Oxidative stress and mitochondrial dysfunction in Parkinson's disease

A chronological model for Parkinson's disease

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Introduction

Parkinson's disease is characterized by the loss of dopaminergic neurons in the *substantia nigra* (SN) in the midbrain and a deficit of dopamine in the terminal synapses in the striatum, but a simple model presenting the stages leading up to this condition has so far not been presented.

This article proposes a simplified model that schematically represents the chronology of the major events believed to be involved in the pathogenesis of Parkinson's disease in a way designed to be accessible to patients. The model also proposes which steps may be subject to influence through medical or patient intervention, so that patients can make informed decisions about how to manage their own condition. This model covers the progression of Parkinson's disease from benign redox imbalance in brain cells to chronic oxidative stress which initiates a cascade of two major events: (i) mitochondrial dysfunction, a condition which reduces the energy available to host cells and (ii) degeneration of vulnerable axons in the striatum region of SN neurons as a consequence of this energy loss. The model links these major events and draws attention to the considerable delays occurring between the beginning of the events and the observation of symptoms eventually produced by them, a situation which masks the true progression of the disease.

The model was designed to be a chronological representation of the progression of Parkinson's disease. For this to be both feasible and useful as a tool, it was designed to respect a number of conditions.

- Each stage in the model is supported by evidence of its physical existence,
- The chronology of events is respected,
- Each stage has identifiable characteristics that differentiate it from other stages,
- There are feasible mechanisms driving the progression from one stage to another,
- The model is adaptable to take account of complementary factors and variants,
- The model offers the possibility being tested experimentally.

To build this model, evidence for the three major conditions already identified in the progression of Parkinson's disease; age-related oxidative stress, mitochondrial damage and loss of dopaminergic SN neurons was investigated. There are convincing arguments for the processes that link these conditions and make up the basic version of the model. Each process has also been examined in more detail to consider the potential roles other factors having the capacity to modify or invalidate the simplified model, such as α-synuclein, genetic variants, toxins or lifestyle. These additional factors add complexity to the model but help to understand how the pathogenesis and development of Parkinson's disease is multifactorial. This article presents the simplified model only. The more complex model will be presented at a later date.

1 - Age-related changes in cellular function

The ageing process involves small but constant changes in cellular function caused by programmed changes in gene expression, reduced mitochondrial function and imperfect repair of damage to DNA, membranes and cellular organelles. These develop along a common pathway for all cells and generally lead to chronic but sub-symptomatic conditions. With advancing age, certain cell types may become proportionately more dysfunctional triggering established disease conditions. For Parkinson's disease the most affected cells are dopaminergic (DA) neurons that originate in the SN but reach far into the striatum with an extensive axon arborescence. Here we propose how benign cellular redox imbalance and normal mitochondrial ageing can lead to irreversible degeneration of dopaminergic neurons under certain conditions. In this pathway, the effects of oxidative stress and mitochondrial damage are multiplied in regions of the brain where the mechanisms which should normally restore a balanced state are impaired. Under these conditions, these two processes, working in concert generate a cascade of two major events; mitochondrial dysfunction followed by axon degeneration of DA neurons. The progression from the healthy state to neuron failure can be described in terms of specific stages.

The best of health: redox balance

Redox homeostasis and oxidative stress are concepts that may not be easily understood by patients. They are the result of the equilibrium between the creation and rapid elimination of highly active chemical entities called Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS). These are continuously generated as by-products when mitochondria in cells make energy from glucose and oxygen. An important type of ROS is the superoxide anion (O_2^-) which, because of its extreme reactivity, has a very short half-life (~1ns). It rapidly oxidizes any molecule or tissue in close proximity unless it is neutralised by antioxidant molecules or converted to other, more stable forms of ROS such as H_2O_2. ROS oxidise components or contents of the cells that produce them; lipid membranes, proteins, enzymes, mitochondria and DNA. This process is called oxidative stress (OS) and the damage it causes generates inflammation and reduces the performance of the cells. Redox homeostasis (redox balance) therefore corresponds to a lack of oxidative stress. Cells use a gene-based mechanism to maintain the redox balance at a healthy level inside cells. The main actor in this process is a protein called Nrf2 (Nuclear factor erythroid 2-related factor 2). Nrf2, also known as the Master Regulator of Anti-oxidant Responses.[1,2] reacts to signals of excessive ROS and by migrating to the nucleus and binding a segment of DNA called Antioxidant Response Elements (ARE). This initiates the transcription of a battery of genes to express antioxidant and detoxifying enzymes, anti-inflammatory cytokines and simultaneously suppresses inflammatory cytokines.

