PARKINSON'S UK CHANGE ATTITUDES. FIND A CURE. JOIN US.

Cambridge Branch Newsletter – January-February 2022

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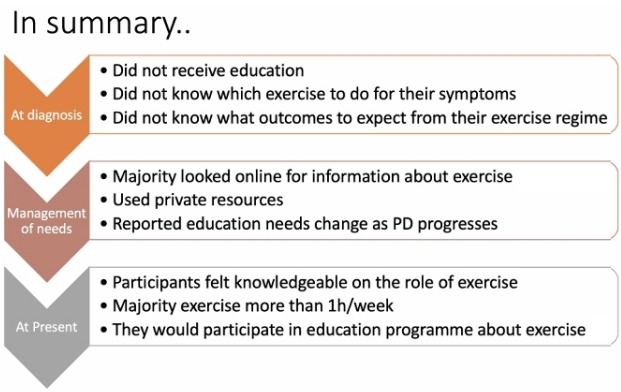
BRANCH MEETINGS

PwP SHOULD BE TOLD ABOUT EXERCISE

Below is a summary of the findings revealed by research done by Ledia Alushi, a physiotherapist now studying for a PhD at Cambridge University. Her survey is titled 'The role of physical health education for people newly diagnosed with Parkinson's'. Ledia told us about her plans for the survey a few months ago, and recruited members to provide the information she was looking for.



In part, it is not good news – but not surprising either. When they are first diagnosed, few People with Parkinson's (PwP) receive any information about exercise – and are certainly not told that it can be an extremely beneficial and important part of their whole treatment regime.

But it is not all bad news. Many people surveyed had the initiative to seek information for themselves, learnt about the value of exercise, and as a result are putting that into practice!

The survey says that the majority of people who took part exercise more than one hour per week. What is not yet known – and this is a worldwide question – is what exactly is the best form of exercise for PwP to take? Even so, the evidence has built up over the last few years, suggesting that consistent and fairly vigorous exercise can have nothing but an overall beneficial effect on the vast majority of PwP. Some healthcare workers say the effect of exercise is comparable to medication. Most believe it should be seen as an important aspect of treatment. Surveys like Ledia's can only help by strongly backing up that position.

HOW EVA ESCAPED THE NAZIS TO WORK WITH NYE BEVAN AND WRITE FOR TRIBUNE

A remarkable story about survival and success in the darkest days of European history was told at the November meeting by Maggie Challis, whose mother, Ilse, is a member of the branch. Maggie told us about her aunt, Eva Metzger, who was born in 1921 in Mainz, Germany, into a relatively prosperous family, members of the well integrated, long-standing Jewish community there.

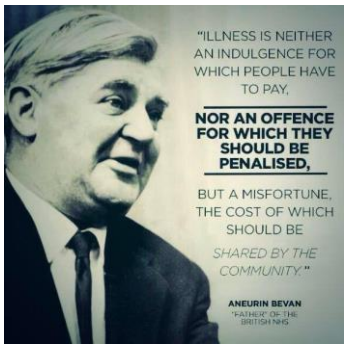
"The photo of Eva, which Ilse has had on her bedside table for as long as I can remember," Maggie says.

Eva's early childhood was reasonably trouble free, but by 1936, with Hitler now Chancellor, the future was looking grim. With great foresight, Eva's family decided she should go to live in England, where at the age of 15 she started at her new school, in Eastbourne. Within two terms, Eva's English had progressed so well she wrote a poem in her new language, which was published in the school magazine! This was the start of a decade of publications in various prestigious journals.

Then in 1938, her mother came to visit Eva and later that year the terrible event of Kristallnacht occurred. The rest of her family now realised they had to get out of Germany. Ilse was brought to England by a

colleague of her father's, and Eva's school offered to take her in and educate her free of charge, not knowing if the bill would ever be paid. Although their parents did get out of Germany, many other family members perished in concentration camps.

