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April 2020 Research Roundup

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Here's our **April Research Roundup** with the latest research news and opportunities for you.

GET CONNECTED

Beyond dopamine in Parkinson's

It may be vital to look beyond dopamine to find a way to slow the progression of Parkinson's.

For much of the last 50 years, Parkinson's has been considered a condition based on dopamine signalling, but this simplistic view means today many of its symptoms are inadequately managed by the drugs available. So what is going on and what other chemicals are involved?

There are many different types of chemical messengers used all over our bodies. For instance, insulin released from the pancreas encourages cells to take up sugar from the blood, while adrenaline is produced by the adrenal glands to increase heart rate and get the body ready for the fight or flight response. But signals don't always involve a whole body response, individual cells communicate with each other by sending chemical messages as well. In fact, they do this all the time — sending out hundreds of different signals that relay a host of information about the status of the cell and its environment.

The brain uses lots of chemical messengers to orchestrate complex communications that allow us to think, feel, move, remember and much more. These chemical messengers are known as neurotransmitters ("neuro" meaning relating to nerves or the nervous system) and are used by individual parts of the brain, allowing them to carry out their function.

What is dopamine?

Dopamine is a neurotransmitter that is involved in how we move and learn, our memory and attention, and even responsible for addictive behaviours. At the start of the 1950s, we knew almost nothing of the importance of dopamine in our daily lives. It was Dr Arvid Carlsson, a Nobel Prize-winning Swedish scientist, who first discovered how dopamine is involved in controlling movement. He showed that rabbits with lowered levels of dopamine lost their ability to move, and regained movement when given levodopa — a drug that can be turned into dopamine.

This discovery became the basis of how we treat Parkinson's — a condition caused by the loss of dopamine-producing cells — and still underpins the gold standard drugs available today.

More than just dopamine

This year marks 20 years since Dr Carlsson was awarded the 2000 Nobel Prize in Physiology or Medicine alongside Paul Greengard and Eric Kandel in the field of "signal transduction in the nervous system". And our understanding of how brain cells communicate in Parkinson's has come a long way in this time. A number of other chemical signalling pathways are now known to be affected in the condition and may be responsible for many of the symptoms that are not improved by levodopa based medication.

Some of the neurotransmitters affected in Parkinson's and possible associated symptoms include:

- acetylcholine — changes in thinking, concentration and memory as well as uncontrolled movements and the production of too much saliva
- norepinephrine — mood and sleep disturbances, and mild memory and thinking problems
- serotonin — changes in mood, fatigue and depression
- endocannabinoids — alterations in appetite, pain and may play a role in psychosis symptoms such as hallucinations
- glutamate — may impact movement, learning and memory, pain, and mood
- GABA (gamma-aminobutyric acid) — alterations in movement, anxiety and vision

Now researchers need to understand more about the balance of these chemicals and how they are causing symptoms in order to find better treatments. Here we discover more about the role of GABA and how researchers are targeting it in the pursuit of better treatments for Parkinson's.

GABA — a traffic light for brain cells

GABA is considered an inhibitory neurotransmitter because it blocks, or inhibits, certain brain signals. Just like red and green lights are both needed to control traffic, a careful balance of excitatory and inhibitory neurotransmitters are needed for effective control of signalling within the brain. For instance, in anxiety, where brain cells are over stimulated, GABA works to slow down signals to reduce the feeling of being overwhelmed.

A protective role for GABA involving calcium

Back in 2012, researchers found that dopamine-producing brain cells release GABA as well as dopamine. So in Parkinson's when dopamine-producing cells are lost over time, as well as the depletion of dopamine, there is a decrease in the levels of GABA. This is significant as GABA has a role in controlling levels of calcium. You might be more familiar with the role calcium plays in keeping our bones strong and healthy. But calcium is also vital for brain cells. In brain cells, calcium controls the release of dopamine, but too much calcium at the wrong time and place can kill cells. GABA works as an inhibitory signal, a stop light, to block calcium from entering cells. This has a protective effect on brain cells as it stops them from being overwhelmed with an influx of calcium which can result in death.

Most of the current drug treatments for Parkinson's aim to boost or mimic dopamine in Parkinson's to overcome the loss of this neurotransmitter. But now we know the important role that other neurotransmitters have, and that they may have protective effects, maybe we should turn our attention beyond dopamine. By finding ways to mimic the action of GABA we might be able to reestablish the careful balance of neurotransmitters in the brain and develop better treatments.

Mimicking the protective effects of GABA

In 2014, Parkinson's UK funded work to find out more about GABA and its links to dopamine. Today this research could see drugs that target GABA being repurposed for Parkinson's. Gabapentinoids are drugs, including gabapentin and pregabalin, which are currently used to treat epilepsy, restless leg syndrome, and neuropathic pain. These drugs copy the action of GABA. Professor Stephanie Cragg and her team think that gabapentinoids will be able to protect brain cells by stopping too much calcium for entering cells just like GABA. They hope that preserving cells could help maintain dopamine levels and ultimately slow or prevent the progression of Parkinson's.

What are the researchers doing?

In a pioneering new study, which started last year, Professor Cragg and her team are measuring the effects the drugs have on the levels of dopamine and calcium using a powerful technique called "fastscan cyclic voltammetry". Using an extremely small electrode (we're talking micrometers in size) inserted into the brain of a mouse model of Parkinson's and brand new reporter dyes, the team is trying to understand how these drugs work. This technique is looking at how the calcium is moving into the cells, and will try and understand how the drugs boost dopamine, what kind of dose is required and which neurons are affected. They will also look to see if these drugs can fix problems in already affected cells, like the build-up of toxic molecules such as alpha-synuclein.

