

Alzheimer's Disease and Amyloid Deposition Could Be Downstream of Mitochondrial Energy Failure, Ion Pump Dysfunction, and Rac1 Dysregulation

Ayah Al-Qasrawi*

Faculty of Medicine, Yarmouk University, Irbid, Jordan

Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by progressive loss of memory, cognition, and behavior. Increasing evidence suggests that mitochondrial dysfunction, amyloid- β (A β) accumulation, oxidative stress, and reduced ATP production contribute to neuronal damage. We propose that AD may begin with early neuronal energy failure caused by aging-related mitochondrial dysfunction and reduced availability of metabolic substrates. Chronic ATP deficiency may dysregulate ion pumps, disrupt osmotic balance, and induce cellular stress, this in turn will affect proteostasis, intracellular signaling, and cytoskeletal integrity. The alteration of Rac1-dependent actin remodeling may impair axonal transport and synaptic function, which can promote A β accumulation and tau hyperphosphorylation. Thus, metabolic and osmotic disturbances may act as driver and contributors to neurodegeneration. If this model is validated, this framework suggests that neuronal energy homeostasis through modulation of Rac1 signaling, glucose metabolism, and mitochondrial electron transport may help delay synaptic dysfunction and cognitive decline in AD.

Keywords: Alzheimer's disease, synaptic dysfunction, chronic ATP deficiency, Rac1-dependent actin.

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that irreversibly affects memory, thinking, and behavior, and is the most common cause of dementia. It is often misdiagnosed as a consequence of aging in the elderly. Pathologically, synaptic dysfunction occurs at the early stages and then progresses into a neurodegenerative tau complex with neuronal cell death in later stages [1]. The microtubule-associated protein Tau plays a crucial role in neurodegenerative processes and may lead to a promising therapeutic target for Alzheimer's disease (AD) treatment [2]. To maintain neuronal homeostasis, the apoptotic process depends on axonal transport of membranous organelles and other molecular complexes. Axonal transport allows stimulation and modulation of numerous molecular cascades, thus playing a central role in the establishment of neuronal polarity, axonal growth and stabilization, and synapse formation [3]. Axonal transport is classified into anterograde axonal transport and retrograde axonal transport. Efficient retrograde transport is crucial for autophagosome maturation and function, preventing the distal accumulation of aging proteins and organelles. EM studies have consistently shown a low and variable number of more highly dynamic microtubules at axon terminals [4]. This type of axonal transport is implicated in AD. Meanwhile, lysosomal proteolysis alterations are essential for the control of intracellular components and the maintenance of cellular homeostasis. The disruption of the proteolysis pathway is considered the main cellular defect that initiates and accelerates the progression of Alzheimer's disease [5].

Astrocytes are the largest glial cells in the brain and are responsible for multiple functions, including providing metabolic substrates to neurons, regulating ion homeostasis, regulating neurotransmitters, stimulating synaptogenesis and synaptic activity, and preserving the blood-brain barrier (BBB) integrity. Any external injury stimuli change the astrocytes into a reactive status. Reactive astrocytes are prevalent in AD and can acquire harmful and protective functions

in response to A β and tau [6]. Rac1 plays an essential role in the astrocyte-mediated inflammation. The inhibition of Rac1 can modulate the inflammatory response in astrocytes. Rac1 affects the morphology of astrocytes by dynamic regulation and the reorganization of the actin cytoskeleton [7].

Neurons and astrocytes collaborate for neurotransmitter recycling; this phenomenon is known as the glutamate/GABA-glutamine cycle. Neurotransmitter recycling is significantly linked to astrocyte energy metabolism. In synaptic failure in AD, the astrocytes undergo metabolic remodeling, which considerably affects the glutamate/GABA-glutamine cycle [8]. Glutaminolysis plays a central role in cellular function and energy homeostasis. Reduced glutamate and increased glutamine have been reported in the brain cortex of AD patients. Glutamate-sensing-based signaling neurons react with N-methyl-D-aspartate receptor (NMDAR), and when overstimulated, this in turn results in Ca²⁺ influx-mediated excitotoxicity [9]. Whereas the inhibition of Na⁺/K⁺-ATPase during ischemia, hypoglycemia, and epilepsy may cause neurotoxic actions on glutamate. Presynaptically, inhibition of the Na⁺/K⁺-ATPase destroys the sodium gradient, which drives the uptake of acidic amino acids and a number of other neurotransmitters.