With her father in an internment camp in the Isle of Man, and her sister at school, Eva, now with her mother in London, was evacuated to a family in Wales and accommodated by a woman called Phoebe Bevan. She was the mother of one of the great British political figures of the 20th century, Aneurin (or Nye) Bevan, widely regarded as the driving force behind the formation of the National Health Service.



Eva began working for Nye as a secretary and general administration assistant, helping him deal with his duties as the MP for Ebbw Vale. Bevan would go on to become Minister of Health in Clement Attlee's new post-war Labour government, becoming the youngest member of the cabinet at 47. Inspired by a 'Medical Society' in his home town, Bevan led the establishment of the NHS, with the aim of providing medical care free to everyone at the point-of-need. The NHS Act was passed in 1946, nationalising more than 2500 hospitals throughout the UK.

Apart from working together, Eva and Nye had something else in common: they both wrote poetry. Nye refers to Eva in a book about him written by Labour MP Nick Symonds-Thomas. Eva wrote prolifically, and had pieces published regularly in Tribune magazine. Her writing varied widely – from short stories to 'prose poems', to humorous articles, plays, and she even wrote music!

Later, being effectively bilingual, she was recruited by the intelligence services and worked at Latimer House, a large country house in Bucks used by MI5 and MI6. Captured Germans were held there before being transferred to prisoner of war camps. Eva worked as a translator and interpreter, and it was there that the first inklings of the horrors of the Nazi concentration camps emerged. She was subsequently moved to the 'London Cage', a notorious interrogation centre sited in the most unlikely of places: Kensington Palace Gardens, one of the capital's most exclusive, expensive locations!

Sadly, Eva was not well. She was diagnosed with Hodgkin's disease (cancer of the lymphatic system), which made her increasingly weak. Treatment then for such cancers was not well established, and the 'therapy' she did receive was not effective. She managed a trip to Switzerland with her father in 1949, but in 1950, she died at the age of just 29.

Her sister, Ilse, outlived her by many years, becoming a dentist, moving to Cambridge and taking on roles such as being a JP, and the first female Lay Chair of the Cambridge Council of Churches. At the age of 64, she achieved her ambition of gaining a degree, and graduated from the Open University in 1989. Now aged 96, and suffering with Parkinson's, she is living in a care home in Cambridge.

If you want to find out more about this fascinating family, contact Maggie at maggiechallis-@hotmail.com or contact Keith Howlett who can provide copies of the small booklet Maggie has written, which contains both the story of the sisters and many of Eva's works.

FIRST MEETING OF WORKING AGE GROUP SET FOR FEBRUARY 5: MEMBERS WANTED!

We are helping to establish a new Working Age Group for PwP, many of whom cannot attend our Friday events because of work and other commitments. It will be on Saturday, February 5, at Hemingford Abbots Village Hall, High Street, Hemingford Abbots, Cambs PE28 9AH. It starts at 10.30 and will end at 1.30, after a sandwich lunch. After tea and coffee on arrival, and an Introduction to Parkinson's UK local support services, at 11 there will be various workshops for the participants to discuss local expectations, and their needs for social support. This will be followed at 12 by either a speaker or an activity, then at 12.30, by a social lunch. There will also be an information stand. For tickets, see Cambridgeshire working age event or contact Julie Wilson at jmwilson@parkinsons.org.uk, or 0300-123-3675.

VIEWPOINT

One criticism has quite frequently been levelled at the healthcare facilities currently operating to support people with Parkinson's (PwP). This says that when anyone is diagnosed with Parkinson's, more help – in the broadest possible sense of the word – should be offered automatically, and immediately. And the criticism is of course that it isn't.

The ideal would be this: literally as a newly diagnosed patient leaves the neurologist's consulting room, they are given a package containing pretty much everything available to help PwP deal with what is often a devastating diagnosis. (For example, they should be told how important exercise is, see first article on page 1).

In fact, this criticism can be extended beyond Parkinson's, to all kinds of UK health services and support systems. There are tools, resources and facilities available to everybody, as part of the NHS, with the potential to be extremely useful, at least, and possibly much more.