Stage 1: Oxidative stress increases with age, exacerbated by mitochondrial decline, environmental, epigenetic and genetic factors

Oxidative stress increases: as part of the ageing process, human cells are programmed to produce less Nrf2 protein and more of a control protein called Keap1 (Kelch-like ECH- associated protein 1), which regulates how much Nrf2 is released to bind to ARE.[3,4] This change in the ratio of Nrf2/Keap1 progressively increases oxidative stress in cells where Nrf2 is normally active.[5,6] Oxidative stress (OS) remains under control, but the range is shifted towards more oxidising conditions.

Mitochondrial function decreases: mitochondria, the organelles that produce energy for cells, also decline with age. The volume of mitochondrial DNA, the integrity of the organelles and their functional capacity decrease due to oxidative damage induced by ROS and the accumulation of mutations. Progressively, several functions are modified including reduced energy production and increased ROS generation and greater need for mitochondrial recycling. Mitochondrial recycling is

the quality control process that extracts damaged components of mitochondria, creates new organelles and removes debris.[7–11]

These two changes are both moving in the same direction; they are synergistic and self sustaining.

Other factors contributing to oxidative stress are toxins derived from food, poor diet or exposure to pesticides or toxic chemicals as well as lack of exercise and obesity.[12,13] Genetic mutations are known to contribute to the development of familial and early onset Parkinson's disease by contributing to oxidative stress and damaging mitochondria.[14–17] Finally epigenetic labelling may also be factor in driving age-related diseases by restricting the cell's access to gene expression.[18–20]

Stage 2: Oxidative stress becomes a severe or chronic condition

All the factors contributing to oxidative stress and mitochondrial decline progress together to follow a common pathway where oxidative stress begins to affect many different cell types. Chronic oxidative stress occurs when the levels of ROS regularly exceed safe values for long periods. This is the starting point for the pathogenesis of age-related diseases such as cardiovascular, urinary tract and neurodegenerative diseases.[6,21,22] At this stage, although symptoms may be present, they not be sufficiently well defined to lead to a specific diagnosis.

Stage 3: Zones with reduced mitochondrial QC capacity - "Cascades"

Chronic oxidative stress and mitochondrial decline can continue along this path producing reduced cellular function and increased inflammation in cells and tissues without triggering a specific disease, because *in the vast majority of of cases,* the control and repair systems are able to restore redox balance and mitochondrial quality control. The cases where these systems cannot restore such balance are rare and are specifically related the topology of the sites which limit the capacity of transport of proteins and essential elements required for good control and maintenance between the nucleus and the site in question. Specifically, mitochondria are simply more vulnerable at sites where the control and repair systems can no longer keep pace with the demand.

One region where these systems are severely impaired is in the distal axons (axons far from the nucleus) and synapses of dopaminergic (DA) neurons. Each DA neuron has a very extended and complex axonal arborescence reaching from the SN far into the striatum, supplying dopamine to more than a million synapses. This generates a considerable local energy demand which can only be satisfied by mitochondria in the axons and synapses concerned. All the supplies required for the control, maintenance and repair must be transported along this route and the most distant axons present the greatest difficulties in terms of just-in-time delivery. A sudden surge in ROS in mitochondria in a distal axon, requires a nano-second response by antioxidants if oxidative-stress damage is to be avoided. If local reserves of antioxidant molecules are insufficient, reinforcements must be generated by Nrf2 action in the nucleus and transported to the point of use.

In this model, vulnerable zones where these conditions prevail are the physical departure points for neurodegenerative diseases from chronic oxidative stress and mitochondrial decline. In DA neurons, evolution can follow one of two trajectories; (i) if the maintenance systems can restore redox balance and mitochondrial quality control, the axons will continue to function satisfactorily, maybe with reduced performance; (ii) if the maintenance systems can no longer restore redox balance and mitochondrial recycling, this will initiate the first of two destructive events occurring successively. Uncontrolled ROS will induce lipid peroxidation[23] and impairment of an enzyme (Complex I) essential for energy production by mitochondria and failure of the quality control cycle.[24–27] This in turn generates more ROS in a vicious circle that causes more mitochondrial dysfunction (cascade 3.1). When mitochondria can no longer meet the energy demand of the distal axons in the striatum as a consequence of mitochondrial dysfunction, the most vulnerable axons and synapses cease to function normally due to energy shortages (cascade 3.2).

