ROLE OF METALLOTHIONEINS IN NEUROPROTECTION AGAINST PARKINSON’S DISEASE

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Introduction: Parkinson’s disease (PD) has hallmark symptoms of tremor and difficulty initiating movement. It is considered a disease of aging, primarily affecting individuals 65 years and above. Intracellular aggregates of the protein, alpha-synuclein, are the major pathological hallmark of PD and are linked to neurotoxicity. Raised extracellular copper has also been reported in PD and may be linked to alpha-synuclein aggregation. In this project, the potential neuroprotective role of the metal-binding proteins, metallothioneins (MT), has been explored in relation to copper-induced alpha-synuclein aggregation. The specific aims of the study were: 1) to investigate if metallothionein transfection can inhibit copper-induced alpha-synuclein aggregation in the SHSY-5Y neuroblastoma cell line; 2) to determine if up-regulation of endogenous expression of metallothionein by use of the synthetic glucocorticoid, dexamethasone, can prevent copper-induced aggregation of alpha-synuclein in SHSY-5Y cells. Methods: SHSY-5Y neuroblastoma cells were treated with 100\textmu M copper to cause alpha-synuclein aggregation. Cells were either transiently transfected with MT-2-GFP or MT-3-GFP isoform expression vectors or treated with dexamethasone at various concentrations to induce endogenous MT expression. Immunofluorescence confocal microscopy was used to quantify alpha-synuclein aggregates under the different treatment conditions. Results: Transfection with MT-2-GFP or MT-3-GFP caused reduced copper-dependent alpha-synuclein aggregation. Dexamethasone treatment resulted in a significant (\textit{p} < 0.01), dose-dependent up-regulation of MT expression in the SH-SY5Y cell line and a significant reduction in alpha-synuclein intracellular aggregates (\textit{p} < 0.01). Conclusion: Metallothioneins (MT) show neuroprotective capability against copper-induced alpha-synuclein aggregation. Efficient MT up-regulation by the glucocorticoid, dexamethasone, was found, with a concomitant reduction in alpha-synuclein aggregation. (249 words).