But do we all know about them? A completely non-scientific random questionnaire conducted verbally would suggest not. For example: My Chart. Ever heard of it? Or what about SystmOnline, and Airmid? Then there is PillSorted. Or an NHS Health and Wellbeing Coach?

Then there are services like Parkinson's Nurses, and Parkinson's UK giving vital advice on issues such as driving, insurance (for example travel). Those of us who have got used to having Parkinson's over quite a few years probably just assume everybody knows about these. But lots probably don't.

MyChart is a 'patient portal' (its website says) that is integrated with the electronic patient record system "empowering patients to be more involved in their care through access to their records." You need to register yourself to get MyChart working for you. But once you have done that, you can quickly build up extremely useful data about your medical experience: from appointment details to clinical correspondence, test results, medications and known allergies.

With SystmOnline, you can book appointments, order medication, change your pharmacy, and look at your records back to childhood, among many other services. Naturally, everything is done online. PillSorted will handle your prescriptions (electronically), sort, pack and then deliver them free to your home. It also gives free medical advice is.

As for the NHS Health & Wellbeing coaches – perhaps it's a good thing hardly anyone knows about them. Given what we have had to live through over the last two years, we might all need our very own!

NEWS, EVENTS & PEOPLE

HELP FORM A CardMedic GROUP

CardMedic is an organisation looking to help people communicate, who for whatever reason find that difficult. They talked to us at our June meeting last year and are now looking to form a group of people to take the project further, as they explain here.

"At our talk, we showed flashcards, and asked for views about the wording and symbols used. We are forming small User Groups to discuss this further with potential users of CardMedic's website and app. Rather than forming one large group, featuring people with conditions that vary widely, several smaller groups will comprise people living with a similar condition or disability.

CardMedic in action.

"Once we have created a group, our aim is to meet with you via Zoom, and your carers if you want them there, and get your opinion about various ideas we are developing, and what CardMedic is doing generally. The meetings will be informal and last about an hour, once every three months.

"What you will need to do: First, you need to tell us you want to join a small group. You can do this by emailing Gilly Nicol (gillynicol@cardmedic.com) or Michèle Gasper (michelegasper@cardmedic.com). We will ask you to sign an agreement, so you know exactly what we are asking. This will protect you and your privacy, and also protect CardMedic.

"What we will need to do:

We will send you the agreement and ensure you are clear about what you are being asked to do. We will introduce you to other people in the group, and tell you what we are going to talk about in the meetings, and what dates have been set. If at any time you want to stop being a member of the group, that is perfectly ok. We look forward to hearing from you!"

PIONEER OF DOPAMINE THEORY & L-DOPA TREATMENT TELLS HIS REMARKABLE STORY

An amazing story surrounds the discovery that lack of dopamine is central to Parkinson's, and the emergence of L-DOPA as by far the most effective – indeed even miraculous – treatment for the condition that has ever emerged. It is an important story, not just for Parkinson's, but the whole area of neurodegenerative diseases.

This story is told by Oleh Hornykiewicz (pictured), who worked in the Department of Molecular Neurosciences at the centre for brain research, part of Vienna University. Sadly, Oleh died in May 2020, but thankfully not before he wrote a paper for the Journal of Parkinson's Disease, entitled simply L-DOPA, which tells the amazing story. At times, it reads more like a series of episodes from a medical thriller. What follows is a brief summary of the story. For the full version click here: https://parkinsonscambridge.files.wordpress.com/2022/01/paper-re-ldopa-history.pdf

As it says at the beginning of the article, one of Oleh's seminal

accomplishments was the discovery that Parkinson's was due to dopamine deficiency in the brain. This all happened extremely quickly – as he says, in the four years between January 1957 and December 1960, dopamine, "made a splendid career for itself." Until then, astonishingly, dopamine was regarded as a very minor element involved in the synthesis of noradrenaline. Within a few years, it was firmly established as a key neurotransmitter.

In autumn 1956, Oleh went to work at a laboratory in Oxford, where he was given the task of assessing what dopamine actually does. Quite quickly, he performed some key experiments, which established that dopamine possesses its own physiological activity, independent of and different from noradrenaline.

