Perceiving Parkinson's

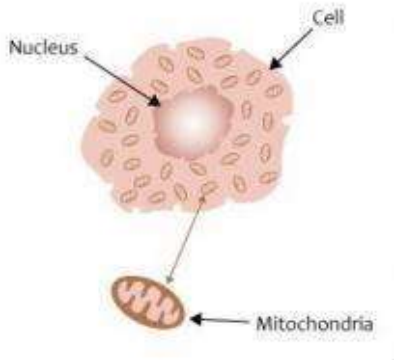
Mitochondria Dysfunction In Parkinson's (Day 21)

We now move from the gut bacteria to a different kind of "bacteria."

Far back in time, 1.5 billion years ago, a large eukaryotic cell may have engulfed and internalized one or more smaller bacteria resulting in a **symbiotic**, mutually beneficial relationship. In this relationship, the eukaryotic cell provided a stable environment for the bacteria, and the bacteria made energy for the eukaryotic cell. The arrangement became permanent, and these bacteria or **mitochondria** now live within nearly every human cell.

Within each mitochondrion exists a structure called the **electron transport chain** that consists of four subunits called **Complexes I**, **II**, **III**, and **IV**. The electron transport chain **produces energy**, allowing mitochondria to function as "batteries" for their cell.

Each cell contains a **population** of several hundred mitochondria that interact through **fusion** (two mitochondria merge together into a larger one) and **fission** (one mitochondrion splits apart into two smaller ones). Through fusion and fission, mitochondria change their shape and size, allowing them to move from one part of the cell to another so that they can **distribute energy** throughout the cell.

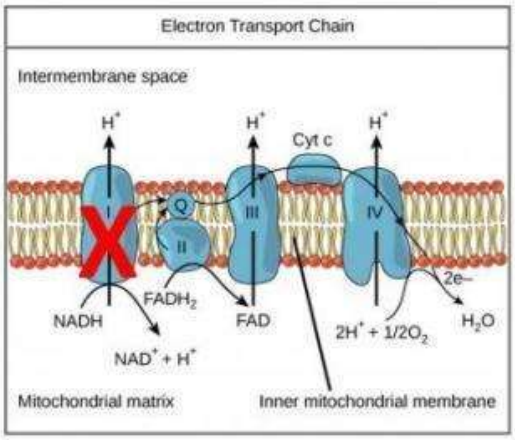


There are several hundred mitochondria per cell.

Accumulating evidence shows that **mitochondria are dysfunctional in Parkinson's**. This dysfunction affects both energy production and energy distribution within the cell.

First, the mitochondria in Parkinson's have **impaired energy production**. In the autopsied brains of people who had Parkinson's in life, the mitochondrial electron transport chain is damaged, specifically at **Complex I which is impaired by 30%**; this may not sound too bad, but there are reasons to believe

that if enough of the mitochondria within a cell are affected by this 30% impairment, the end result is a critical **failure of energy production** within the cell.



In Parkinson's, Complex I of the electron transport chain is 30% impaired (shown by the red X).

Second, the mitochondria in Parkinson's **do not undergo fission and fusion properly**. In genetic forms of Parkinson's, there are significant defects in the genes that regulate fusion and fission. Emerging evidence also suggests that fission and fusion are **impaired** in non-genetic forms of Parkinson's. Since fusion and fission allow the mitochondria to change their shape and size and move around within the cell, this translates into a **failure of energy distribution** for the cell.

Thus, in Parkinson's there is a "double whammy" of failed energy production and failed energy distribution, leading to overall **energy failure** within certain cells. This is particularly problematic for **neurons**, which have high energy demands yet also possess **complex structural features** that make them even more susceptible to energy failure:

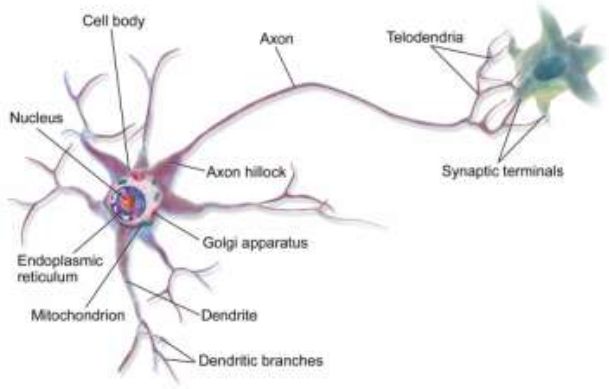
(1) Neurons have **long projections** called axons and dendrites that can extend the length of a single neuron by several centimeters or more. The mitochondria in neurons must work extra hard to produce and distribute energy along these long projections.

(2) Some neurons, such as substantia nigra neurons, are **highly branched**, with each neuron containing up to several hundred thousand connections. The mitochondria in substantia nigra neurons must work extra hard to produce and distribute energy throughout their extensive connections.

(3) Some neurons, such as substantia nigra neurons, have **little or no myelin**, an insulating substance that helps relay signals more efficiently. The mitochondria in substantia nigra neurons must work extra hard to produce and distribute energy along their poorly myelinated projections.

Therefore neurons, especially substantia nigra neurons, have some of the **highest energy demands** of any cell in the body yet at the same time their long projections, extensive branching, and lack of myelin make it **very challenging** for their mitochondria to produce and distribute energy for them. Even a

slight degree of mitochondria dysfunction, as occurs in Parkinson's, may result in critical energy failure and tilt the neuron into dysfunction or death.



Neurons have high energy demands, yet complex structural features.

Thus, we have learned two more things - in Parkinson's, the mitochondria electron transport chain is damaged, resulting in impaired energy production, and the mitochondria don't undergo fusion or fission properly so they can't move around the neuron efficiently, resulting in impaired energy distribution. This **mitochondria dysfunction is a core feature of Parkinson's**. Since neurons have high energy demands yet complex structural features that make it difficult for their mitochondria to produce and distribute energy compared to other cells, neurons are even more susceptible to mitochondrial dysfunction than other cells. The more we know about the factors leading to mitochondria dysfunction, the more we may reveal about the neuron-killing process in Parkinson's.

Matt (Neurologist, Waikato Hospital).

References

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(4) Sulzer et al. 2013. Neuronal Vulnerability, Pathogenesis, and Parkinson's Disease. Movement Disorders 28(1), 41-50.