Glutamine Transporter ASCT2's Novel Antioxidant Role in Parkinson's Disease

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Parkinson’s Disease (PD) is the second most common neurodegenerative disease, and it plagues millions of people worldwide. PD is characterized by the loss of dopaminergic neurons, associated with increased oxidative stress. Glutathione (GSH) is a prominent antioxidant; in PD, however, GSH levels are significantly diminished. A precursor of GSH is the amino acid glutamine, which is converted to glutamate and then to GSH. The carrier for glutamine is a transport membrane protein, identified as ASCT2, and this protein regulates glutamine uptake. In various forms of cancer, inhibition of ASCT2 has led to oxidative stress-mediated apoptosis. This research sought to elucidate the role ASCT2 can play in PD progression by using α-synuclein transfected SH-SY5Y neurons as an in vitro model of PD. V-9302 is a competitive inhibitor of ASCT2 and was used to diminish ASCT2 transport and glutamine uptake to examine the in vitro hallmarks of PD progression. Increasing V-9302 concentrations (decreased ASCT2 activity) led to lower cell viability, higher Reactive Oxygen Species levels, and higher α-synuclein levels. Also, increasing V-9302 concentrations led to a decrease in intracellular glutamine, glutamate, and GSH levels. In addition, a power regression model was generated for each of glutamine, glutamate, and GSH vs α-synuclein to test the biomarker potential of each of these molecules measure PD progression. Each of these molecules fits the regression model in a significant fashion. The findings suggest that inhibition of ASCT2 leads to the heightened hallmarks of PD progression. Future research could examine the exciting therapeutic potential of upregulating ASCT2 on PD progression.