Until then, it wasn't even known that dopamine played an important role in the brain. Another scientist central to this discovery was Kathleen Montagu, who worked at a research laboratory at Runwell Hospital in Wickford, near London. She demonstrated that dopamine occurred in substantial amounts in the brain, a discovery that Oleh says "excited him enormously."

Kathleen's discovery triggered many experiments looking at the role of dopamine in the brain and how various drugs could affect this. As Oleh says, this was a case of the pharmacology of dopamine (its response to drugs) being investigated before its neurophysiology – what it actually does in the brain – had even been established.

"This situation may sound odd, but it is not for the first time in the history of medical research that pharmacology paved the way for the physiology," he says.

In fact, pioneering work by another researcher, Marthe Vogt, had shown in 1954 that neurotransmitter-like substances in the brain (in this case noradrenaline) were distributed very unevenly. This showed that where neurotransmitters were located in the brain had a lot to do with what they actually did. Marthe's study was a landmark and can rightly be regarded as a model for all subsequent studies in the field of neurotransmitter research.

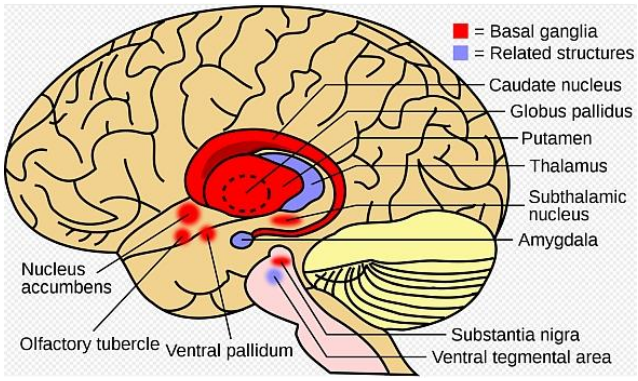
It was followed five years later by two other researchers (Bertler and Rosengren) who showed that about 80% of all the dopamine in the brain was to be found in only two places, the caudate nucleus and the putamen, both part of the striatum. This was a notable event in the history of Parkinson's, and not only because of the basic discovery. It was the first time ever, in print, that anyone had suggested these findings could be connected with parkinsonian symptoms.

Oleh says he did not need to read this twice, and that in a flash, he saw in his mind the brain-dopamine riddle solved: the clear connection between dopamine in the striatum, and the depletion of this causing Parkinson's in humans. Within weeks, he completed his study of dopamine

in rats and turned to the human brain. He recorded all his information, the techniques he used, and the individual dopamine results in a special 'experimental protocol notebook'.

In total, he and his team dissected and analysed six brains of people who had had Parkinson's, and around 25 other non-Parkinson's brains. Only the six Parkinson's brains had severely reduced dopamine levels in the caudate and putamen. The experiments were set up so that if dopamine was present, the tissue turned a distinct pink colour. "I could see, by the lack of the pink colour in the samples of Parkinson's patients, the striatal dopamine deficiency in Parkinson's – for the first time ever – with my own naked eye!" Oleh says.

Then an odd incident occurred. Collaborating with him on the experiments was Herbert Ehringer, and Oleh asked him to write up the results. To help Ehringer do this, Oleh handed over his precious experimental protocol notebook. When the draft of the results came back, there was no notebook. "It somehow got lost" was the reply to his urgent requests. The reader is left wondering what exactly went on. Oleh simply says: "Our 1960 paper from my dopamine/Parkinson's project was the first and, sadly, the last on this subject bearing also Ehringer's name. Alas, my experimental protocol notebook – the evidence – has not turned up to this day. What a loss for the history of Parkinson's!"



Oleh converted the draft into a publishable paper, which was immediately accepted for publication in a journal and appeared in print three months later – extremely quick for academic papers. That was December 1960. The results were immediately accepted by the research community, he says: "They have become common textbook knowledge. For the first time ever, a specific chemical abnormality was found in a specific region of the human brain, in a specific neurodegenerative brain disorder. This discovery has become a model for all subsequent research into the causes and treatments of neurodegenerative disorders in general."

