Cephalexin as a Potential Novel Treatment for Parkinson’s Disease Through Modulation of Gut Inflammasome Activity and Neuroprotective Pathways

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Introduction: Parkinson’s disease (PD) is characterized by the loss of dopamine producing neurons. Many pathways involving mitochondrial dysfunction and synaptic function are involved in this loss. Evidence states the disorder originates in the GI tract, where inflammatory pathways promote aggregation of a-synuclein before its brain propagation. Cephalexin, an antibacterial agent, hasn’t previously been explored in this context. This study investigates whether Cephalexin affects inflammatory signaling associated with a-synuclein and pathways related to dopaminergic neuron survival. Methods: EGC cells were exposed to Cephalexin with and without Rotenone. Cell viability assays were performed. Molecular docking was used to evaluate interactions with inflammasome proteins. Caspase-1 induction was measured, and mRNA sequencing was conducted to identify gene expression changes. Statistical significance was determined using a Student's t-test or Wald's test. Results: Cephalexin significantly improved cell survival under Rotenone induced cytotoxicity, indicating a protective effect (53.188% vs Rotenone’s -13.401, $p < 0.05$). Molecular docking predicted strong interactions between Cephalexin and IL-1ß and Caspase-1. Cephalexin downregulated Caspase-1 activity (-45.31772575% vs Rotenone’s 131.4381271%, $p < 0.05$). Cephalexin downregulated pro inflammatory cytokine expression (IL-1ß, IL6R). Cephalexin also upregulated genes involved in neuronal survival, mitochondria production, and synaptic function (MEF2C, UBE2D3, TRIP10, DUSP16, LIN54). Conclusion: Cephalexin may slow gut inflammatory signaling contributing to early a-synuclein pathology while activating neuroprotective transcriptional pathways. This ability highlights Cephalexin as a promising therapeutic for PD.

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