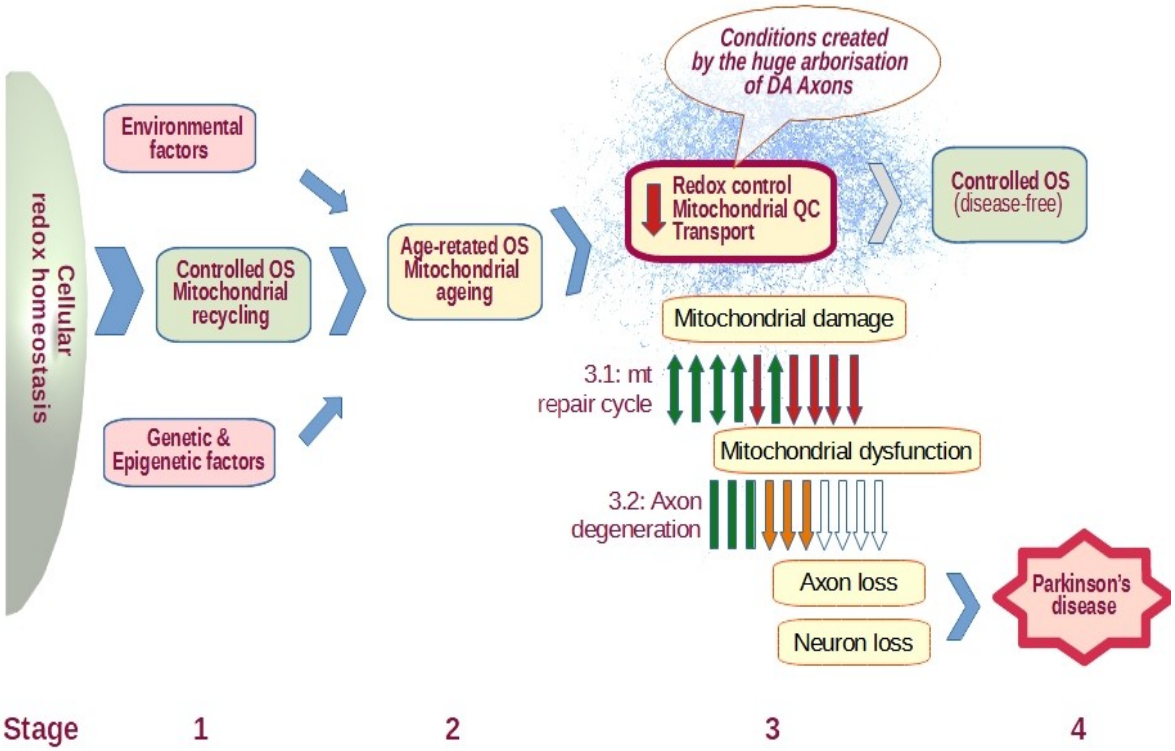

Fig 1: *Schematic representation of the stepping stones and cascades in the basic model for the pathogenesis of Parkinson's disease. OS: oxidative stress, mtD: mitochondrial dysfunction.*

Cascade 3.1: Mitochondrial dysfunction and repair

Mitochondria are the main source of energy in cells, providing ATP through oxidative phosphorylation. Oxidative phosphorylation also generates reactive oxygen species (ROS) which impair the Complex I enzyme, the first of 4 enzymes enzymes in the electron transport chain. If this ROS is not rapidly quenched by the action of Nrf2, it will cause further damage to Complex I as part of a vicious circle of oxidative stress and mitochondrial damage.[9–11,24–29]

The consequences of this condition, called secondary mitochondrial dysfunction (mtD), are multiple: reduced ATP energy production, impaired calcium signalling[30], increased oxidative stress and inflammation and a surge in demand to recycle damaged mitochondria and dispose of waste fragments (mitophagy). The onset of mtD is a critical physical transformation of the mitochondrial condition which directly impacts the host cells. In this model we are focused on DA neurons in the SN which defines Parkinson's disease, but mtD may also occur in other cell or neuron types and lead to additional complications or variants of PD. Other neurodegenerative or age-related diseases such as Alzheimer's disease, cardiovascular diseases, urinary tract or digestive tract diseases may also be initiated by a similar failure of mtD.[31–35]

