

Obesity As A Neuroendocrine Modulator Of Alzheimer’s Disease: Roles Of Adipokines And Adipose-derived Extracellular Vesicles

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Introduction

- Alzheimer’s disease (AD) is marked by **amyloid-β** plaques, **hyperphosphorylated** tau, neuroinflammation, synaptic **dysfunction**, and neuronal loss.
- Obesity** is an increasingly recognized **modifiable** risk factor for cognitive decline and AD.
- Traditional models emphasize systemic metabolic dysfunction, but newer evidence implicates **adipose-brain signaling**.
- Adipokines, extracellular vesicles (EVs), and depot-specific adipose biology may directly influence CNS pathology.

Objective

- Primary objective:** synthesize evidence positioning obesity as a neuroendocrine modulator of AD.
- Secondary objective:** examine visceral, subcutaneous, and perivascular fat depots as differential contributors to AD risk and progression.
- Integrate adipokine dysregulation, EV trafficking, and adipose heterogeneity within one mechanistic framework.

Methods

- Database: PubMed.
- Search terms: “Obesity AND Alzheimer’s Disease”, “Adipokine”, and “Extracellular Vesicles”.
- Timeframe: 2011-2026.
- Initial search: 3,140 articles; refined searches: 136 **adipokine**-related and 16 **EV**-related articles.
- After screening and synthesis, **30** sources were included. The study types included were **preclinical**, **translational**, and **observational** literature.

Results: Key Findings

- Visceral adipose tissue** (VAT) promotes inflammatory **remodeling**, insulin resistance, **oxidative** stress, and **BBB** dysfunction.
- Leptin resistance and adiponectin deficiency impair **PI3K/Akt**, **AMPK**, synaptic signaling, and mitochondrial function.
- Adipose-derived EVs carry **miRNA** and lipid cargo that alter **APP** processing, tau **phosphorylation**, **microglial** activation, and synaptic maintenance.
- Depot-specific adipose heterogeneity shapes AD risk through distinct **inflammatory**, **vascular**, and **vesicular** signaling profiles.
- Obesity may function as an **active** depot-brain communication system rather than a passive metabolic comorbidity.

Visceral Obesity as the Peripheral Driver of Neuroinflammation

- VAT undergoes adipocyte **hypertrophy**, local **hypoxia**, and M1 **macrophage** infiltration in obesity.
- Increased **TNF-α**, **IL-6**, and **IL-1β** amplify systemic and central inflammation.
- VAT-induced insulin resistance disrupts **IRS-1 → PI3K/Akt**, weakening neuronal survival and synaptic plasticity.
- Excess free fatty acids (FFAs) and ROS activate **NF-κB** and **NLRP3**, promoting Aβ accumulation and tau phosphorylation.
- BBB disruption allows **inflammatory** mediators and EV cargo to access the CNS.

Regional Adipose Tissue Heterogeneity

- Adipose tissue is not uniform; **neurodegenerative** risk depends on depot-specific biology.
- VAT is the most **pro-inflammatory** and metabolically disruptive depot.
- Perivascular fat may worsen **endothelial** dysfunction, **vascular** tone, and **BBB** integrity through local paracrine signaling.
- Subcutaneous** fat is generally less inflammatory than VAT, suggesting adipose **distribution** matters more than total adiposity alone.
- Depot-specific EV cargo may differentially affect neuronal **transcription**, microglial **activation**, and amyloid **aggregation**.