A glutamate exocytosis can also occur as inhibition of the enzyme causes membrane depolarization, and it is only possible when ATP levels are sufficiently high [10]. Brain glucose metabolism is implicated in multiple processes by which glucose is converted into ATP to be used for energy homeostasis: glycolysis in the cytoplasm, the Krebs cycle, and oxidative phosphorylation in the mitochondria. In the brain, energy production relies on the oxidation of glucose. ATP is utilized by neurons to reverse ion fluxes associated with action potentials in postsynaptic excitation. It is estimated that 70% of the energy derived from glucose oxidation is required to convert glutamate, the major neurotransmitter in the brain [11]. Although most studies reported that in the aged or AD brain, insulin is insensitive, the cur-

*Corresponding Author: *Ayah Al-Qasrawi, Faculty of Medicine, Yarmouk University, Irbid, Jordan

Citation: Ayah Al-Qasrawi*, Alzheimer's Disease and Amyloid Deposition Could Be Downstream of Mitochondrial Energy Failure, Ion Pump Dysfunction, and Rac1 Dysregulation.. Jour of Clin & Med Case Rep, Imag 2026; 6(5): 1247.

rent literature does indeed support that brain insulin resistance (IR) includes a reduction in IR signaling alteration and/or a reduction in the ligand or its transport at the BBB [12]. However, disruptions in IGF-I signaling have been reported in AD pathogenesis, such as beta-amyloid accumulation, glucose metabolism dysregulation, oxidative stress, chronic inflammation, and neuronal death [13]. Remarkably, ageing is characterized by a gradual decline in NAD⁺ levels in rodents and humans. This decline in NAD⁺ levels is linked causally to numerous ageing-associated diseases [14]. Meanwhile, mitochondrial dysfunction is the main driver of the formation and accumulation of A β . Some studies stated that increased mitochondrial A β , γ -secretase, and oxidative stress, along with ATP levels depletion in brain mitochondria, can contribute to neurodegeneration [15].

Hypothesis

Amyloid–tau complexes remain the central pathological hallmark of Alzheimer’s disease (AD). We propose that disturbances in neuronal energy metabolism and osmotic homeostasis may precede and contribute to the development of these pathological features. Chronic ATP deficiency in the aging brain may impair protein and carbohydrate degradation pathways, enhance oxidative stress, disrupt intracellular signaling, and destabilize cytoskeletal protein networks, thereby increasing susceptibility to amyloid- β accumulation and tau hyperphosphorylation.

Aging is commonly associated with reduced availability of metabolic substrates due to decreased nutritional intake, impaired glucose utilization, multimorbidity, and polypharmacy. In parallel, age related mitochondrial dysfunction and cerebral hypometabolism contribute to persistent neuronal ATP deficiency. This energy deficit compromises ATP-dependent ion transporters, particularly Na⁺/K⁺-ATPase and Ca²⁺-ATPase, which are essential for maintaining ionic gradients and osmotic homeostasis. Failure of these transport systems disrupts ionic equilibrium, induces osmotic stress and cellular swelling, and impairs glymphatic clearance of metabolic waste, thereby altering the neuronal microenvironment.

Chronic ATP deficiency further impairs proteostasis, increases oxidative stress, disrupts intracellular signaling pathways, and destabilizes the cytoskeletal network. Reduced ATP availability limits ATP–actin binding, thereby impairing G-actin dynamics, F-actin polymerization, and cytoskeletal remodeling. In parallel, chronic metabolic stress may dysregulate Rac1 signaling, a key regulator of actin cytoskeletal organization, synaptic plasticity, and memory formation, further exacerbating cytoskeletal dysfunction.

These combined alterations disrupt the coordinated actin microtubule system required for efficient axonal transport, including retrograde axonal transport. Collectively, metabolic, osmotic, cytoskeletal, and transport dysfunction converge to impair synaptic integrity and create a permissive environment for amyloid- β accumulation, tau hyperphosphorylation, and progressive neurodegeneration. In this framework, we propose that Alzheimer’s disease may originate, at least in part, from an early failure of neuronal energy homeostasis that compromises ATP-dependent regulation of ionic gradients and osmotic balance. Mitochondrial dysfunction and reduced cerebral metabolism decrease the energy available to maintain neuronal homeostasis, leading to chronic metabolic and osmotic stress. This stress increases neuronal vulnerability, disrupts synaptic function, and facilitates the initiation and progression of amyloid- β and tau pathology. Rather than replacing the established amyloid–tau cascade hypothesis, this model positions metabolic and osmotic dysregulation as upstream contributors that may initiate neurodegenerative processes.