The process of recovery from dysfunctional to normal mitochondria is dependent on restoring redox homeostasis by the Nrf2/ARE pathway. In neurons where Nrf2 still has this capacity, mitochondrial populations can then recover normal function by activating the mitochondrial quality-control cycle. Mitochondrial dysfunction, which starves neurons of energy and is accompanied by increased OS and inflammation, very likely corresponds to the prodromal stage of Parkinson's disease where non-specific and non-motor symptoms may be observed.

Cascade 3.2: Degeneration of DA axons in the striatum

Neurons suffering chronic energy shortages through mitochondrial dysfunction will be unable to sustain full dopamine release in the most distant axonal regions. Mitochondria in these distal axons are particularly vulnerable because of their very extended supply lines and by OS-induced impaired calcium signalling which controls the transport of supplies along axons. There is growing evidence from post-mortem and imaging studies that axon degeneration in the striatum precedes the loss of whole SN neurons and is a predominant feature of early PD.[36–38] If chronic oxidative stress persists unabated, both mitochondrial dysfunction and axon degeneration will progress simultaneously leading to further loss of the axonal arborescence of DA neurons and the onset of both motor and non-motor symptoms of PD.

Stage 4: Axon degeneration exceeds the 60% threshold for normal movement control

Stage 4 differs from stage 3 specifically in terms of the quantitative progression of mitochondrial dysfunction and DA axon degeneration. In particular, when DA axon degeneration or complete loss of DA neurons exceeds the critical threshold (>60% loss) in the striatum, normal motor function will be impaired, leading to the diagnosis of PD. This ultimately characterises fully-developed Parkinson's disease. This stage may not be detected until many years after the initial damage to axons and DA neurons began.

2 - Evidence of oxidative stress and mitochondrial vulnerability in DA neurons

Oxidative stress, mitochondrial dysfunction, and energy deficiency are implicated in many neurological and neurodegenerative diseases, despite these illnesses not being classified as mitochondrial diseases.[28,39–42] Both of these conditions have been demonstrated by post-mortem examination of brains and peripheral tissues of patients with PD.[43] Furthermore, the role of oxidative stress as a major contributing factor for mitochondrial dysfunction is now well established.[44,45] Oxidative stress is a common underlying condition of cellular dysfunction in genetic and idiopathic Parkinson's disease.[46] Increased levels of oxidised lipids, proteins and DNA, and decreased levels of reduced glutathione have been systematically found in the SN of PD patients.[47]

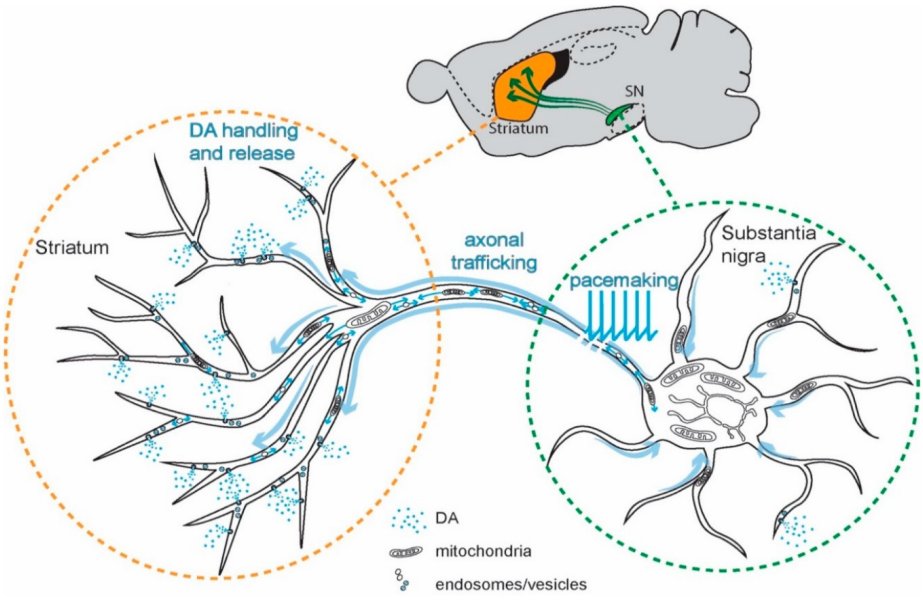

Fig 2: *Schematic representation of an SN dopaminergic neurons showing axonal projections and factors contributing to its high bioenergetic demands. Image gratefully reproduced from E Zampese and D J Surmeier, ref. [49].*

