

Transcriptomic Validation of the GSK3 β -PGC1 α Axis as a Metabolic Target for Lithium in the Alzheimer's Hippocampus

Carlos Wagner Leal Cordeiro Júnior^{1,2}, Maria Eduarda Dorneles Ferraz³, Samuel Cândido Freres⁴, Carlos Roberto Sales⁵, Rafael Everton Assunção Ribeiro da Costa⁶, Vanessa de Jesus Rodrigues de Paula²

¹Department of Health Sciences, Universidade Nove de Julho (UNINOVE), Mauá, Brazil. ² LIM-27, Institute of Psychiatry, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo (FMUSP), São Paulo, Brazil. ³ Department of Health Sciences, Faculdades Integradas do Norte de Minas (FUNORTE), Montes Claros, Brazil. ⁴ Federal University of Paraná (UFPR), Curitiba, Brazil. ⁵ UNINASSAU, Vilhena, Brazil. ⁶ State University of Campinas (UNICAMP), Campinas, Brazil.

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INTRODUCTION

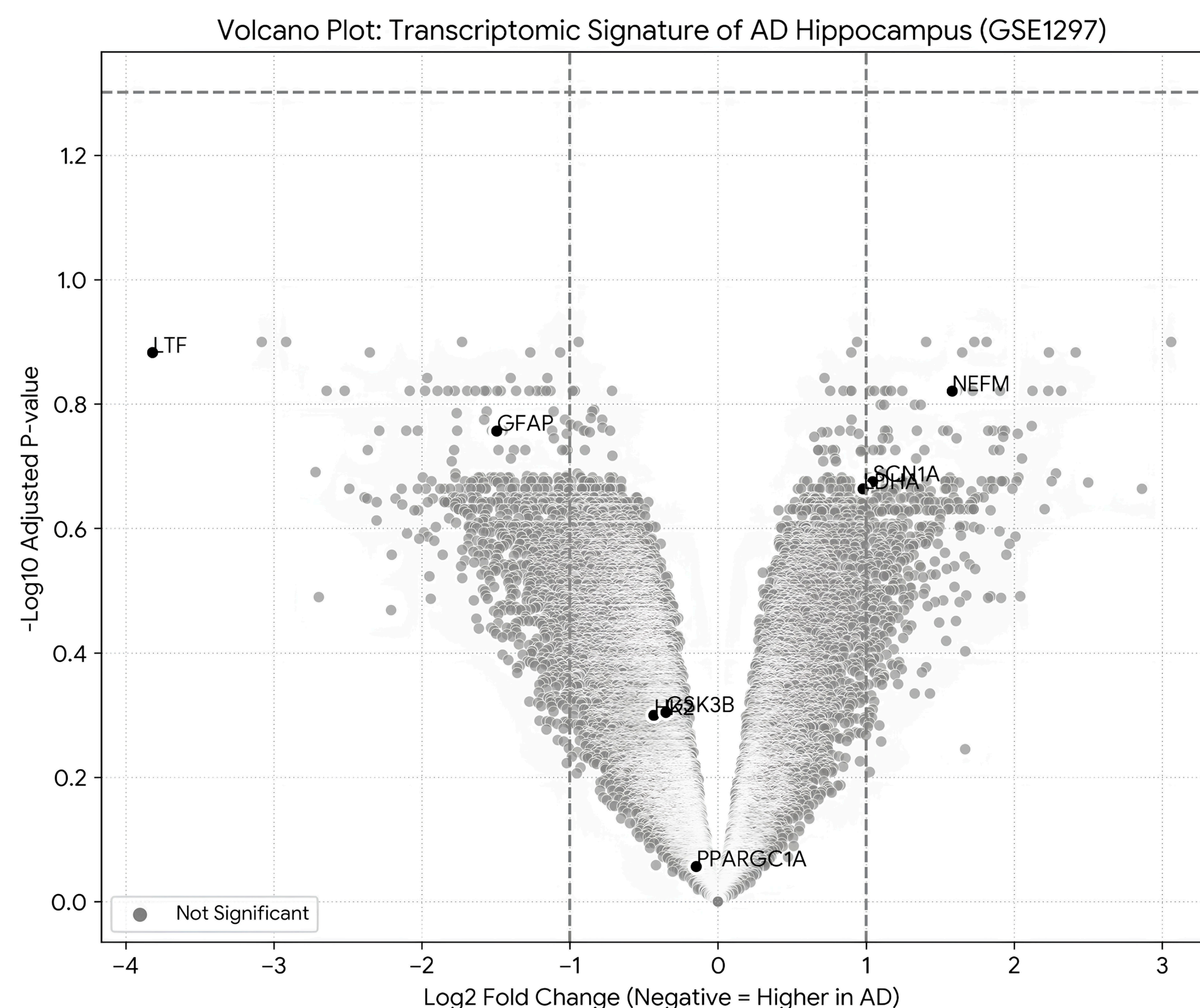
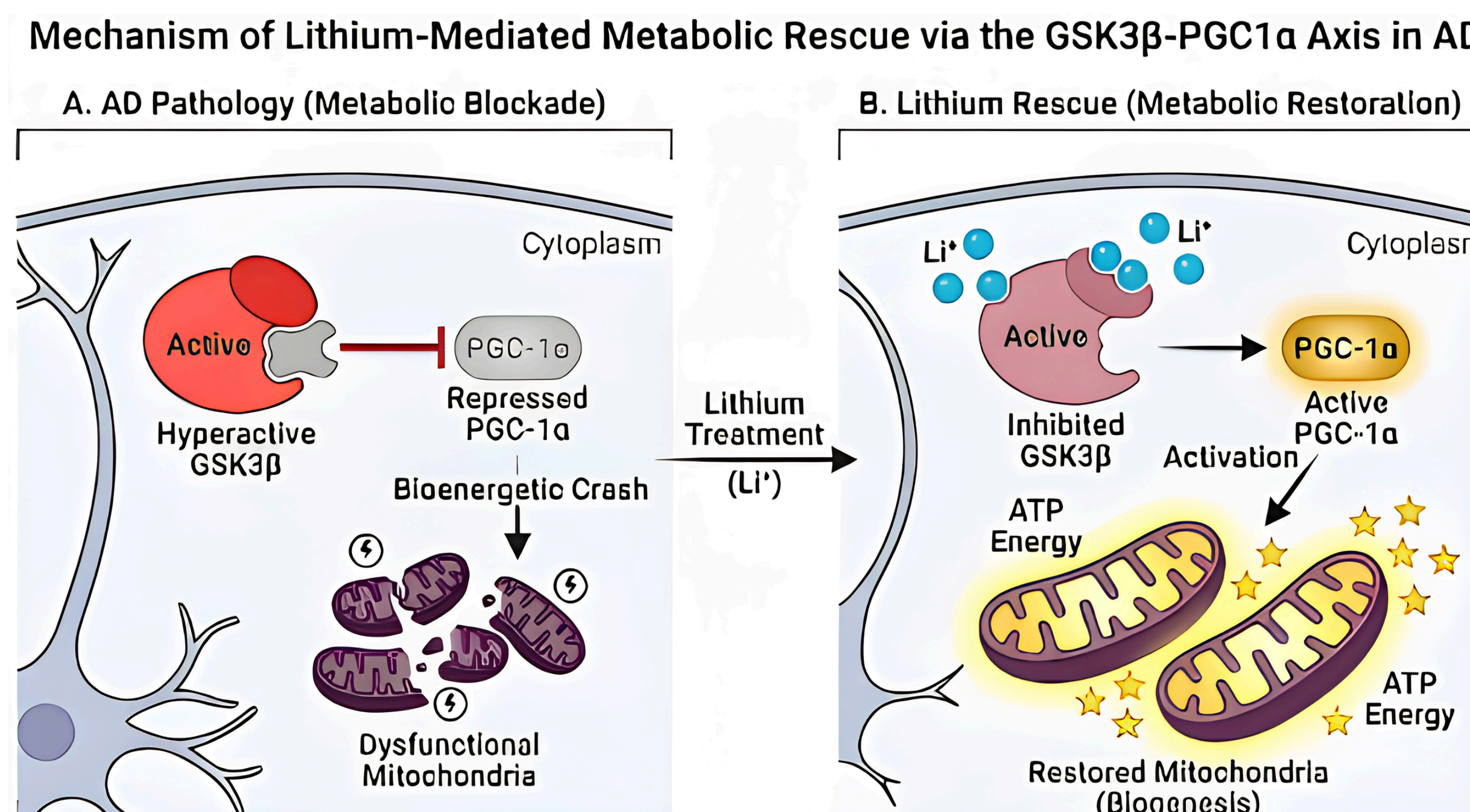
Mitochondrial dysfunction and the shift towards aerobic glycolysis (Warburg effect) are central pathogenic features of Alzheimer's Disease (AD), driven in part by the hyperactivity of Glycogen Synthase Kinase-3 beta (GSK3 β). This study investigated the transcriptional dysregulation of the GSK3 β -PGC1 α axis in the human hippocampus to provide a mechanistic rationale for repurposing Lithium, a direct GSK3 β inhibitor, as a metabolic rescuer capable of restoring bioenergetic homeostasis.

