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A Pathophysiology of Parkinson's Disease and it's Applications

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About the Study

Parkinson's disease pathophysiology is defined as the death of dopaminergic neurons as a result of changes in biological activity in the brain as a result of Parkinson's disease. There are a number of proposed mechanisms for neuronal death in Parkinson's disease, but not all of them are well understood. Protein aggregation in Lewy bodies, disruption of autophagy, changes in cell metabolism or mitochondrial function, neuroinflammation, and blood-brain barrier breakdown resulting in vascular leakiness are five proposed major mechanisms for neuronal death in Parkinson's Disease.

Protein aggregation

Protein bundling, or oligomerization, is the first major proposed cause of neuronal death in Parkinson's disease. The protein alpha-synuclein is found in higher concentrations in the brains of Parkinson's disease patients, and because it is insoluble, it aggregates to form Lewy bodies (shown to the left) in neurons. Traditionally, Lewy bodies were thought to be the primary cause of cell death in Parkinson's disease; however, recent research suggests that Lewy bodies cause other cell death-causing effects. In any case, Lewy bodies are widely accepted as a pathological marker of Parkinson's disease.

Lewy bodies first appear in the olfactory bulb, medulla oblongata, and pontine tegmentum, and patients are asymptomatic at this stage. Lewy bodies form in the substantia nigra, areas of the midbrain and basal forebrain, and the neocortex as the disease progresses. This mechanism is supported by the fact that -synuclein lacks toxicity when it cannot form aggregates; that heat-shock proteins, which aid in refolding proteins prone to aggregation, have a beneficial effect on PD when overexpressed; and that reagents that neutralise aggregated species protect neurons in cellular models of -synuclein overexpression.

The protein alpha-synuclein appears to be a key link between decreased DNA repair and Parkinson's disease. ATM (Ataxia-telangiectasia Mutated), a major DNA damage repair signalling kinase, is activated by alpha-synuclein. Alpha-synuclein binds to breaks in double-stranded DNA and aids in the process of non-homologous end joining DNA repair. It has been proposed that cytoplasmic aggregation of alpha-synuclein to form Lewy bodies reduces its nuclear levels, resulting in decreased DNA repair, increased DNA double-strand breaks, and increased neuronal programmed cell death.

The breakdown of the blood-brain barrier is the fifth major proposed mechanism for cell death. Endothelial cells, pericytes, and astrocytes are the three cell types that tightly regulate the flow of molecules in and out of the brain *via* the BBB. BBB breakdown has been measured and identified in specific brain regions in neurodegenerative diseases, including the substantia nigra in Parkinson's disease and the hippocampus in Alzheimer's disease. Protein aggregates or cytokines produced by neuroinflammation can interact with cell receptors and alter their function in the BBB. VEGF and VEGF receptors, in particular, are thought to be dysregulated in neurodegenerative diseases.

The interaction of the VEGF protein with its receptors promotes cell proliferation, but it is thought to be disrupted in Parkinson's and Alzheimer's disease. This causes cells to stop growing, preventing the formation of new capillaries through angiogenesis. Disruption of cell receptors can also impair cells' ability to adhere to one another through adherens junctions.

Without new capillary formation, existing capillaries deteriorate and cells begin to separate from one another. As a result, gap junctions begin to fail. Gap junctions in endothelial cells in the BBB regulate the flow of nutrients to the brain, preventing large or harmful molecules from entering the brain. However, as gap junctions dissolve, plasma proteins can enter the brain's extracellular matrix. This mechanism is also known as vascular leakiness, and it occurs when capillaries degenerate, allowing blood and blood proteins to "leak" into the brain. Vascular leakiness can eventually cause neurons to change their function and move toward apoptotic behaviour or cell death.

Several proposed mechanisms could result in the loss of brain cells. In damaged cells, one mechanism involves an abnormal accumulation of the protein alpha-synuclein bound to ubiquitin. This insoluble protein builds up inside neurons, forming inclusions known as Lewy bodies. Lewy bodies first appear in the olfactory bulb, medulla oblongata, and pontine tegmentum, according to the Braak staging, a classification of the disease based on pathological findings proposed by Heiko Braak; individuals at this stage may be asymptomatic or have early nonmotor symptoms (such as loss of sense of smell, or some sleep or automatic dysfunction).

Lewy bodies form in the substantia nigra, areas of the midbrain and basal forebrain, and finally the neocortex as the disease progresses. These brain regions are the primary sites of neuronal degeneration in Parkinson's disease, but Lewy bodies may not cause cell death and may even be protective (with the abnormal protein sequestered or walled off). Other forms of alpha-synuclein (for example, oligomers) that are not aggregated in Lewy bodies and Lewy neurites may be toxic. The presence of Lewy bodies in cortical areas is common in dementia patients. Neurofibrillary tangles and senile plaques, which are hallmarks of Alzheimer's disease, are uncommon unless the person is mentally ill.

Other cell-death mechanisms include dysfunction of the proteasomal and lysosomal systems, as well as reduced mitochondrial activity. Iron accumulation in the substantia nigra is frequently observed in conjunction with protein inclusions. It may be related to oxidative stress, protein aggregation, and neuronal death, but the mechanisms are not fully understood.