Vitamin C uptake rewires microglial redox state to modify Alzheimer’s disease

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Vitamin C depletion is a consistent feature of the Alzheimer’s disease (AD) brain, yet decades of clinical trials using dietary supplementation have consistently failed to demonstrate benefit. This long-standing paradox suggests that the critical limitation lies not in systemic availability, but in the cellular mechanisms regulating uptake and redox balance within the brain. Microglia, as central regulators of neuroinflammation and proteostasis, are highly vulnerable to redox imbalance. Here, we identify a progressive, disease associated downregulation of the sodium-dependent vitamin C transporter SVCT2 (Slc23a2) specifically in microglia as the crucial bottleneck for ascorbate utilization in AD.

We hypothesized that bypassing this transport deficiency via targeted genetic intervention could restore microglial redox homeostasis and modify disease progression, either by preventing the onset of pathology or rescuing established deficits. To test this, we selectively overexpressed SVCT2 in the microglia of 5xFAD mice, employing both preventative (pre-onset) and therapeutic (post-onset) strategies.

Enhancing SVCT2 expression successfully increased intracellular ascorbate and triggered a profound rewiring of microglial redox metabolism. This redox reprogramming established a unique, “hybrid” neuroprotective microglial phenotype, characterized by the co-expression of homeostatic markers (e.g., Cx3cr1, Csf1r) alongside select disease-associated microglia (DAM) genes (CD11c and Lpl), thereby preserving protective functions while engage and decrease the Amyloid burden. Functionally, SVCT2-driven redox restoration improved synaptic bioenergetics and significantly decreased amyloid plaque burden. Consequently, this prevented the development of synaptic dysfunction, cognitive decline and memory deficits.

Remarkably, therapeutic SVCT2 overexpression initiated after disease onset successfully rescued synaptic plasticity and memory performance. Crucially, this cognitive rescue occurred despite leaving the established amyloid pathology unchanged. We found that this late-intervention effect was mediated by the redox regulation of microglial secretory pathways, highlighting that neuronal support depends critically on the functional redox state of microglia rather than amyloid clearance alone.

In conclusion, our findings resolve the clinical paradox of vitamin C in AD by demonstrating that neuroprotection is determined not by systemic supplementation but by the brain's cellular uptake capacity. We establish SVCT2 as a novel redox-based, disease-modifying target and provide a strong mechanistic rationale for therapeutic strategies aimed at restoring microglial function to counteract neurodegeneration.