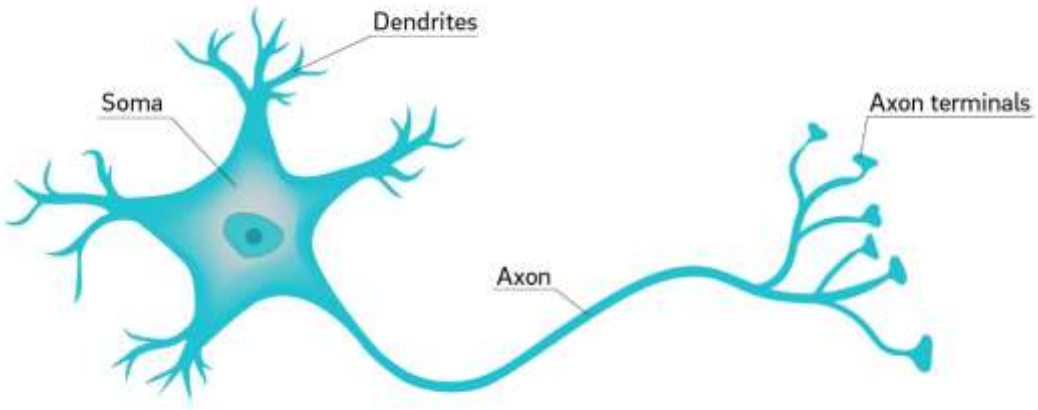
Adjourning Alzheimer's

Mitochondria Dysfunction (Day 18)

Now that we have described the chief pathological hallmarks of Alzheimer's (neuron loss, excess amyloid beta, and tau accumulation), let's step back and consider **the neurons themselves**. Neurons possess several unique features that make them different from other cells in the body.

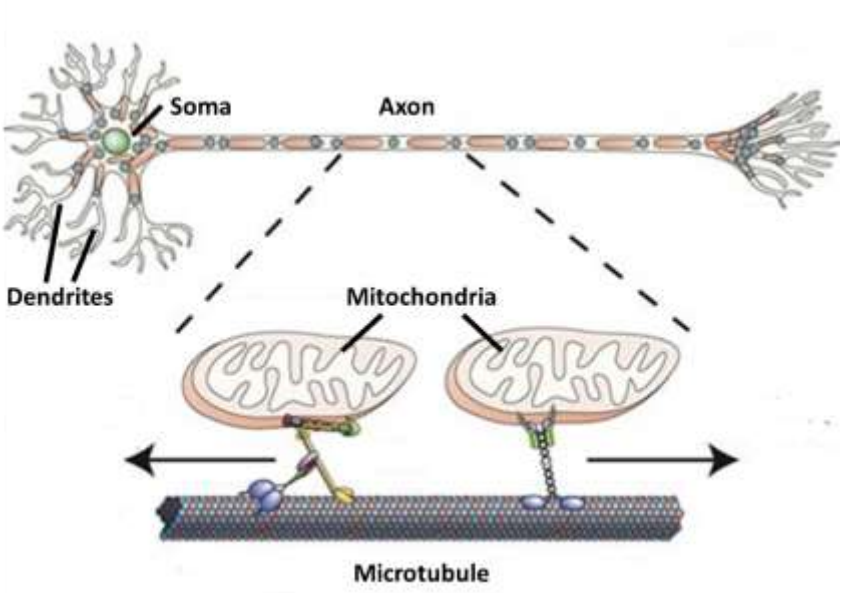
Neurons consist of a **soma** (body), an **axon** (a long projection that conducts signals to other neurons), and innumerable **dendrites** (projections that receive signals from other neurons). A neuron's axon may be **over a meter** long and the dendrites may number in the **hundreds of thousands**. Despite these colossal structural features, neurons must maintain a standing capacity to conduct multiple signals at any given time. This requires a lot of energy; in fact, neurons are among the highest energy-consuming cells in the body (the brain constitutes 2% of the body weight but consumes 20% of its energy). There must be something rather fantastic inside neurons that allows them to do this, and indeed there is - mitochondria.



A neuron consists of a soma, axon, and innumerable dendrites.

Mitochondria are small, ellipsoid-shaped "batteries" that travel within neurons, producing energy where and when it is needed. Mitochondria constantly undergo two opposing processes - **fusion** (two or more mitochondria joining to create a larger one; allows damaged mitochondria to join with healthy ones so they can be repaired) and **fission** (a larger mitochondrion splitting to create two or more smaller ones; allows larger mitochondria to split into smaller ones that can travel down the long, thin axon and dendrites).

Mitochondria travel using "tracks" called **microtubules**; about one-third of the mitochondria within any neuron are moving along these tracks at any given time.



Mitochondria are ellipsoid-shaped “batteries” that travel using “tracks” called microtubules.

Since neurons rely on mitochondria for their huge energy needs, it is vital for them to keep a **healthy mitochondria pool** at all times. The health of this pool is determined by three indices:

(1) Mitochondria **population dynamics** is the number and distribution of mitochondria within the neuron. They must be evenly distributed throughout the neuron, from the soma (where they repair themselves) to the axon and dendrite terminals (where they generate energy for signal conduction). Fusion and fission must be balanced (fusion for repair, fission to create smaller mitochondria that can travel down the axon).