METHODS

We performed a differential expression analysis on the GSE1297 dataset (NCBI GEO), comprised of Affymetrix HG-U133A microarrays of laser-microdissected CA1 hippocampal neurons from severe AD patients (n=7) and age-matched healthy controls (n=9). Data processing utilized the GEO2R platform powered by the R/Bioconductor limma package. We applied a linear model with Empirical Bayes moderation (eBayes) to calculate stable t-statistics for the limited sample size. To control for false positives, p-values were adjusted using the Benjamini-Hochberg False Discovery Rate (FDR) procedure. Target analysis correlated the expression of the inhibitory kinase (GSK3B) with mitochondrial biogenesis markers (PPARGC1A) and glial reactivity signatures (GFAP, LTF).

RESULTS

PPARGC1A (PGC-1 α) was significantly suppressed in AD tissues, accompanied by marked neuronal loss and severe reactive astrogliosis. Persistent GSK3B activity suggests a central role in metabolic dysfunction, supporting lithium as a potential metabolic rescuer through GSK3 β inhibition.



CONCLUSIONS

We identified a specific "metabolic crash" in the human AD hippocampus characterized by the suppression of the PGC-1 α axis. These results validate the use of Lithium in precision medicine for AD, not merely as a neuroprotective agent, but as a metabolic modulator capable of reversing the glycolytic inflammatory phenotype and restoring mitochondrial function via GSK3 β inhibition.

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CONTACT



@carlos.leal@uni9.edu.br

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