaired mitochondrial activity may promote the accumulation of toxic protein species, restoration of mitochondrial function may potentially reduce these pathological processes. Therefore, elucidating the relationship between mitochondrial bioenergetics and classical AD-related pathways is essential for the identification of novel therapeutic approaches [24].

Experimental studies investigating the association between mitochondrial DNA (mtDNA) alterations and AD have provided important insights into disease mechanisms. In one experimental model, Ntera2D1 (NT2) cells depleted of endogenous mtDNA and repopulated with platelet-derived mtDNA obtained from AD patients demonstrated reduced cytochrome c oxidase activity, increased production of reactive oxygen species (ROS), and enhanced activation of antioxidant defense mechanisms. These findings suggest that mtDNA alterations may contribute to mitochondrial dysfunction and oxidative stress in AD [25].

Additionally, mtDNA deletions have been associated with increased expression of cell cycle arrest-related proteins, including p21 and p53, together with further impairment of cytochrome c oxidase activity, ultimately promoting ROS-mediated neuronal injury [26]. Mitochondrial dysfunction also contributes to amyloid pathology, as increased oxidative stress and ROS generation may enhance amyloid precursor protein (APP) processing, resulting in increased production and accumulation of amyloid-β (Aβ) [27].

Therapeutic strategies targeting mitochondrial pathways and metabolic regulation are currently under active investigation as potential approaches for modifying AD progression [23, 28].

AUTOPHAGY AND PROTEIN CLEARANCE

Dysregulation of autophagy is increasingly recognized as an important contributor to Alzheimer's disease (AD) progression. The accumulation of pathological proteins in AD results not only from their increased production but also from impaired mechanisms of cellular clearance [30,31]. The autophagy–lysosomal system plays a crucial role in the removal of misfolded proteins and damaged cellular organelles, thereby maintaining neuronal homeostasis.

In AD, impairment of autophagic flux, lysosomal dysfunction, and reduced degradative capacity contribute to the accumulation of amyloid-β (Aβ) and hyperphosphorylated tau within neurons, promoting cellular toxicity and neuronal loss. Studies have demonstrated abnormal accumulation of autophagic vacuoles in dystrophic neurites of AD brains, suggesting a defect in efficient clearance mechanisms rather than excessive initiation of autophagy. Moreover, impaired lysosomal acidification disrupts enzymatic degradation processes and further promotes pathological protein aggregation [31].

Importantly, autophagy dysfunction is closely interconnected with other major pathological mechanisms of AD. Oxidative stress and mitochondrial dysfunction may impair autophagic pathways, while accumulated protein aggregates can further compromise lysosomal function, creating a self-perpetuating cycle of neuronal injury.

Current therapeutic approaches aim to enhance autophagic activity and restore lysosomal homeostasis. Pharmacological modulation of pathways involving mechanistic target of rapamycin (mTOR), transcription factor EB (TFEB), and lysosomal biogenesis is under investigation as a potential disease-modifying strategy. Therefore, regulation of autophagy may represent a promising therapeutic direction for reducing pathological protein accumulation and preserving neuronal function in AD.

LIPID METABOLISM AND APOE

Disruption of lipid metabolism represents an important component of AD pathogenesis. The apolipoprotein E (APOE) ε4 allele is the strongest genetic risk factor associated with late-onset AD and plays a critical role in lipid transport, cholesterol metabolism, and neuronal homeostasis [32].

APOE participates in lipid trafficking, neuronal repair mechanisms, and maintenance of synaptic integrity. The ε4 isoform has been associated with impaired lipid transport, reduced synaptic plasticity, and increased amyloid-β (Aβ) aggregation [32]. Alterations in cholesterol homeostasis may influence amyloid precursor protein (APP) processing by promoting amyloidogenic pathways. Furthermore, changes in neuronal membrane lipid raft composition can affect the activity of secretases involved in Aβ generation.

Lipid abnormalities also contribute to neuroinflammatory processes. Disturbed lipid signaling may activate microglia and astrocytes, resulting in increased production of pro-inflammatory mediators. In addition, alterations in phospholipid and sphingolipid metabolism have been associated with synaptic dysfunction and progressive neuronal degeneration.

Therapeutic strategies aimed at restoring lipid homeostasis, including modulation of cholesterol metabolism, APOE-associated pathways, and lipid signaling networks, may provide multidimensional benefits and represent potential approaches for slowing AD progression [33].

RECEPTOR-MEDIATED PATHWAYS

Receptor-mediated mechanisms contribute significantly to AD-related pathology. The receptor for advanced glycation end products (RAGE) is involved in oxidative stress induction, neuroinflammatory signaling, and the transport of amyloid-β across the blood–brain barrier [34].