(2) Mitochondria **structure** refers to the mitochondria cristae (inner membrane), which contains numerous electron transport chains (protein complexes that produce energy, consisting of complexes I to IV). To maximally produce energy, all four complexes must remain undamaged.

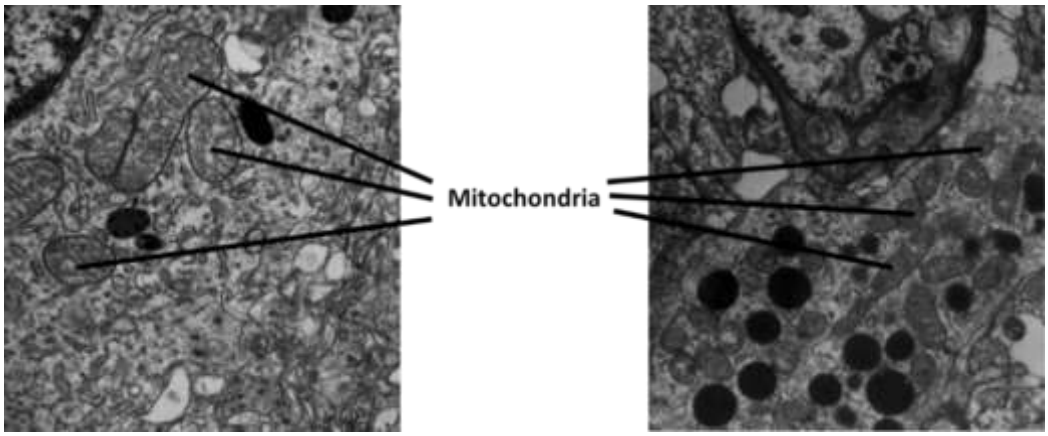
(3) Mitochondria **function** refers to the primary role of mitochondria, which is to produce energy for the neurons they reside within. Intact function relies on intact population dynamics and structure.

Extensive evidence shows that **mitochondria are dysfunctional** in Alzheimer’s, on all three indices:

(1) In Alzheimer’s, **mitochondria population dynamics are altered** - Their numbers are reduced, and they are unevenly distributed, with many clustering in the soma. Fusion and fission are not balanced, with a loss of uniform mitochondria size (most are too small, though some are too large) and ellipsoid shape (most are too round, though some are too long).

(2) In Alzheimer’s, **the mitochondria structure is altered** - The cristae are disrupted and broken. Moreover, the electron transport chains are damaged, particularly complex IV.

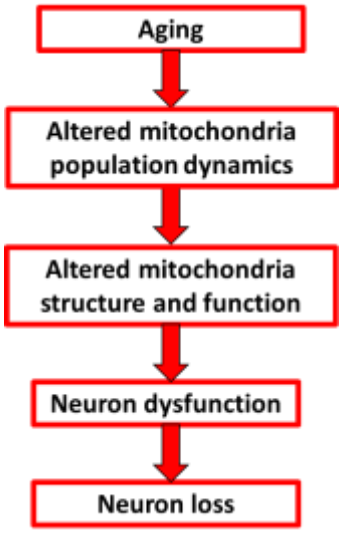
(3) In Alzheimer's, **mitochondria function is altered** - Due to the altered population dynamics and structure, mitochondria energy-producing capacity is impaired, which means energy failure for the neuron.



In human brain tissue, normal mitochondria (left figure) are ellipsoid, whereas those in Alzheimer's (right figure) are often too small, and too round (or too long).

Mitochondria dysfunction is **widespread** in Alzheimer's. It occurs in many brain structures, including those that suffer neuron loss (such as the hippocampus and cerebral cortex), but also in those that do not (such as the basal nuclei and cerebellum), and even in non-neuronal cells (such as muscle and blood cells). The dysfunction appears years or decades before the neuron loss.

Some researchers support the **mitochondria cascade hypothesis**, which posits that aging triggers mitochondria dysfunction, followed by neuron death due to energy failure.



The mitochondrial cascade hypothesis posits that aging triggers mitochondria dysfunction.

The mitochondrial cascade hypothesis is quite promising, but there are two potential **weaknesses**:

(1) **It describes mitochondria dysfunction as an inevitable feature of aging.** However, mitochondria dysfunction is not an inevitable feature of aging (just as Alzheimer's is not an inevitable feature of aging). Many neurons in cognitively normal elderly people show no mitochondria dysfunction, so there must be something else that tips a person's mitochondria into a state of dysfunction.

(2) **Neurons that do not die in Alzheimer's still show mitochondria dysfunction**. Although neurons in the basal nuclei and cerebellum show mitochondria dysfunction in Alzheimer's, they remain relatively unaffected by neuron loss. In addition to mitochondria dysfunction, something else must be required to produce the neuron loss seen in the hippocampus and cerebral cortex.

To sum up, neurons must maintain a standing capacity to generate large amounts of energy at any time; to do this, they must maintain a healthy pool of mitochondria. In Alzheimer's, mitochondria are dysfunctional in their ability to produce energy for neurons; however, the dysfunction is not entirely explained by aging, nor is the dysfunction alone sufficient to kill most neurons. Along with tau accumulation, **mitochondria dysfunction and the ensuing energy failure within the neuron play a major role in driving neuron loss in Alzheimer's, but there is more to the story**. Deeper still.

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References

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