The discovery of the critical link between dopamine deficiency and Parkinson's was only half the story. In November 1960, Oleh says he knew this was not the moment to wind down and relax. Instead, it was time to take the crucial practical step: treat patients.

Here is a direct quote from Oleh's academic article – and there can be very few such papers ever published in an academic journal containing this sub-heading, reminiscent of a tabloid newspaper:

THE L-DOPA MIRACLE

If the adage that "the most incredible thing about miracles is that they happen" needed proof, the L-DOPA effect in the PD patient would convince even the most recalcitrant unbeliever.

Oleh says the idea of using L-DOPA came quite naturally to him, and in November 1960, he proposed a clinical trial involving injections. This was conducted by Walther Birkmayer, head of the neurology ward at a clinic for old people, many of them with Parkinson's. There was clearly no love lost between Oleh and Burkmayer – Oleh says Burkmayer actively delayed ("sabotaged") his proposal for eight months. But in July 1961, the first patients were injected with L-DOPA.

"The effect was so stunning that Birkmayer immediately called me up and asked to come and see for myself," Oleh says. "I came – and saw the 'L-DOPA miracle' happen right before my own eyes."

Those who have seen the film Awakenings will have some idea of what Oleh is talking about. People who had hardly moved at all for decades stood up and walked about. Oleh describes the 'miracle': "The effect of a single intravenous administration of L-DOPA, was, in short, a complete abolition or substantial relief of akinesia (inability to move). Bed-ridden patients who were unable to sit up; patients who could not stand up when seated; and patients who, when standing could not start walking. After L-DOPA, they performed all these activities with ease. They walked around with normal movements and they could even run and jump. The voiceless, aphonic speech, blurred by pallilalia (involuntary repetition of syllables, words, or phrases) and unclear articulation, became forceful and clear as in a normal person. For short periods of time the patients were able to perform motor activities which could not be prompted to any comparable degree by any (other) known drug."

You might think that given this dramatic success, L-DOPA treatment would have rapidly become widely available for PwP. Unfortunately, that is not how the world of commercial pharmacology works. The marketing experts said the Parkinson's market was far too small to commercialise a non-patentable substance like L-DOPA.

So, several years went by before a doctor in New York, George Cotzias, started a clinical practice in which he gave the drug orally to patients in gradually increasing doses. This became known as the Cotzias regimen, and Oleh acknowledges that this helped to convert "our dramatic short lasting IV (intravenous) L-DOPA anti-parkinson effect into a sustained dramatic improvement by oral L-DOPA."

Nevertheless, some prominent brain scientists and neurologists remained unconvinced, finding the 'L-DOPA miracle' simply unbelievable. Almost certainly without realising it, they were echoing something that the discoverer of the condition himself had said. In his famous 'Essay on the Shaking Palsy', Dr James Parkinson expressed a disheartening final judgement that in this disorder, "employment of internal medicines is scarcely warrantable". This was certainly understandable when he wrote his essay, in 1817!

But as Oleh concludes: "We can easily imagine how much he would be marvelling today, and how delighted he would be at hearing about, and seeing with his own eyes, the miracle worked again and again by L-DOPA, today's gold standard of drug treatment of Parkinson's – as a single drug so far unsurpassed, and in my judgement unsurpassable."

SCIENCE & RESEARCH

FIREFLIES' LIGHT-PRODUCING PROTEIN HELPS SLOW DOWN ALPHA-SYNUCLEIN PRODUCTION

US researchers at Utah University have identified a molecule that slows the production of alpha-synuclein (αS), the protein that forms toxic aggregates in the brains of PwP. Using gene editing techniques, they inserted a gene that encodes a light-producing protein from fireflies into lab-grown human cells, positioning it where it would be turned on whenever the αS gene was active. Under the right growing conditions, the human cells glow when the αS gene is on, and dim when it becomes less active.