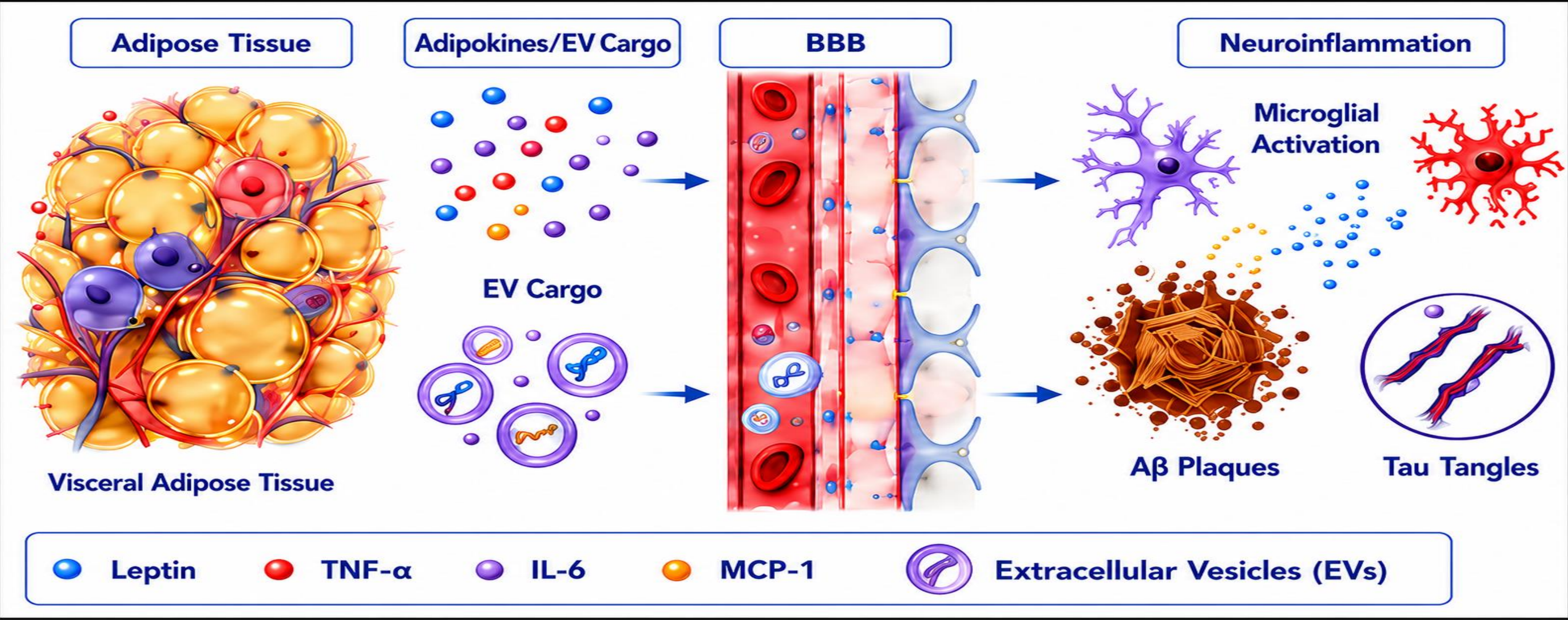
AB/Tau Acceleration and Lipid Dysregulation

- Hyperinsulinemia** competitively saturates IDE, reducing Aβ degradation.
- Obesity shifts APP toward **β-secretase** processing, increasing amyloidogenic cleavage and plaque formation.
- Loss of PI3K/Akt increases neuronal **GSK-3β/CK16** activity and tau hyperphosphorylation.
- miRNA-mediated microglial **lipid droplet** formation may impair clearance and intensify **neuroinflammation**.
- Lipid raft and obesity-driven lipid remodeling reinforce **protein** aggregation and **proteostatic** failure.

Central Adipokine Signaling Dysfunction

- Leptin** normally supports JAK2/STAT3, PI3K/Akt, AMPK, and synaptic plasticity.
- Obesity causes leptin resistance via **SOCS3/PTP1B**, increasing Aβ production and GSK-3β activity.
- Adiponectin supports **AMPK/PPAR-α**, mitochondrial function, anti-inflammatory signaling, and microvascular homeostasis.
- Hypoadiponectinemia promotes **ceramide** accumulation, oxidative stress, microglial activation, and impaired **Aβ** clearance.
- Dual-adipokine failure amplifies **metabolic** dysfunction, **neuroinflammation**, and synaptic impairment.

Figure 1. Obesity-related adipose-brain communication in Alzheimer’s Disease.



Adipose-Derived Extracellular Vesicles, miRNA/Lipid Cargo, and EV-Based Signaling

- Adipose EVs can cross the BBB and deliver **miRNA**, **proteins**, and **lipids** to neural cells.
- EV miRNAs target **CREB/BDNF**, **RAGE1**, APP/tau **regulators**, and **apoptosis** pathways.
- Obesity alters EV lipid cargo, accelerating **Aβ** fibrillization and **pro-inflammatory** microglial activation.
- EVs reinforce **PI3K/Akt** suppression, **GSK-3β** activation, and **NF-κB** signaling within the CNS.
- Adipose mesenchymal stem cells-derived EVs may enhance **Aβ** degradation and represent a therapeutic avenue.

Conclusions

- Obesity acts as a **neuroendocrine** modulator of AD, not only a systemic metabolic risk factor.
- VAT** inflammation, **depot-specific** adipose signaling, dual-adipokine failure, and **EV** cargo converge on AD pathways.
- These mechanisms promote **Aβ** accumulation, **tau** pathology, **microglial** activation, BBB dysfunction, and **synaptic** decline.
- Future studies should define depot-specific EV cargo, clarify **central leptin/adiponectin** signaling, and test targeted interventions.

Therapeutic Implications / Discussion / Future Directions

- Resveratrol**-loaded TG-Res-CS/TPP nanoparticles improve insulin signaling and reduce oxidative stress.
- Nano-formulated dihydromyricetin decreases **inflammation**, restores **proteostasis**, and promotes Aβ **degradation**.
- These approaches target **disrupted pathways** including insulin resistance, ROS, neuroinflammation, and impaired Aβ clearance.
- Current evidence is preclinical; broader future strategies include exercise, GLP-1 receptor agonists, bariatric surgery, and EV/adipokine-targeted interventions.

Selected References



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