Impairment of Complex I of the electron transport chain is a common feature of mitochondria isolated from PD patients.[27] Magnetic Resonance Spectrometry *in vivo* has revealed that mitochondrial dysfunction is not restricted to the *substantia nigra,* but can occur in almost all regions of the brains of Parkinson's disease patients[48].

The link between parkinsonism and mitochondria was identified in the early 1980s. The neurotoxin, MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) which causes a form of Parkinson's disease inhibits complex I of the electron transport chain. Complex I is reported to be reduced by about 30% in the SN and frontal cortex of Parkinson's disease patients on autopsy.[24,25]

Dopaminergic neurons of the SN carry a very high bioenergetic burden because of the huge axonal branching that supplies dopamine to more than a million synapses.[49,50] The extremely long supply lines to these regions from the nucleus make redox control and mitochondrial quality control much more difficult to achieve in real time,[51–54] making mitochondria in these neurons particularly vulnerable to oxidative stress and mitochondrial dysfunction. This creates the conditions for a closed loop vicious circle involving OS damage to Complex I, axonal transport failure, mitochondrial dysfunction and finally energy shortages.

3 - The role of the Nrf2/ARE pathway in mitochondrial dysfunction

The role of Nrf2 in activating the antioxidant response (ARE) system to combat oxidative stress and inflammation in neurons is well established.[1–4,55–58] Nrf2 also plays a role in sustaining mitochondrial function by facilitating quality control, increasing the availability of substrates for respiration and ATP production and increasing the mitochondrial membrane potential.[59–64] One of the most potent activators of Nrf2 is the natural isothiocyanate sulforaphane which is readily available in broccoli seeds and sprouts as its precursor molecule glucoraphanin.[22,55,65–67]

In a landmark study of an animal model of Parkinson's disease, A Jazwa, et al[57] demonstrated that upregulation of Nrf2 by sulforaphane provided protection from MPTP-induced parkinsonism in mice. The neurotoxin, MPTP inhibits Complex I of the electron transport chain and directly triggers mitochondrial dysfunction and parkinsonism[24,25]. Without sulforaphane treatment, analysis of brain sections showed a 60% loss of SN neurons and an 80% loss of dopamine in the striatum six days after injection of MPTP. Prior treatment with sulforaphane protected against 50% of the loss of SN neurons but only 20% of the loss of dopamine release in the striatum. The ratio of losses due to MPTP and the protection provided by sulforaphane indicates important role played by NRF2 in counteracting OS, but also the greater vulnerability of mitochondrial dysfunction in DA axons in the striatum compared to the SN.

Upregulating Nrf2 attenuates non-motor PD symptoms

In a recent experiment designed and executed by the author, previously diagnosed with Parkinson's disease in 2018, a daily dose of a special broccoli seed tea containing sulforaphane considerably reduced fatigue, apathy, sleep problems and urinary incontinence over a period of a few weeks, but moderately increased tremor over the same period. Intrigued by this result, the author shared this information with other PD patients who collectively established a protocol to standardize the experimental method and data recording. Eight Parkinson's patients then carried out individual (n-of-1) studies to test their own symptom responses and subsequently shared their results.[68]

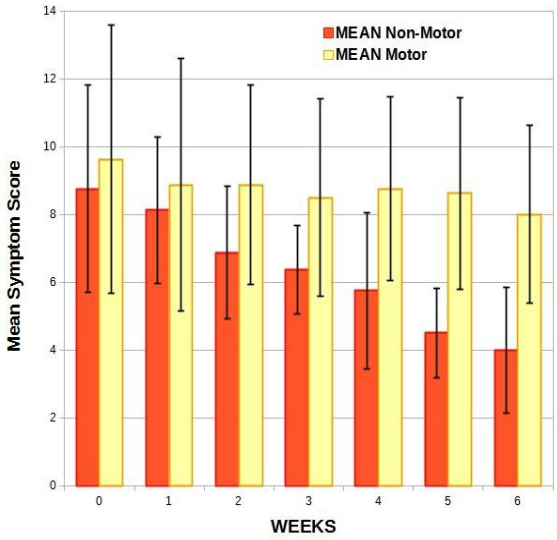

Fig. 3: *Evolution of mean symptom scores of non-motor and motor symptoms for all 8 participants. Error bars are standard deviations.*

Analysis of the data showed that non-motor symptoms were considerably attenuated over a period of 6 weeks whereas motor symptoms remained largely unchanged.