Discussion

Tau is the largest microtubule-associated protein (MAP) in neuronal cells. It constitutes four key domains: an N-terminal acidic projection domain, a proline-rich region (PRP), a microtubule-binding domain containing conserved repeats, and a C-terminal tail. PRR has an impact of regulation tubulin interactions and correlates with AD disease through diminishing tubulin dimer binding and slowing microtubule polymerization [16,17].

During aging, in the hippocampus, endogenous neurogenesis, brain plasticity, and cognitive function all decline. In parallel, both glycolysis and the TCA cycle become less efficient, which is altered by the depletion of energy supply or disruption of brain demands. The brain might supplement its energy requirements by utilizing ketone bodies when glucose levels are insufficient. Meanwhile, the hippocampal sub-regions help the generation of episodic memory in healthy individuals. The hippocampus is one of the earliest brain areas that is damaged by Alzheimer’s (AD). Although in the early stages of AD, the hippocampus shows rapid tissue loss, when this disease progresses, the medial temporal and hippocampal regions are atrophied. These structural markers were detected by magnetic resonance imaging (MRI) [18-20]. A Rac1-dependent forgetting mechanism was reported in a mouse AD model. It also noted that Rac1 activity in the hippocampus is significantly elevated in the same study [21].

In the aged brain, there are significant alterations in concentrations of metabolites and their effects on adenosine triphosphate (ATP) supply in neurons and astrocytes. Hence, they reported reduced sodium/potassium adenosine triphosphatase (Na⁺/K⁺-ATPase) activity as the leading cause of impaired neuronal action potentials. Suggested interventions capable of restoring the brain’s metabolic flexibility and action potential generation include increasing the nicotinamide adenine dinucleotide (NADH) cytosol-mitochondria shuttle, NAD⁺ pool, the ketone β -hydroxybutyrate, lactate, and Na⁺/K⁺-ATPase, while reducing blood glucose levels [22]. In mammals, the hypothalamic-neurohypophyseal system (HNS) is responsible for extracellular osmoregulation. The HNS components that involved in osmotic control is composed of specialized osmosensing magnocellular neurosecretory cells (MNCs), located in the hypothalamic supraoptic and paraventricular nuclei through secreting the neuropeptides arginine- vasopressin (AVP) and oxytocin (OXT) into the circulation. Hence, this can adjust kidney function, the primary organ involved in the osmoregulation [23].

Conclusion

From this proposed framework, if validated, several therapeutic modalities may emerge. Targeting Rac1-dependent signaling pathways may represent a promising strategy to restore cytoskeletal dynamics, synaptic plasticity, and memory function, given its central role in actin organization and neuronal structural remodeling. In parallel, strategies aimed at enhancing neuronal ATP availability, which include modulation of carbohydrate utilization pathways to improve glycolytic flux and substrate availability for ATP production, are particularly beneficial in aging or metabolically disrupted neurons. Improving energy supply may help restore the activity of ATP-dependent ion pumps, thereby stabilizing ionic gradients, osmotic balance, and overall neuronal homeostasis.

Furthermore, metabolic reprogramming approaches that support glycolysis as an alternative or complementary energy source to mitochondrial oxidative phosphorylation may offer neuroprotective benefits under conditions of mitochondrial dysfunction. Such a shift could help sustain ATP production during periods of impaired elec-

tron transport chain activity, thereby preserving synaptic function and delaying the progression to more severe neurodegenerative processes. Overall, we propose that preserving cellular energy balance through modulation of Rac1 signaling and metabolic pathways that control glucose utilization through NAD⁺ may represent a novel, promising therapeutic strategy to delay the progression of synaptic failure and cognitive decline in Alzheimer's disease.

Ethical statement

This manuscript is a theoretical medical hypothesis and does not involve research with human participants or animals. Ethical approval and informed consent were therefore not required.

Declaration

Conflict of Interest: The author declares no conflicts of interest. Consent to Participate/Publish: Not applicable.

Funding

The author did not receive any funding.

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this work, the author did not AI and AI-assisted technologies.