They used these light-producing cells to screen a vast collection of molecules – more than 150,000 – for their effects on the αS gene. They were able to do this thanks to a high-throughput robotic system, and the result was a molecule called A-443654, which looked to be the most likely inhibitor of αS production.

Further tests found that the molecule not only lessened activity of the αS gene in human cells, including neurons taken from a Parkinson's patient, but also led to fewer copies of the gene being produced. Another sign of therapeutic potential was that it relieved stress on the systems cells use to deal with broken, misshapen, or otherwise unwanted proteins.

Alleviating this stress means cells are no longer overwhelmed by high levels of αS, and it may also free up those systems to break down aggregates that have already formed. "We can stop production, but we also need to degrade what's already aggregated," they say. Further research is needed to determine whether A-443654 itself can be developed into a potential treatment for Parkinson's. Meanwhile, the team plans to explore additional molecules identified by their screening process as potential inhibitors of αS production.

WALKING ADDS TO BREATH MUSCLE TRAINING

A new study by researchers at Istanbul University in Turkey suggests that walking can add to the benefits of 'respiratory muscle training' in PwP. This training consists of specific exercises designed to improve the function of the muscles used in breathing. Patients who followed an eight-week walking programme as well as respiratory muscle training showed greater improvements in their ability to exhale compared with patients who had the muscle training only.

Some PwP have breathing problems, including shortness of breath and sleep breathing disorders. Their breathing muscles may become weakened, and a vicious circle starts: their capacity for exercise decreases, and this results in less physical activity and walking difficulties. Several studies have shown that respiratory muscle training can strengthen breathing muscles, and walking may have similar effects.

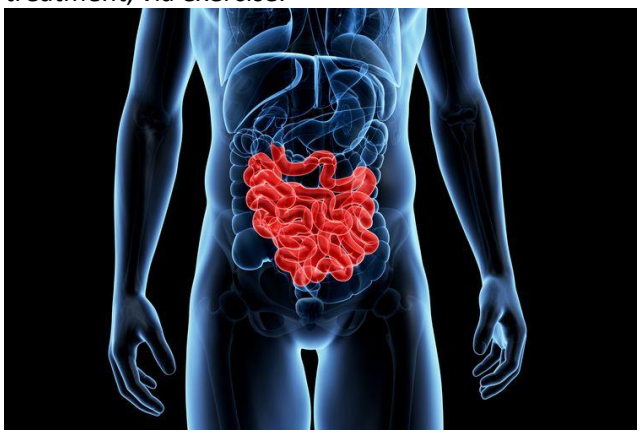
After eight weeks of training, people in the study who had done both the training and walking showed greater improvements than those who did only the training. For example, their 'maximal expiratory pressure' – a measure of the effort exerted by breathing muscles during a forceful exhalation – was higher.

Meanwhile, an Australian study is testing whether walking in a swimming pool is more beneficial for people with orthostatic hypotension. This is a condition caused by the impaired release, upon standing, of the signalling molecule norepinephrine, an important regulator of blood pressure. Patients with this condition often experience dizziness, light-headedness, fatigue, and blurred vision, which can increase the risk of falls that may cause injury.

Exercise guidelines from many organisations including the American College of Sports Medicine recommend 30 minutes or more of aerobic activity – such as brisk walking at moderate to vigorous intensity – three days per week.

DOES EXERCISE HELP BY IMPROVING THE GUT?

A possible link between the gut and the brain has been widely discussed by Parkinson's experts for years. And some gut-related problems, particularly constipation, are well established symptoms. Now, the hope is that understanding the mechanisms and pathology of these faults will lead to more effective treatment, via exercise.



Perhaps the gut-brain link shouldn't have surprised people so much – the gut 'microbiome' actually produces neurotransmitters, like dopamine and serotonin, and can send these to the brain. The term 'microbiome' describes the trillions of microbes in our bodies, including things like bacteria, fungi, parasites and viruses.

Recent research shows that PwP could be experiencing gastrointestinal symptoms because their gut microbiome isn't functioning properly. Researchers at the University of Southern California, have shown that exercise can reduce some of the cognitive and motor symptoms in PwP.