In addition to receptor-mediated mechanisms, systemic factors such as vascular dysfunction, chronic inflammation, and peripheral metabolic disturbances may influence disease progression [5]. These observations further support the concept of AD as a complex systemic disorder involving interactions between central nervous system mechanisms and peripheral physiological processes.

DISCUSSION

The limited clinical efficacy of amyloid-targeting therapies has emphasized the need for a more comprehensive understanding of Alzheimer's disease (AD) pathogenesis [2]. Current evidence supports a multifactorial model in which several interconnected pathological processes contribute to disease initiation and progression rather than a single dominant mechanism [4,5].

Neuroinflammation and microglial dysfunction are increasingly recognized as key contributors to AD pathophysiology. However, microglial activation represents a complex process that may exert both neuroprotective and neurotoxic effects depending on the cellular environment, disease stage, and specific molecular pathways involved [16,17]. Therefore, therapeutic strategies aimed at restoring immune balance may be more beneficial than complete suppression of inflammatory responses.

Similarly, metabolic disturbances and mitochondrial dysfunction are closely associated with neuronal vulnerability and disease progression. Impaired mitochondrial bioenergetics, increased oxidative stress, and altered cellular metabolism may interact with classical AD-related mechanisms, contributing to progressive neuronal dysfunction and degeneration [22,23].

Defects in protein clearance pathways further promote the accumulation of toxic aggregates and amplify pathological processes. Dysfunction of the autophagy–lysosomal system, together with impaired removal of amyloid-β and tau species, represents an important mechanism linking intracellular homeostasis disruption with neuronal injury [30,31]. In addition, lipid metabolism abnormalities and APOE-associated pathways contribute to disease complexity by influencing amyloid processing, synaptic function, and neuroinflammatory responses [32].

Collectively, these findings support the development of multi-target therapeutic approaches capable of addressing several interconnected pathological mechanisms simultaneously. Such strategies may include modulation of neuroinflammation, restoration of metabolic and mitochondrial function, enhancement of protein clearance pathways, and correction of lipid homeostasis disturbances.

Moreover, non-pharmacological interventions, including regular physical activity, may influence multiple disease-related mechanisms by improving metabolic regulation, reducing inflammatory responses, and supporting mitochondrial function. These observations highlight the importance of integrated approaches that combine pharmacological and lifestyle-based strategies in future AD prevention and treatment.

CONCLUSIONS

The traditional view of Alzheimer's disease (AD) as a disorder primarily driven by amyloid-β and tau pathology is gradually evolving toward a broader concept

of AD as a complex, multifactorial disease involving multiple interconnected biological systems. Current evidence indicates that neuroinflammation, metabolic disturbances, impaired protein clearance mechanisms, mitochondrial dysfunction, and lipid dysregulation represent important contributors to disease progression.

This expanded understanding of AD pathophysiology has important implications for therapeutic development. Given the network-based nature of the disease, interventions targeting a single pathological pathway may have limited efficacy, particularly during advanced stages of neurodegeneration. Future therapeutic strategies should therefore focus on integrated, multi-target approaches aimed at modulating several disease-related mechanisms simultaneously.

Further research should prioritize personalized therapeutic models that combine molecular biomarkers, clinical characteristics, and lifestyle-related factors to optimize prevention strategies and improve individualized patient outcomes.

PRACTICAL IMPLICATIONS

The recognition of AD as a multifactorial disorder has important implications for clinical practice, preventive medicine, and health promotion, emphasizing the need for interdisciplinary cooperation among neurology, internal medicine, rehabilitation, and exercise sciences.

Regular physical activity represents one of the most promising non-pharmacological interventions, as it may positively influence several mechanisms involved in AD progression, including neuroinflammatory regulation, mitochondrial function, vascular health, and cerebral blood flow [16,21]. Preventive strategies should also include lifestyle modifications such as maintaining a balanced diet, optimizing body weight, and improving metabolic health, including insulin sensitivity, which may contribute to reducing the risk of cognitive decline [22,23].

In clinical practice, combining lifestyle-based interventions with pharmacological therapies may provide additional benefits by addressing multiple pathological pathways simultaneously [32]. Furthermore, the development and implementation of reliable biomarkers may facilitate earlier identification of individuals at increased risk and enable timely preventive interventions before extensive neurodegenerative changes occur.

Overall, a holistic approach integrating pharmacological treatment, lifestyle modification, early risk assessment, and personalized care may represent a promising direction for improving long-term outcomes in individuals at risk of or affected by AD.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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