



Parkinson's Disease: Physiopathology and Contributing Factors

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DESCRIPTION

Dopaminergic neurons in the brain die due to changes in Parkinson's disease-related biological activity, which is the pathophysiology of Parkinson's disease (PD). Although many different theories have been put forth, not all of them have a complete understanding of how neuronal death occurs in PD.

The main causes of neuronal death in Parkinson's disease are protein aggregation in Lewy bodies, disruption of autophagy, modifications to cell metabolism or mitochondrial function, neuroinflammation, and blood-brain barrier (BBB) collapse leading to vascular leakiness.

Protein aggregation

Protein bundling, or oligomerization, is the primary hypothesis for the cause of neuronal death in Parkinson's disease. Patients are asymptomatic at this stage as Lewy body's first manifest in the olfactory bulb, medulla oblongata, and pontine tegmentum. Lewy bodies form as the disease worsens in the substantia nigra, certain regions of the midbrain and basal forebrain, and the neocortex.

Autophagy disruption

Autophagy is a process by which internal cell components are digested and reused, and it is the second most important mechanism for neuronal death in Parkinson's disease. The regulation of cellular activity by autophagy has been demonstrated to be important for brain health. Parkinson's disease and other disorders of various types can result from disruption of the autophagy system.

Dysregulated mitochondrial breakdown has also been linked to autophagy malfunction in Parkinson's disease.

Changes in cell metabolism

The mitochondrial organelle, which produces energy, is the third main hypothesized cause of cell death in Parkinson's disease. The disruption of mitochondrial function in Parkinson's disease prevents the body from pro-

ducing energy, which ultimately leads to death.

The *PINK1* and Parkin complex, which has been demonstrated to promote mitochondrial autophagy, is thought to be the mechanism behind mitochondrial malfunction in Parkinson's disease (also known as mitophagy). A protein called *PINK1* is generally carried into the mitochondrion, but it can also build up on the outer surface of damaged mitochondria.

Accumulated *PINK1* then attracts Parkin, who starts the breakdown of malfunctioning mitochondria as a "quality control" process. The *PINK1* and *PRKN* genes are hypothesized to be altered in Parkinson's disease, limiting the breakdown of damaged mitochondria, leading to aberrant mitochondrial function and shape, and ultimately cell death. Age-related accumulation of mitochondrial DNA (mtDNA) mutations has also been observed, suggesting that this mechanism of neuronal death is more susceptible as people get older.

Reactive oxygen species production is yet another mitochondrial-related mechanism for cell death in Parkinson's disease (ROS). ROS are very reactive oxygen-containing molecules that can impair mitochondrial and cellular function. Age-related declines in mitochondrial function lead to an increase in net ROS generation, which ultimately leads to cell death since mitochondria can no longer eliminate ROS while continuing to produce them.

According to research, alpha-synuclein and dopamine levels in the mitochondria and endoplasmic reticulum are probably responsible for both oxidative stress and the symptoms of PD. Separate pathogenic events that together lead to cell death in PD appears to be mediated by oxidative stress. It's possible that oxidative stress, which causes cell death, is the common factor underpinning several processes. DNA damage brought on by oxidative stress. Such damage is amplified in the substantia nigra of PD patients and may result in the loss of nigral neuronal cells.