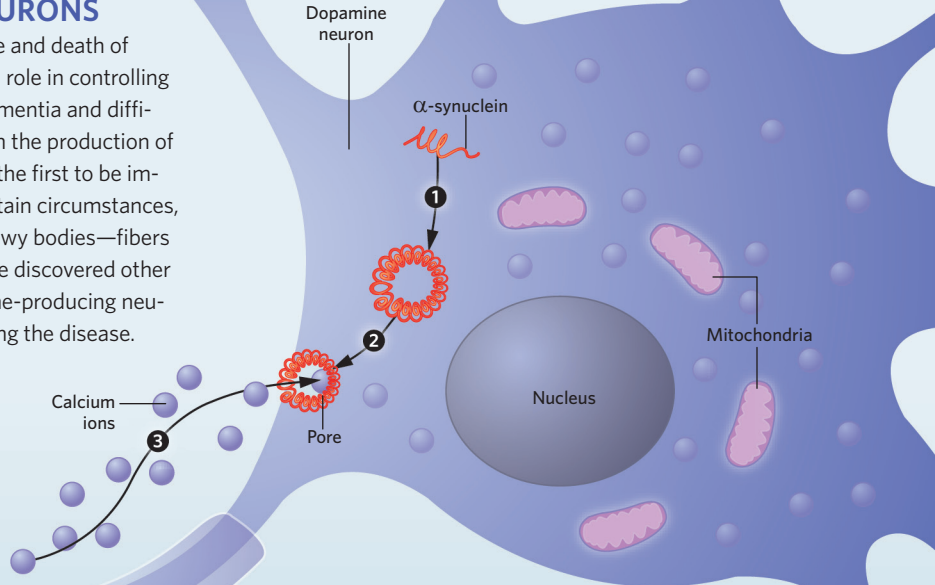


DEATH OR DAMAGE OF DOPAMINE NEURONS

The hallmark pathology of Parkinson's disease is the damage and death of dopamine producing neurons in the brain. Dopamine plays a role in controlling movement, cognition, learning, and mood, explaining the dementia and difficulty with motor control exhibited by patients with deficits in the production of this key neurotransmitter. The α -synuclein gene was one of the first to be implicated in this disease. It produces a protein that can, in certain circumstances, aggregate to form bundles that are a major component of Lewy bodies—fibers that disrupt normal cell processes. Recently researchers have discovered other mechanisms by which this protein damages or kills dopamine-producing neurons, as well as other genes that may also play a role in driving the disease.

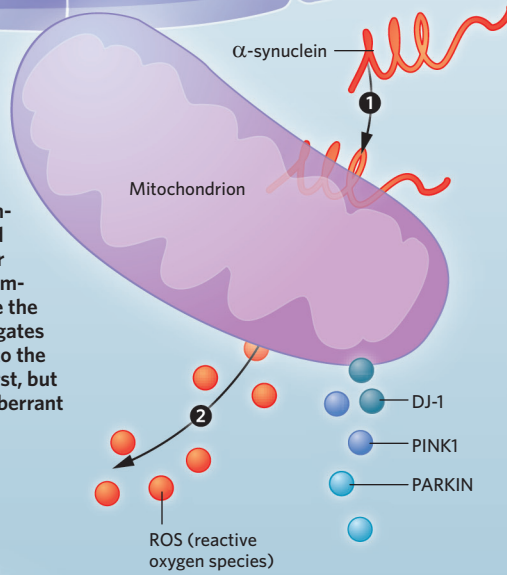
A BURSTING THE MEMBRANE

Some researchers propose that single α -synuclein molecules bind together in a doughnut shape **1** that inserts into the plasma membrane and forms a pore **2**. The hole allows calcium ions—a tightly regulated ion that helps neurons propagate signals—to accumulate in the cell at toxic levels **3**.



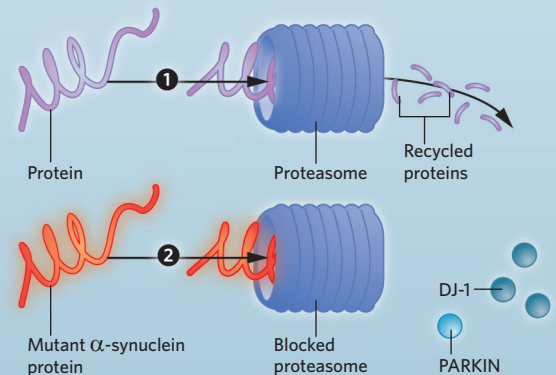
B MITOCHONDRIAL DAMAGE

Some evidence suggests that an overabundance of α -synuclein **1** causes mitochondrial dysfunction which can lead to neuron death. However, other researchers have shown that damaged mitochondria can instigate the formation of α -synuclein aggregates **2**, which in turn become toxic to the cell. It's unclear which comes first, but it appears that each feeds the aberrant production of the other.



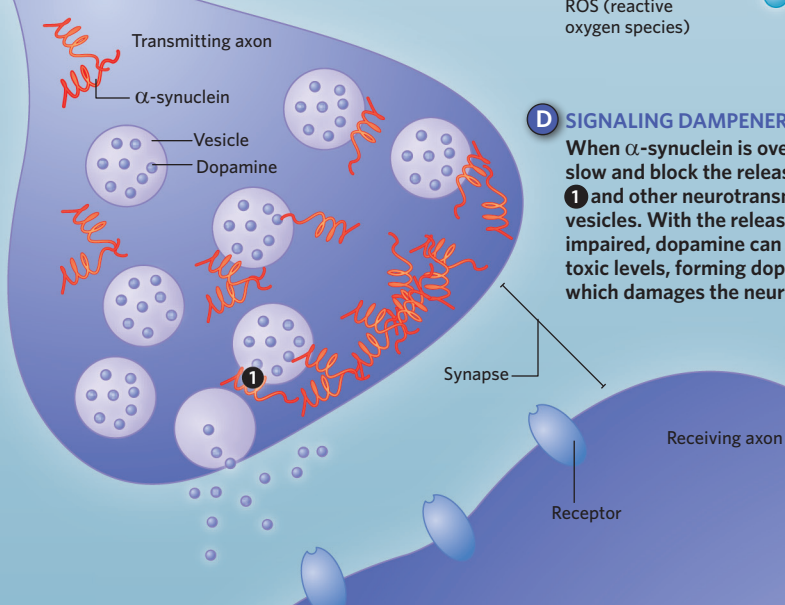
C RUINED RECYCLING

Rather than an overabundance of α -synuclein, some think that it's a mutant form of the protein that contributes to disease. Mutant forms of the protein are not easily degraded by the cell's recycling machinery **1**, such as the proteasome and autophagy-lysosome pathways and thus interferes with the normal recycling **2** of damaged organelles and proteins, creating a deadly back-up of junk-proteins in the cell.



D SIGNALING DAMPENERS

When α -synuclein is overproduced, it can slow and block the release of dopamine **1** and other neurotransmitters stored in vesicles. With the release increasingly impaired, dopamine can accumulate to toxic levels, forming dopamine quinone, which damages the neuron.



ROLE OF AUTOSOMAL RECESSIVE GENES

Mutations that render these genes inactive or less productive produce some Parkinson's-like effects.

- DJ-1 is a molecular chaperone with roles in antioxidant gene expression and possibly counters oxidative stress in mitochondria
- PARKIN normally tags proteins with ubiquitin and plays a role in mitochondrial homeostasis
- PINK1 is normally involved in maintaining normal mitochondrial function and may act in concert with PARKIN