An unifying mechanism underlying dopaminergic and non-dopaminergic degeneration in Parkinson's disease?

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Parkinson's disease (PD) is a highly disabling neurodegenerative disease affecting mainly elderly individuals. Until recently, the massive degeneration of nigral dopamine neurons has been the focus of pharmacological treatment and pathophysiological research. However, the pathological process underlying PD is not restricted to degeneration of nigral dopamine cells, but involves also the accumulation of aggregated proteins into Lewy bodies in a series of well defined brain areas. The relevance of pathological protein aggregation for PD pathogenesis became evident with the discovery that one of the major components of Lewy bodies, i.e. the protein α-synuclein, appeared to underlie some of the rare autosomal forms of PD. In fact, Lewy bodies may be observed in a few susceptible brain areas prior to dopaminergic degeneration in the substantia nigra pars compacta. Projection neurons that accumulate non-degradable lipofuscin and neuromelanin pigments appear particularly susceptible to developing Lewy bodies. With age, the latter pigments accumulate progressively into lysosomal degradation vesicles. As these pigments are highly redox active and bind lysosomal enzymes, lipofuscin and neuromelanin granules could jeopardize cellular degradation capacity. The lysosomal system is solely responsible for the turnover of organelles, suggesting that even small defects in the lysosomal system lead to incomplete removal of oxidatively damaged mitochondria. This may result in enhanced generation of reactive oxygen species and, possibly, the delayed renewal of dysfunctional mitochondria. In addition, α-synuclein aggregates are removed via the lysosomal degradation pathway. Consequently, lysosomal dysfunction may cause the accumulation of the α-synuclein aggregates into Lewy bodies. Taken together, aging-accompanied pigment accumulation could jeopardize lysosomal function which, in turn, may be the basis of the pathological events observed in post mortem material of PD patients, i.e. mitochondrial dysfunction, protein aggregation and oxidative stress.

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