WHAT GOES WRONG IN PARKINSON'S?

This article is intended as a simple overview of the current thinking behind what goes wrong in Parkinson's. The focus is potential problems inside the nerve cell (neuron), not problems resulting from dopamine-releasing neurons losing the ability to communicate.

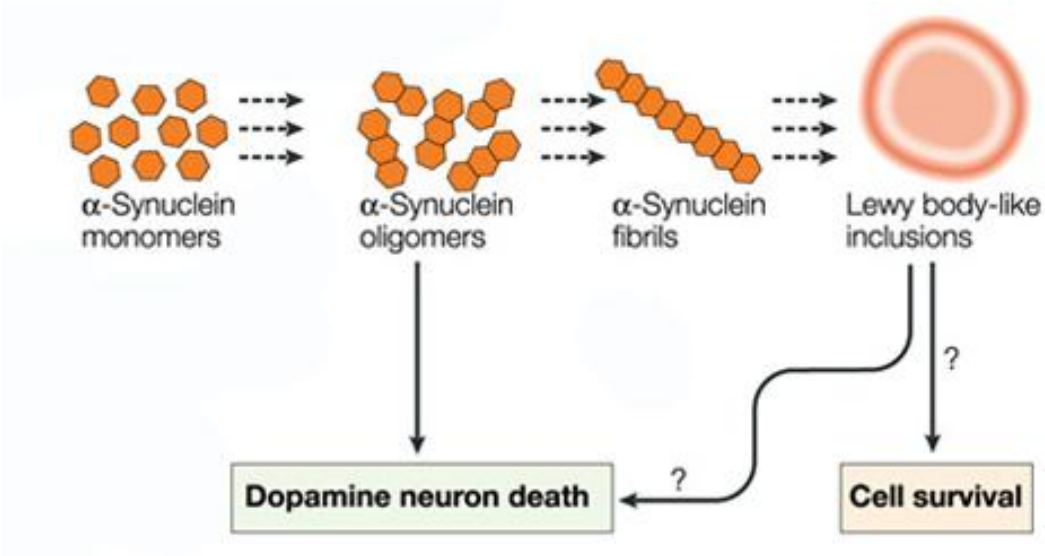
If you meet one person with Parkinson's, you've met one person with Parkinson's. This saying captures the great variety in the issues faced by people with Parkinson's (PwPs). This variety also seems to apply to the underlying molecular mechanisms. We do not know that all or just some of the things that can go wrong actually do go wrong in every PwP. The same end result that affects PwPs in different ways may well come from a variety of different molecular pathways.

What do we know about what can go wrong inside neurons?

PROTEINS MISFOLD

Proteins are long chains of building blocks that fold into 3-D structures to function. The endoplasmic reticulum (ER), the protein factory of the cell, can become stressed and errors can occur in the folding of some proteins. Alpha-synuclein (αSN), a protein that normally helps cells to export vesicles, small packages of chemical messengers, might be particularly important in Parkinson's. Misfolding of αSN can cause it to clump together in twos, threes and fours etc, then to oligomers. Eventually, oligomers can accumulate into fibre-like structures called fibrils.

The oligomers (and possibly fibrils) of αSN could be especially damaging and could spread from one neuron to another, where they appear to start off the decline and eventual death of the next neuron.



We know that people with some inherited forms of Parkinson's have a mutation in (or multiplication of) the gene for αSN, which might promote the misfolding of the protein, making it more likely to form oligomers and fibrils.

MITOCHONDRIA MALFUNCTION

Mitochondria are the power stations of the cell. In Parkinson's, at least two things can go wrong with them. First, they can become inefficient and start to break down sooner than normal. A similar phenomenon is seen in Type 2 diabetes, and some researchers think there are links between the two conditions.

Second, the normal recycling of old and tired mitochondria can go wrong. This means there is a buildup of old and defunct power stations, clogging up the normal road network of the cell.

Dopamine-releasing neurons in the brain are relatively large and have connections (synapses) with many other neurons. It takes a lot of energy to run them, and they appear to be particularly sensitive to problems with mitochondria.

LYSOSOMES GO WRONG

Lysosomes are bags of enzymes that digest large molecules imported by the cell, as well as being a key part of recycling out of date and unwanted cellular components. In Parkinson's, they can become clogged up and inefficient. They eventually stop working, leading to the equivalent of a rubbish strike.