Figure 3 shows the evolution of the grouped motor and non-motor symptoms, averaged over all 8 participants. The mean grouped non-motor symptom scores followed a rapid and regular decline by 54.3% over the 6-week period, whereas motor symptom scores were much less affected (-14.8%).

The symptoms most strongly attenuated over the course of the experiment were fatigue, lack of motivation and urinary disorders. Every participant reported an improvement in fatigue and the overall score for fatigue was reduced by 90%. These symptoms are known to be related to compromised energy production in diseases caused by mitochondrial dysfunction. Urinary urgency and frequency, symptoms which have a strong impact on quality of life also responded well. Loss of sense of smell, a non-motor symptom which occurs in the very early stages of Parkinson's disease, did not respond.

In this experiment, sulforaphane, a potent activator of Nrf2 strongly attenuated non-motor symptoms of Parkinson's disease patients, whilst leaving motor symptoms largely unchanged, implying a reversible mechanism for the former and an irreversible mechanism for the latter, consistent with cascades 3.1 and 3.2 of the proposed model. If this result can be independently confirmed, we believe that this new observation should open the way to new investigations into the pathogenesis of Parkinson's disease. The cascade model proposed here is consistent with the chronology of the events and the dynamics of the symptom response to Nrf2 upregulation.

4 - Relation between the proposed cascade events and PD symptoms

The dynamics of the different mechanisms in play in the cascade transitions merit consideration.

Mitochondrial dysfunction at cascade 3.1 is dependent on the dynamic equilibrium between the production and elimination of ROS, coupled to the response of the quality-control system for mitochondria to adapt to a changing redox state. Increasing OS will result in progressively more severe mitochondrial dysfunction which, due to the energy deficit in host cells is likely to have a direct and rapid impact on symptoms such as fatigue, motivation and sleep. Considering the reverse process, once mtD is established, action to reduce OS should enable mitochondria to recover, but the timescale for the regeneration of healthy mitochondria will be regulated by the dynamics of the mitochondrial quality-control system, a process with a turnover time of days or weeks depending on the cell type.[9–11,69–71]

The cascade at 3.2, causes irreversible damage to distal DA axons in the striatum. Restoring redox balance should still enable mitochondria in undamaged axons to recover as in 3.1, but the consequences of the axon degeneration will remain. However these consequences will not be fully observed until stage 4.

This model throws light on the potential for slowing or even halting PD, up to the point of triggering mitochondrial dysfunction at stage 3.1. Beyond that point, irreversible damage to DA axons occurs, even though it may not be fully transformed into motor symptoms until the threshold value of ≥60% loss of dopamine release in the striatum is exceeded many years later. This draws our atten-

tion to the importance of being able to recognise the signs and symptoms of stage 3.1 as early as possible by developing reliable biological markers for this stage.

In the broccoli seed tea experiment, all 8 patients had reached the equivalent of Stage 4 of this model prior to the experiment. The lack of impact on motor symptoms suggests that upregulating Nrf2 had little or no additional effect on dopamine availability in striatal synapses. The strong impact on non-motor symptoms is however consistent with improved energy supply enabling better overall function of DA or other neuron types. The dynamics of the changes observed over 6 weeks in non-motor symptoms are consistent with the timescale of mitochondrial renewal and the life cycle of mitochondria, equivalent to the slowing or halt of the mtD cascade at stage 3.1, and with no change in axon degeneration at stage 3.2. It is important not to interpret the reduction of non-motor symptoms in terms of disease reversal. Once stage 4 has been reached, non-motor symptoms may however be a guide to the rate of disease progression. The aim should be to stabilise non-motor symptoms at the lowest possible level.

