

Targeting E-selectin As A Modulator Of Brain Endothelial Dysfunction In Alzheimer Disease

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Targeting E-selectin represents a mechanistically distinct and complementary approach to endothelial stabilization in AD

INTRODUCTION	METHODS	RESULTS
Brain endothelial dysfunction is an early and pervasive feature of Alzheimer Disease (AD) and is closely linked to abnormal protein aggregation, neuroinflammation, and synaptic injury. E-selectin (SELE) is an inducible endothelial adhesion molecule which mediates endothelial-immune interactions. Emerging evidence indicates that carbonyl stress and non-enzymatic glycation amplify endothelial activation, including SELE expression in AD. We here aim to evaluate SELE as a candidate therapeutic target in AD.	We performed a targeted review of endothelial activation pathways relevant to AD. Druggable nodes influencing SELE expression, ligand binding, and downstream signaling were curated from preclinical and clinical literature. Agents were prioritized based on endothelial specificity, relevance to glycation- and inflammation-linked activation states, ability to modulate leukocyte-endothelial interactions or microvascular function and established human safety or clinical trial experience. Finally, mechanistic overlap and complementarity with other endothelial targets implicated in AD (e.g., junctional and glycocalyx-associated pathways) were evaluated to inform rational combination strategies and translational feasibility.	Endothelial E-Selectin (SELE) as a Therapeutic Node in Alzheimer Disease Carbonyl stress and glycation amplify endothelial activation and reveal actionable therapeutic pathways 1 Upstream Drivers of SELE Induction Healthy → Activated Brain Endothelium Healthy endothelium → Activated endothelium Carbonyl stress / methylglyoxal (MG) Advanced glycation end products (AGEs) AGE-RAGE signaling NF-κB and MAPK activation Glycocalyx disruption / endothelial stress SELE altered in early preclinical AD transcriptomic studies Glycocalyx E-selectin (SELE) Soluble mediators 2 SELE at the Endothelial Interface Luminal (Blood) Leukocyte rolling → Activation → Firm adhesion Leukocyte ligands (sialyl LewisX, PSGL-1) ↑ SELE on activated endothelium SELE links endothelial activation to: - Immune cell engagement - Microvascular dysfunction - Junctional stress / permeability changes - Neurovascular inflammation Basement membrane Abluminal (Brain) Astrocyte endfoot Neuron / synapse Protein aggregation (Aβ, tau) Glial activation (astrocytes, microglia) Synaptic injury (spine loss, dysfunction) 3 Therapeutic Opportunities Reduce endothelial carbonyl stress Examples: Benfotiamine, Nrf2-GLO1 activation Lowers methylglyoxal and oxidative/glycation stress Suppress SELE induction Examples: NF-κB / MAPK pathway modulation Reduces SELE transcription and endothelial activation Block SELE-ligand interactions Examples: Selectin antagonists, Glycomimetic inhibitors Prevents leukocyte rolling and adhesion Stabilize endothelium Examples: S1PR1, Tie2, ROCK modulation Strengthens barrier, junctions, and vascular tone Prioritization criteria - Endothelial specificity - Relevance to glycation/inflammation - Leukocyte-endothelial modulation - Microvascular function - Human safety / clinical experience Conceptual Model Carbonyl stress / AGEs → SELE induction → Endothelial-immune activation → Neurovascular dysfunction → Protein aggregation, neuroinflammation, synaptic injury → Targeting SELE offers a complementary, endothelial-focused therapeutic strategy in AD.