Data Availability

This manuscript is a hypothesis article and does not report original research data. Therefore, no datasets were generated or analyzed during the current study

References

1. [Abdulkhalik AA, Kim B, Almoghrabi YM \(2026\) Amyloid- \$\beta\$ and tau in Alzheimer's disease: pathogenesis, mechanisms, and interplay. *Cell Death Dis* 17: 21.](#)
2. [Haj-Yahya M, Lashuel HA \(2018\) Protein semisynthesis provides access to tau disease-associated post- translational modifications and paves the way to deciphering the tau PTM code in health and disease states. *J Am Chem Soc* pp. 140.](#)
3. [Guillaud L, El-Agamy SE, Otsuki M, Terenzio M \(2020\) Anterograde axonal transport in neuronal homeostasis and disease. *Front Mol Neurosci* 13: 556175.](#)
4. [Nirschl JJ, Ghiretti AE, Holzbaur ELF \(2017\) The impact of cytoskeletal organization on the local regulation of neuronal transport. *Nat Rev Neurosci* 18: 585–597.](#)
5. [Tammineni P, Jeong YY, Feng T \(2017\) Impaired axonal retrograde trafficking of the retromer complex augments lysosomal deficits in Alzheimer's disease neurons. *Hum Mol Genet* 26: 4352–4366.](#)
6. [Pang Y, Yang J, Liu J, Xie Z, Wang J \(2026\) Metabolic interactions in the brain: the crucial roles of neurons, astrocytes, and microglia in health and disease. *Front Neurosci* 20: 1731771.](#)
7. [Jiang F, Wang N, Meng Q \(2026\) Mechanistic role of astrocytic Rac1 protein in Alzheimer's disease *Aging Dis* 17:1916–1931.](#)
8. [Andersen JV, Schousboe A, Verkhratsky A \(2022\) Astrocyte energy and neurotransmitter metabolism in Alzheimer's disease: integration of the glutamate/GABA-glutamine cycle. *Prog Neurobiol* 217: 102331.](#)
9. [Kumar MA, Baba SK, Khan IR, et al. \(2020\) Glutamine metabolism: molecular regulation, biological functions, and diseases. *MedComm* 6: e70120.](#)
10. [Lees GJ \(1991\) Inhibition of sodium-potassium-ATPase: a potentially ubiquitous mechanism contributing to central nervous system neuropathology. *Brain Res Brain Res Rev* 16: 283–300.](#)
11. [Mosconi L \(2013\) Glucose metabolism in normal aging and Alzheimer's disease: methodological and physiological considerations for PET studies. *Clin Transl Imaging* 1: 217–233.](#)
12. [Frazier HN, Ghoweri AO, Anderson KL \(2019\) Broadening the definition of brain insulin resistance in aging and Alzheimer's disease. *Exp Neurol* 313: 79–87.](#)
13. [Zegarra-Valdivia J, Arana-Nombera H, Perez-Fernandez L \(2025\) Insulin-like growth factor impact on Alzheimer's disease: role in inflammation, stress, and cognition. *Curr Issues Mol Biol* 47: 233.](#)
14. [Covarrubias AJ, Perrone R, Grozio A, Verdin E \(2021\) NAD⁺ metabolism and its roles in cellular processes during ageing. *Nat Rev Mol Cell Biol* 22: 119–141.](#)
15. [Bhatia S, Rawal R, Sharma P \(2022\) Mitochondrial dysfunction in Alzheimer's disease: opportunities for drug development. *Curr Neuropharmacol* 20: 675–692.](#)
16. [Jiang G, Xie G, Li X, Xiong J \(2025\) Cytoskeletal proteins and Alzheimer's disease pathogenesis: focusing on the interplay with tau pathology. *Biomolecules* 15: 831.](#)
17. [Acosta K, Brue CR, Holubovska P \(2025\) Structural insights into the role of the proline-rich region in tau function. *Structure* 33: 465–74.](#)
18. [Ge I, Kirschen GW, Wang X \(2021\) Shifted dynamics of glucose metabolism in the hippocampus during aging. *Front Aging Neurosci* 13: 700306.](#)
19. [Rao YL, Ganaraja B, Murlimanju BV \(2022\) Hippocampus and its involvement in Alzheimer's disease: a review. *3 Bio-tech* 2022;12:55.](#)
20. [Gunasekaran TI, Sanchez D, Reyes-Dumeyer D \(2025\) Frequency of microvascular pathology and hippocampal atrophy on magnetic resonance imaging in a community study of Alzheimer's disease with blood-based biomarkers. *Ann Neurol* 98: 1027–1043.](#)
21. [Zhang H, Ben Zablah Y, Zhang H \(2022\) Inhibition of Rac1 in ventral hippocampal excitatory neurons improves social recognition memory and synaptic plasticity. *Front Aging Neurosci* 14:914491.](#)
22. [Shichkova P, Coggan JS, Kanari L \(2025\) Breakdown and repair of metabolism in the aging brain. *Front Sci* 3:1441297.](#)
23. [Mecawi AS, Varanda WA, da Silva MP \(2022\) Osmoregulation and the hypothalamic supraoptic nucleus: from genes to functions. *Front Physiol* 13: 887779.](#)