

Immunometabolic Reprogramming of Microglia in Obesity-Associated Alzheimer's Disease

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Introduction

- Alzheimer's disease (AD) is the leading cause of dementia
- AD is increasingly recognized as a chronic neuro-inflammatory disorder
- In AD, microglia become hyper-reactive, promoting amyloid- β (A β) and tau pathology
- Obesity is an independent risk factor for AD
- Obesity causes chronic low-grade systemic inflammation that contributes to brain inflammation

Objective

- Obesity promotes chronic microglial immunometabolism
- This inflammatory state accelerates AD pathology
- This review explores how obesity-driven metabolic stress reprograms microglial immunometabolism
- Identifies potential therapeutic targets to reduce obesity-related AD risk

Methods

- **Design:** Comprehensive literature review using PubMed Advanced Search.
- **Search Terms:** (microglia[Title]) OR (obesity[Title]) OR (Alzheimer's Disease [Title]) AND (obesity[Text Word]) AND (Alzheimer's Disease[Text Word]) AND (microglia[Text Word]) AND (inflammation[Text Word])
- **Yield:** 34 peer-reviewed English-language articles (2007–2026).
- **Article Types:** Peer-reviewed, systematic reviews, preclinical models, and clinical studies

Results

Obesity Drives Neuroinflammation

- Adipose tissue releases TNF- α , IL-6, leptin & free fatty acids
- Gut dysbiosis increases circulating LPS (2-3x)
- Blood-brain barrier permeability increases
- Peripheral inflammation reaches the CNS

Microglia Become Metabolically Dysfunctional

- Shift to glycolysis
- NF- κ B, MAPK & NLRP3 pathways activated
- Continuous IL-1 β and ROS production
- Reduced A β and tau clearance

Genetics Amplify the Damage

- Lipid-droplet accumulating microglia (LDAMS) develop
- Foam-cell phenotype impairs phagocytosis
- APOE4 promotes glycolytic, inflammatory microglia
- TREM2 mutations reduce lipid sensing and A β clearance
- Microglia adopt disease-associated phenotype

Potential Reversal Targets

- TLR4 inhibition (TAK-242):
 - Restores neurogenesis and memory
- β -hydroxybutyrate:
 - Restores autophagy
- PPAR- γ agonists
 - Improve A β phagocytosis
- Omega-3 fatty
 - Suppress NF- κ B signaling
- TREM2 activation
 - Restores microglial homeostasis

Conclusion

- Obesity-driven inflammation disrupts the blood-brain barrier
- Microglia become glycolytic, lipid-laden, and chronically inflammatory
- Dysfunctional microglia reduced- β (A β) clearance and accelerate neurodegeneration
- APOE and TREM2 amplify microglial metabolic dysfunction, driving Alzheimer's disease progression
- Targeting microglial metabolism may help uncouple obesity from neurodegeneration

Reference & Contact Information

