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THE ROLE OF AMYLOID PRECURSOR PROTEIN IN A MODEL OF ALZHEIMER'S DISEASE

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ABSTRACT

Alzheimer's disease (AD) is a devastating disorder that leads to deterioration of cognition and memory. The prevalence of AD dramatically rises with age, and is also much greater in individuals with trisomy 21 (Down syndrome, DS). Many gene products are overexpressed in DS by virtue of having three copies of chromosome 21. Of these gene products, Amyloid Precursor Protein (APP) has received the most attention. However, despite intensive study, the factors contributing to synaptic dysfunction, and thus the cognitive decline observed in AD patients, are not understood. It is, therefore, of crucial importance to understand how synaptic signaling is disrupted. The scientific premise of the current research is to generate animal models of AD and undertake a genetics-based approach to gain a fundamental understanding of how AD changes neuronal function(s).

We have modeled the overexpression of APP in transgenic C. elegans to gain new insights into the pathophysiology of AD. We observed striking disruption of synaptic function in transgenic worms that overexpressed APL-1 (C. elegans homolog of APP). In particular, we found that motor-mediated transport of AMPA-type ionotropic glutamate receptors and glutamate-gated currents were severely disrupted, leading to altered behavior of the animals. These results provide a new conceptual framework for investigating the pathophysiology of synaptic dysfunction in AD.