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METABOLIC ANALYSIS OF DROSOPHILA HEAD: INSIGHTS INTO ALZHEIMER'S DISEASE AND POTENTIAL THERAPIES

Larissa I. M. de Almeida (PG),[1]* Edimilson R. R. Júnior (PG),[2] Eurípedes A. S. Filho (Prof),[3] Thiago M. de Aquino (Prof),[2] Lucas Anhezini (Prof).[1]

larissa.almeida@icf.ufal.br

[1] *Laboratory of in vivo Analysis of Toxicity and Neurodegenerative Diseases, Department of Embryology and Histology, Institute of Biological and Health Sciences, Federal University of Alagoas, Maceió, AL, Brazil.*

[2] *Laboratory of Climatized Environments, Institute of Biological and Health Sciences, Federal University of Alagoas, Maceió, AL, Brazil.*

[3] *Nuclear Magnetic Resonance Research and Analysis Center, Institute of Chemistry and Biotechnology, Federal University of Alagoas, Maceió, AL, Brazil.*

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ABSTRACT

Alzheimer's disease (AD) is the most common neurodegenerative pathology, with the accumulation of amyloid-β (Aβ) peptides as the main pathological feature. However, current treatments only temporarily alleviate symptoms. The expression of mutated Aβ in Drosophila generates phenotypes similar to those observed in patients, such as neurodegeneration and cognitive loss. Approaches such as computational chemistry and metabolomics emerge as promising strategies both to identify potential therapies and to understand the metabolic changes associated with AD. In this context, our main objective was to use metabolomic analysis of the Drosophila head to investigate the metabolic signature throughout the disease progression and to evaluate the metabolic changes caused by Donepezil treatment. Donepezil, a drug considered the gold standard for the treatment of AD, serves as a reference in the development of new AChE inhibitors. For this reason, we used Donepezil as a positive control in our biological assays, administering it via oral exposure in animals. Using the UAS-GAL4 system and a fly line carrying human mutations in the amyloid precursor protein (APP), we induced transgene overexpression in the Drosophila brain. Using liquid nitrogen, we collected the heads of control and Alzheimer's model animals. Each experimental group consisted of eight replicates, and each replicate included 200 heads. After metabolite extraction, the polar fraction of the samples was transferred to NMR tubes. 1H NMR spectra were acquired on a Bruker Ascend 600 MHz spectrometer using a 1D NOESY pulse sequence with water pre-saturation. Dose-ranging testing with Donepezil is ongoing at concentrations of 0.1, 0.5, and 1.0 mg/mL, with the aim of determining the highest biocompatible concentration for subsequent studies. Regarding the analysis of metabolites, we observed that animals expressing APP in the brain showed a higher concentration of gamma-aminobutyric acid (GABA) when compared to the control group. GABA, the main inhibitory transmitter in the brain of adult mammals, is present in high levels in individuals with AD. In addition, the control group presented higher glucose levels than animals with Alzheimer's, since Aβ-induced neurotoxicity is involved in neuronal energy deficits, characterizing AD as a metabolic disease. Therefore, our evidence is promising and will contribute to understanding how brains with APP accumulation evolve for severe cases of Alzheimer's, in addition to identifying which metabolic pathways are affected during disease progression and in response to treatment.