Now, they are proposing what they say is an 'audacious idea': that some of the benefits could be the result of 'restoration' in the gut microbiome. Restoration simply describes getting the gut back performing at its best, functioning as it should.

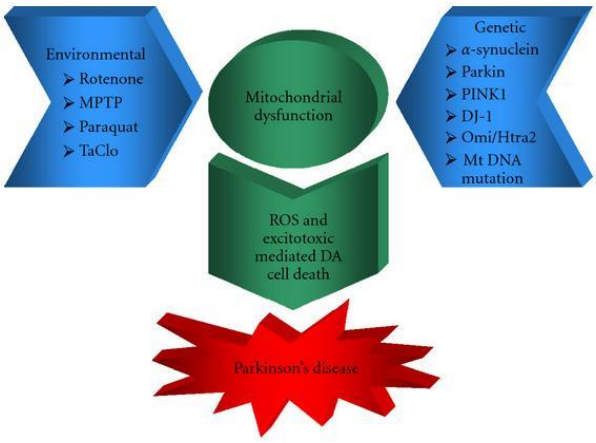
Research in non-Parkinson's disease populations has shown that exercise can help achieve this restoration. So the researchers want to do a long-term study examining how different kinds of exercise, such as strength training versus aerobic exercise, could restore the microbiome and potentially ease Parkinson's symptoms.

"Many PwP suffer from gut symptoms, and if we can understand what's going on in the gut at a fundamental level, we may be able to treat them more effectively, and potentially see restorative benefits," they say.

ACTIVATION PROCESS OF PINK1 PROTEIN CAPTURED FOR FIRST TIME

Australian researchers have solved a decade-long mystery about a protein that could fast-track new Parkinson's treatments. They have produced a 'live

action' view of the protein, called PINK1, in exquisite molecular detail. The discovery explains how the protein is activated in the cell, where it is responsible for initiating the removal and replacement of damaged mitochondria (the sources of energy for cells). When PINK1 is not working correctly, it can starve brain cells of energy, causing them to malfunction and ultimately die, as happens to dopamine-producing cells in Parkinson's.



Damaged mitochondria can lead to Parkinson's

The discovery makes possible the first detailed blueprint for the discovery and development of therapies to slow or even stop the progression. A multi-disciplinary team at WEHI, Australia's oldest medical research institute, used cryo-electron microscopy (EM) to make the discovery.

Until now, only snapshots of PINK1 have been produced, but differences in these has caused confusion about the protein and its precise structure. This time, WEHI has taken a series of snapshots and stitched them together to make a movie revealing the entire activation process of PINK1. "We were then able to reconcile why all these previous structural images were different," a WEHI researcher said. "They were snapshots taken at different moments in time as the protein was activated to perform its function in the cell."

PINK1 protects the cell by marking damaged mitochondria to be demolished and recycled. Defects in PINK1 starve cells of energy by preventing the recycling and replacement of damaged mitochondria with healthy ones. "There are tens of thousands of papers on this protein family, but to see how it actually changes in the process of activation is a world-first," the researcher said.

It could make it easier to develop therapies to 'switch on' PINK1. This could help young people who develop Parkinson's in their 20s, 30s and 40s, because of hereditary mutations in PINK1. Biotech and pharmaceutical companies are already assessing the protein and pathway as a therapy target for Parkinson's and will hopefully find this new structural information very valuable. Cryo-EM, a technique that uses samples cooled to cryogenic temperatures, was first developed in the 1970s. But recent advances in detector technology and software algorithms now make it possible to determine biomolecular structures almost down to the level of individual atoms.

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Facebook: www.facebook.com/parkinsonsukcambridge/
Twitter: https://twitter.com/CambBranchPUK
Help Line 0808-800-0303 (free phone call) Specialist advisers can answer questions on any aspect of Parkinson's
Parkinson's Nurses in our area: for help and information contact the Parkinson's Nurse Team on 0330-726-0077
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