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Spontaneous and induced amyloid-beta peptide localization and its effect on mitochondrial function during brain aging using *Nothobranchius furzeri* as a model

Yusuf Kaan Poyraz[1], Muge Karakaya[1], Olivia Vilela[1], Melissa Page[1]

[1] Louvain Institute of Biomolecular Science and Technology, Université Catholique de Louvain, Louvain-la-Neuve, Belgium

Alzheimer's disease (AD) is a leading cause of dementia, affecting nearly 50 million people worldwide, with its prevalence expected to rise due to increasing life xpectancy. Despite extensive research, its precise pathogenesis remains elusive. Growing evidence highlights the critical role of mitochondria in AD progression. Notably, amyloid-β (Aβ) accumulates not only extracellularly but also intracellularly, particularly within mitochondria during early AD stages. Mitochondrial Aβ induces oxidative stress and impairs ATP production, leading to mitochondrial dysfunction, neuronal apoptosis, and progressive neurodegeneration. For this study, we used Nothobranchius furzeri to investigate age-related neurodegeneration.

N. furzeri naturally develops AD-like neuropathologies, including spontaneous intraneuronal Aβ accumulation, chronic microglial activation, and reduced neurogenesis in the telencephalon, resembling early-stage AD. Telencephalon samples were collected at 8- and 32-weeks post-hatching (wph) to examine Aβ localization, phosphorylated tau (p-tau) levels, microglial response, synaptic degeneration, and apoptosis via qPCR and immunofluorescence staining.

Compared to 8 wph fish, 32 wph fish exhibited statistically significant increases in p-tau, microglial activation, synaptic degeneration, apoptosis, and Aβ accumulation, with a predominant localization within mitochondria, as confirmed by immunofluorescence. While amyloidogenic pathway gene expression remained unchanged, microglia-related genes were statistically significantly upregulated.

To differentiate the impact of intracellular and extracellular Aβ accumulation, we will employ cerebroventricular microinjection (CVMI) of Aβ in male and female fish to model AD-like pathology. This method was successfully validated, demonstrating its feasibility for studying Aβ-induced neurodegeneration. Together, these findings reinforce the pathological role of mitochondrial Aβ accumulation in AD and highlight *N. furzeri* as a valuable model for studying neurodegeneration. Furthermore, this study emphasizes mitochondrial dysfunction as a potential therapeutic target for AD intervention.