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Effects of α-Synuclein on Mitochondria and Pathogenesis of Parkinson Disease

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Many neurodegenerative diseases are associated with a characteristic protein. Parkinson's (PD) is characterized by accumulation of the protein α-synuclein (α-syn) in neurons (accumulations are known as Lewy Bodies). Current research is taking place to help better understand the workings of α-synuclein (α-syn) in the neuronal cells. Recent research suggests that α-synuclein has the ability to inhibit vesicle fusion, alter mitochondrial fission and fusion, and lead to increased fragmentation in mitochondria, which can lead to early neuronal cell death.

Introduction

It is estimated that 500,000 people suffer from Parkinson Disease, with 50,000 new diagnoses annually. PD is a degenerative disorder of the CNS (central nervous system) and results from cell death of dopamine producing cells in the midbrain, specifically the substantia nigra. Symptoms include shakiness, rigidity, trouble walking and later cognitive and behavioral problems may arise. PD is most common among the elderly. Many neurodegenerative diseases are associated with a characteristic protein, but in other cases the mechanisms are unknown. In the case of PD, the protein α-syn is the characteristic protein. α-Synuclein is a small membrane protein that localizes in the axon terminal of neurons and is known to have an effect on neurotransmitter release and affect the mitochondria within the neurons. To better understand the effects of α-syn, research has been conducted, to determine the effects of α-syn on the neurons and on mitochondria; which are starting to be seen as having a primary pathological role in PD, as well as in many other neurodegenerative diseases such as Alzheimer's.

Recent Progress

Before a cure can be found for a disorder such as Parkinson's, it must be understood how the disease works within the body. Current research is being conducted to figure out how to catch Parkinson's early, and how the protein α-synuclein figures into its pathology. Many neurodegenerative diseases are associated with the accumulation of a characteristic protein; in Parkinson's disease that protein is α-Synuclein (α-Syn). As with many diseases the mechanisms are unclear. When overexpressed α-Syn is shown to produce toxicity in yeast and Drosophila (Nemani et al, 2009) but in most mammalians the effects of overexpression are very minimal which leaves the question how α-Syn lead to Parkinson's disease unanswered. To better understand how α-Syn works, researchers injected rats with a wild type human α-Syn. To monitor these effects the rodents were also injected with an antibody that recognizes bout human and rat α-Syn proteins. . Using fluorescence microscopy it is possible to mark neuron vesicles and monitor their release in real time. By using vesicular glutamate transporter 1 with pHlourin it is possible to monitor the vesicles when they are performing exocytosis and endocytosis. When undergoing exocytosis fluorescence increases, when undergoing endocytosis or at rest fluorescence is quenched. Vesicles exhibiting overexpressed α-Syn demonstrate a distinct decrease in fluorescence during exocytosis (Nemani et. Al, 2009). Further experimentation was performed to see whether α-Syn affected the mechanics of fusion or something deeper. Results displayed that α-Syn, while not affecting

the mechanics of fusion does decrease the size of the available pool of vesicles to be released; it also reduces the number of certain membrane proteins associated with synaptic vesicles. More in depth studies take a look at the effects of α-Syn on mitochondrial fission, fusion and fragmentation. To determine the effects of overexpressed α-Syn researchers overexpressed the protein in neuronal SH-SY5Y cells. Cellular imaging monitored changes in the cell. Results showed that overexpression of α-Syn increase mitochondrial fragmentation by 36%-46% (Kamp et al, 2010). To observe the effects of α-Syn on oxidative phosphorylation transfection into COS cells was used to ensure more efficient expression, 24 hours after the cells were transfected the cells expressing α-Syn showed fragmented mitochondria. While at first, cells did not exhibit any changes in respiration rate after 48 hours decreases in respiration were observed followed by cell death (Nakumura et. Al, 2011). The cause of this is a decline in overall size of mitochondria caused by fragmentation. This reduced decline in respiration eventually leads to neuronal death. Though overexpression leads to increased mitochondrial fragmentation, cells that exhibit none or minimal expression of α-Syn do not demonstrate increased fragmentation (Nakumura et. Al, 2011). This means that α-Syn may have a large part in the pathology of PD.

Discussion

Current research displays that α-Syn may have a primary importance in the pathology of Parkinson's disease. This research also displays that the mechanisms used by α-Syn have a physiological role more than an anatomical role. Further experimentation could be used to closely examine the role of α-Syn on the mitochondria; specifically on how it causes signs of physiological aging in the organelle.. Research conducted in these papers could also be used to further the understanding of other neurodegenerative diseases. It could lead other researchers to take a look at the physiological effects of the protein, or how the protein works on the different organelles within the cells of the brain, as opposed to the cell as a whole.

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