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DEFENSE OF THE DOCTORAL

DISSERTATION

"Endothelin-Converting Enzymes and Aβ Homeostasis: Bridging a Missing Link in Early Alzheimer's Disease Pathogenesis"

by

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Monday, September 28th, 2026
9:30 A.M.
Cancer Center, G1196

Join Zoom Meeting:
https://rutgers.zoom.us/j/94107760530?pwd=MUre3Vps6wma2sXTFOZULXfGRbTrhT.1

Meeting ID: 941 0776 0530
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Abstract

FDA-approved Aβ immunotherapies for Alzheimer's disease (AD) target extracellular amyloid but provide limited clinical benefit. Growing evidence suggests that intraneuronal Aβ accumulation precedes plaque formation and may contribute to early synaptic and neuronal dysfunction. The mechanisms underlying age-related Aβ accumulation remain incompletely understood but likely involve impaired clearance within the endosomal–lysosomal network (ELN). Aβ-degrading enzymes endothelin-converting enzyme-1 (ECE-1) and ECE-2 localize to acidic intracellular compartments where Aβ is produced and trafficked, positioning them to regulate both intraneuronal and secreted pools of the peptide. However, the individual contributions of ECE-1 and ECE-2 to Aβ homeostasis remain poorly defined. Using neuronal cell lines, genetic mouse models, and brain fractionation approaches, this dissertation investigated how ECE-1 and ECE-2 regulate endogenous Aβ concentration and determined how this regulation changes with aging.

Conditional deletion of amyloid precursor protein (*App*) demonstrated that excitatory neurons are a major source of intraneuronal/synaptosomal and extracellular Aβ, whereas inhibitory neurons contribute disproportionately to extracellular Aβ. Consistent with these differences, deficiency of ECE-2, which is enriched in GABAergic neurons, increased Aβ primarily in the extracellular compartment, and aged knockout mice exhibited learning and memory impairments. In contrast, conditional deletion of *Ece1* from Camk2a-expressing excitatory neurons selectively increased synaptosomal Aβ with modest extracellular effects. During normal aging, *Ece1* and *Ece2* expression decline, suggesting that age-related reductions in Aβ-degrading capacity may contribute to Aβ accumulation.

The ELN represents a critical intersection between Aβ generation and clearance, with multiple AD-associated risk factors converging on this pathway. In ECE-1-deficient neuronal cells, disruption of lysosomal proteolysis or acidification caused dramatic intracellular accumulation of insoluble, fibrillar Aβ within endosomal compartments without corresponding extracellular increases. These findings suggest that ECE-1 normally buffers Aβ within the ELN and that impaired ECE-1-mediated degradation can exacerbate the effects of ELN dysfunction, promoting intracellular Aβ retention and aggregation.

Collectively, this work demonstrates that Aβ homeostasis is spatially and cellularly organized, with ECE-1 and ECE-2 exerting nonredundant control over distinct Aβ pools. These findings support a model in which age-related impairments in ECE-mediated proteolysis converge with ELN dysfunction to promote Aβ accumulation, potentially contributing to neuronal dysfunction and AD pathogenesis.