One genetic form of Parkinson's involves mutations in the GBA gene, which produces an enzyme, glucocerebrosidase. A reduction in this enzyme's activity can lead to an accumulation of αSN as well as to fatty material blocking the lysosomes.

OXIDATION HAPPENS

Oxidation is a chemical reaction that can damage many different components of the neuron, particularly when the energy-producing systems of the mitochondria go wrong. Normal function of these power stations produces reactive oxygen species (ROS). In Parkinson's, ROS might not be broken down effectively, potentially causing damage to both mitochondria and lysosomes. Oxidative damage can also come from the breakdown of dopamine itself.

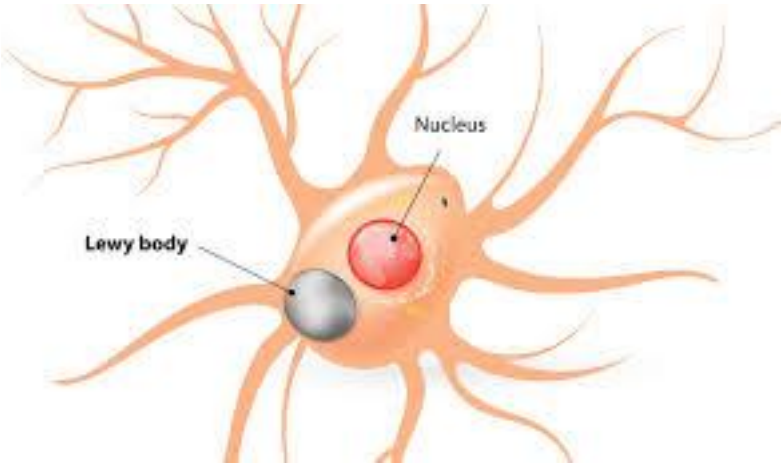
INFLAMMATION SETS IN

Inflammation is part of the body's natural mechanism to get rid of bad stuff, whether it is an internal problem or an external invasion. Microglia, the immune cells of the brain, are key to this. In Parkinson's, microglia recognize that something is going wrong in dopaminergic neurons in the brain and follow their normal procedure of trying to remove the problem. The end result, however, is the death of the neuron.

LEWY BODIES FORM

Under the microscope, Parkinson's brain tissue often has Lewy bodies, odd-shaped deposits containing αSN as well as other proteins and some fats. Lewy bodies are like piles of rubbish in the middle of the street.

It had been thought that Lewy bodies were the cause of neuronal death, but an alternative theory is emerging, suggesting they are actually a defence mechanism that helps the cell to live longer. They've now been discovered in cases of dementia and 10-20% of normal, aged brain tissue.



SO, HOW DOES PARKINSON'S DEVELOP?

We don't know.

One theory (the Braak hypothesis) suggests that Parkinson's starts in the gut, and the pathology travels up the vagus nerve to the brain. It is also thought that it may start in the olfactory bulb, which receives smell and taste signals, and spreads through the brain from there. There are other suspected causes, but

whatever the trigger, there are several pathways that could be at play.

It could start with endoplasmic reticulum (ER) stress that causes proteins to misfold which causes mitochondria to malfunction which causes lysosomes to get blocked up which causes inflammation which eventually kills the cell.

It could start with αSN misfolding which leads to the same chain of events.

It could start with lysosomal malfunction which leads to a buildup of αSN then a

blockage of dead mitochondria which leads to an energy deficit which leads to ER stress which causes αSN misfolding leading to oligomer formation which gives a double whammy to mitochondria resulting in inflammation that eventually kills the cell.

It could start with damaging oxidation, causing mitochondrial and lysosomal malfunction, leading to the buildup of cellular rubbish, leading to inflammation that kills the cell.

Or, it could follow any of the above pathways in different PwP, giving the same end result – the death of essential nerve cells.

There are lots of other molecular actors in this cellular mystery play – LRRK2, DJ-1, calcium channels, RAC-1, glycation, NURR-1, etc. They have turned up for casting, but they have not all been given starring roles. We will hopefully see the full picture over the next few years.

Thanks to Dr Simon Stott, Prof Peter Magill and members of the Oxford branch of Parkinson's UK for helpful comments.

For further information, I recommend https://scienceofparkinsons.com

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