Fatigue

Persistent fatigue, a sensation of global exhaustion unrelated to physical effort, is a common symptom reported by Parkinson's disease patients, often occurring well before diagnosis and remaining throughout its progression. Fatigue has a major impact on quality of life of PD patients, but remains one of the least documented and least researched symptoms of PD [72–74]. Fatigue is also a hallmark symptom of mitochondrial disease.[75] Markers of elevated oxidative stress and mitochondrial dysfunction correlate with disease severity of patients diagnosed with Chronic Fatigue Syndrome.

A chronological model for Parkinson's disease

Figure 4 shows the timeline for the progression of PD according to this model and the points at which different factors may contribute or attenuate disease progression. The major contributions to the pathogenesis of PD occur in the very early stages when there are no clearly defined symptoms. Fully preventing PD can only be achieved at stages 1 and 2 through exercise, good diet, low stress, calorie restriction and preventative measures to avoid triggering mitochondrial dysfunction at stage 3.1. Even so, success is not guaranteed and will depend on the factors driving mitochondrial ageing and OS forward. The importance of identifying reliable markers for stage 2 of this model cannot be overestimated. Similar arguments are likely to apply for other neurodegenerative diseases such as Alzheimer's disease.

Parkinson's disease is already engaged at stage 3.1 when the early signs appear, but by vigorous action to combat OS and mitochondrial dysfunction simultaneously, it may be possible to slow the disease to the point of avoiding the critical threshold of >60% loss of dopamine release in the striatum. If this can be achieved, then quality of life for patients should be very good.

5 - Implications for patients

How can patients know where they are on this journey?

The delay between the reaching the various stages in this model of PD and the occurrence of symptoms is a major handicap to identifying at which stage patients may find themselves. The most well-defined stage is at the onset of motor symptoms which is usually when patients are clinically diagnosed. At this point, both cascade events are already well advanced and loss of striatal axons is severe. We should therefore look at what occurs both before and at this point and investigate possible measures to modify the progress of events.

