GABAergic Dysregulation as a Modulator of Amyloid-Beta Neurotoxicity in Caenorhabditis elegans: A Computational-Behavioral Phenotyping Framework

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Alzheimer's disease is a neurodegenerative disorder characterized by loss of matter in the brain driven by amyloid-ß (Aß) aggregation. In scientific literature, the role of inhibitory neurotransmission, such as GABA, in modulating Aß toxicity remains unresolved. Therefore, this study tests whether GABAergic dysregulation actively amplifies Aß-associated neurotoxicity. To conduct this study, I developed and validated a novel computational framework that quantifies high-dimensional locomotor phenotypes not detectable through conventional assays. Using Caenorhabditis elegans (C. elegans), four strains were analyzed: wild-type (N2) and three Aß-expressing strains (CL2120, LSD1091, LSD2104). Worms were exposed to various concentrations of GABA reagent for 48 to 72 hours. Phenotypes were assessed using manual assays (thrashing and curling) and the computational framework, which integrates computer vision tracking, feature extraction, and statistical modeling. Results revealed previously undetected, dose- and genotype-dependent phenotypic shifts, with elevated GABA significantly exacerbating locomotor dysfunction in Aß strains relative to controls. Principal component analysis and ANOVAs, among other tests, further demonstrated significance across conditions, confirming the sensitivity of the extracted features. The major findings of this study include that (1) the framework enables detection of complex neurodegenerative dynamics, providing a scalable platform for mechanistic studies and therapeutic screening findings and (2) GABAergic dysregulation functions as an amplifier of Aß neurotoxicity, suggesting the viability of excitatory-inhibitory therapeutic methods in the treatment of Alzheimer's disease.

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