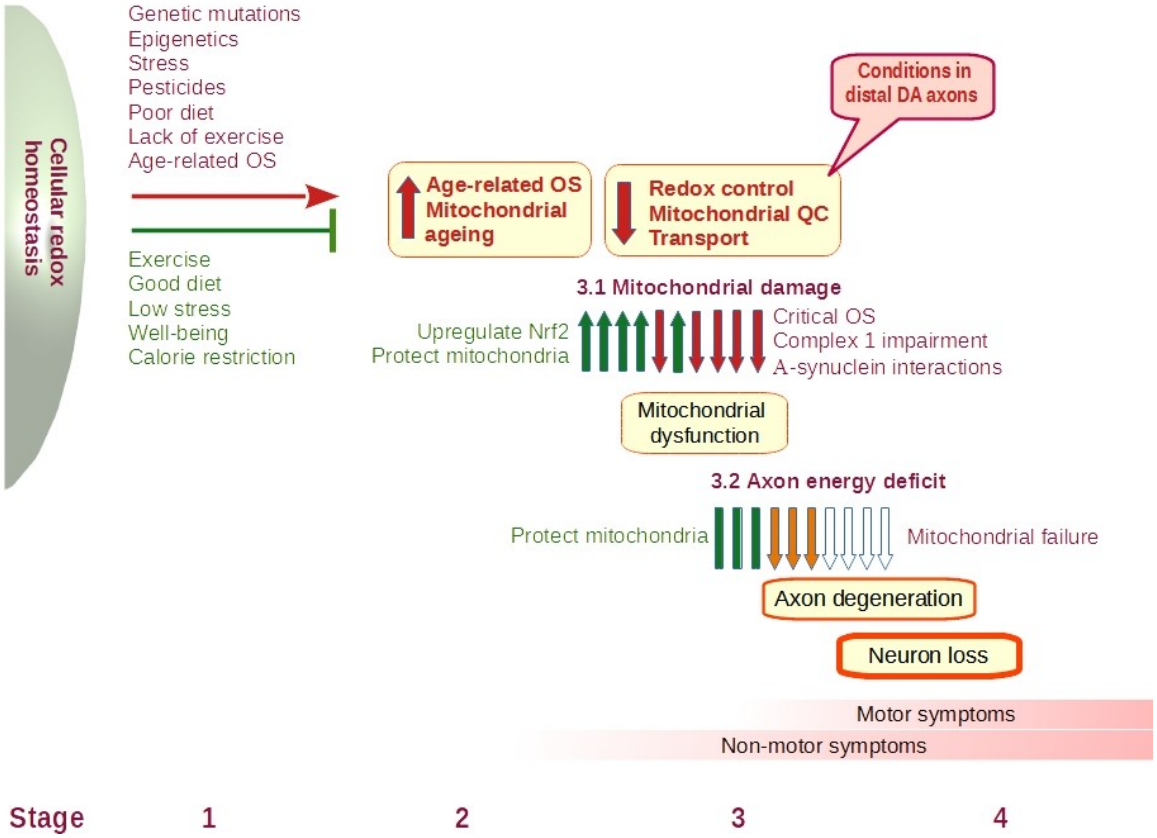

Fig 4: *timeline showing aggravating factors contributing to Parkinson's disease progression (in red) and the stages where interventions might improve the outcome (in green).*

Stage 1: This is the starting point where genetic and epigenetic states set a patient's predisposition for chronic diseases. Environmental and lifestyle factors will amplify or reduce the effects of predisposition. However, age is the most important factor that continuously increases the risk of chronic disease. At this stage, most people are in good health and symptoms are rare and non-specific.

Stage 2: The global and mitochondrial age factors increase oxidative stress creating a range of non-specific symptoms such as more frequent fatigue, aches and pains, difficulty sleeping, less muscular strength, constipation and urinary problems. This is where the first signs of PD begin to emerge, but may not be recognised as such.

Stage 3: The conditions at stage 1, combined with advancing age and added lifestyle factors of risk may increase OS to critical levels in certain cells. Although the cascade of 3.1 must mechanistically precede that of 3.2, they will both be present to some degree at any one time. Mitochondrial dysfunction and the energy shortages that ensue will have a profound qualitative effect on the performance of DA and other neurons. This loss of performance is likely to be the cause of many non-motor symptoms that occur 10-15 years before diagnosis of PD. These include the loss of sense of smell, persistent or acute fatigue, apathy, sleep and balance problems, urinary problems, constipation, confusion etc. Motor function may also be qualitatively affected in terms of some actions becoming slower or less easy to accomplish, but since the axon network region should still be fully covered, specific features may not be identifiable. Only a careful review of all the

symptoms and their progression can help to define this phase. This is where markers of PD and mitochondrial dysfunction are sorely needed.

As stage 3.2 advances towards the point of clinical diagnosis, all PD symptoms and will become more clearly identifiable. The increased severity of non-motor symptoms plus the first clear motor symptoms should be the signal. At this point, the cascade of 3.1 is severely affecting the performance of DA neurons and causing non-motor symptoms, but despite this, the network of axons and synapses in the striatum may still be sufficient to control motor function.

At the point of clinical diagnosis, the cascades of 3.1 and 3.2 will have been fully operational for many years and the threshold of lost DA axons and neurons required to maintain full motor network coverage has already been exceeded. Motor and non-motor symptoms are both fully present.

This is usually the point at which patients are offered Levodopa or dopamine agonist therapy. These therapies considerably help re-establish motor function by making sufficient dopamine available to distal axon terminals. They do not however solve the problem of possible gaps in the some regions of the neural network where many axons may have been lost, nor that of the poor performance of DA or other types of neurons due to mtD and energy shortages. Dopamine therapy does not address these aspects of Parkinson's disease. As a consequence, many patients on levodopa still suffer serious non-motor symptoms.

Stage 4 occurs when the cascades of stage 3 continue unabated thus reducing neuron performance and further increasing axon loss beyond the threshold needed to maintain full motor control.

Conclusions

This simplified model for the pathogenesis of Parkinson's disease is supported by a very substantial base of experimental evidence covering every step in the direction of increasing disease severity. Nevertheless, the cascade stage 3.1 leading to mitochondrial dysfunction and the ensuing energy deficit needs to be tested in clinical trials in the reverse direction; that of restoring redox balance and mitochondrial quality control to normal levels. If this model can be confirmed, stage 3.1 represents an important opportunity for attenuating disease progression. It opens the way to disease-modifying therapy by simultaneously addressing both oxidative stress and mitochondrial dysfunction. These two processes call for different therapeutic approaches which if applied together could transform the synergistic vicious circle driving Parkinson's disease progression into a virtuous circle to slow or even halt it.

Further work

In a future article, the question of which therapeutic methods might be considered to address both oxidative stress and mitochondrial dysfunction will be discussed.

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