Professor Cragg is working alongside people affected by Parkinson's to help shape this research and engage with the local community. Two people with Parkinson's are meeting with Professor Cragg and her team regularly over the course of the project. So far the group has discussed some of the challenges of repurposing drugs and how people affected by Parkinson's can get more involved in lab-based studies. (Go to our website to find out how you can help shape research.)

Drug repurposing

Gabapentinoids are already in use, they are already regularly being prescribed for people with a range of conditions. That means that we already know they are safe for humans to take. That puts us miles ahead. If they can do what we're hoping they will then we will be able to start trialling them in people with Parkinson's straight away. Repurposing existing drugs has the potential to shave years off the time it takes to bring those drugs to the people that need them.

However, we wouldn't recommend that all people with Parkinson's being prescribed this drug as there is still a lot to learn. In fact, recent research has suggested that the use of gabapentinoid drugs may actually be linked to Parkinsonism — a group of conditions that include Parkinson's and share some of the same symptoms. This highlights the need for us to understand more about the role of GABA, and that a careful balance needs to be found when looking at targeting neurotransmitters in Parkinson's.

 *Written by Dr Katherine Fletcher, Research Communications Officer at Parkinson's UK*

Technology that can turn down Parkinson's symptoms?

We investigate a new type of deep brain stimulation that could provide better symptom management.

While much of the news has been focused elsewhere, an international team of researchers have recently published results on a brain stimulation device that may be able to turn down Parkinson's symptoms as required. The study, led by researchers in the Netherlands and carried out at the University of Oxford, looked at the benefit of adaptive deep brain stimulation (aDBS) compared to standard deep brain stimulation.

What is deep brain stimulation?

Deep brain stimulation (DBS) is the main surgical option for Parkinson's. During surgery, very fine wires are carefully inserted into the brain to electrically stimulate particular groups of brain cells involved in controlling movement. These wires are then connected to a battery pack, which is usually placed under the skin in the chest. The effect on symptoms is similar to taking levodopa, but the key advantage is that DBS stimulation is constant and stable — effects don't fluctuate in the way medications can in between taking tablets. The level of electrical stimulation can also be tweaked to give the brain cells the right 'dose' to best control movement, and this can be reviewed and adjusted over time.

DBS is particularly effective for improving simple movements like walking, but it's usually less so for more complex movements like speech and freezing, and can occasionally even make these worse. Some people also experience other unwanted side effects including unusually jerky movement. (Deep Brain Stimulation — explained)

What is aDBS?

While standard DBS can be adjusted, adaptive DBS takes a step towards targeting the stimulation when it is required rather than providing it constantly at the same level. It works by measuring brain waves to adapt the stimulation to manage a person's symptoms in real-time.

What are brain waves?

The brain works by sending electrical signals. The patterns of electrical activity that are emitted from the brain, and can be recorded on medical tests such as an electroencephalogram, are commonly referred to as brain waves. There are different patterns of brain waves and changes in the beta wave activity in an area of the brain known as the subthalamic nucleus have been linked with Parkinson's. These beta waves are present when we are alert, attentive, engaged in problem-solving, decision making, or focused mental activity. But abnormally high levels of beta wave activity are seen in Parkinson's and may be linked to movement symptoms. Indeed, previous trials have suggested that delivering deep brain stimulation in response to high beta wave activity may be more beneficial and cause fewer side effects than constant stimulation, and may even extend the life of the battery implanted under the skin on the chest.

What the researchers did

The study recruited 13 people with Parkinson's who had previously received DBS surgery and needed a battery replacement. By connecting the DBS device to an external brain wave sensor that was worn on the head, the simulator was made to turn on when abnormal beta waves were detected. The team found that aDBS improved slow movement and caused fewer speech problems compared to conventional continuous stimulation. However, for 2 participants it caused tremors to reappear, suggesting the treatment might not work for everyone or could require refinement for those with a prominent tremor.

Towards better deep brain stimulation

Improving deep brain stimulation has the potential to have a huge impact on the quality of life. It is early days and the long term benefits and feasibility of such adaptive treatment have yet to be established. More research is also needed to understand who may benefit from this type of technology and if it can be personalised for those who experience tremor. But with positive results from studies like this, researchers are moving the goalposts for what may be achievable with surgery for Parkinson's.

 *Written by Dr Beckie Port, Research Communications Manager at Parkinson's UK*

Results from the AMBLED trial

A phase 2 trial of an experimental drug that aimed to treat the motor symptoms of Parkinson's and reduce side effects of levodopa has shown disappointing results.

Most treatments for Parkinson's work to mimic or replace the dopamine — a chemical messenger that those with the condition are lacking. The most commonly used medication for Parkinson's, levodopa, works in this way. But while there are many ways this medication has been improved over the years, levodopa cannot always fully manage symptoms and can cause troublesome side effects.

Side effects of Parkinson's medication

As the symptoms of Parkinson's progress, people may experience wearing off of their medication before the next dose is taken. During these times people may feel particularly stiff and slow. As well as this, people may experience dyskinesia — involuntary muscle movements including twitching and jerking. (You can read more about these side effects on our website.)

The AMBLED trial, run by Lundbeck, a global pharmaceutical company that specialises in brain conditions, set out to address these vital limitations of levodopa.

What did the trial involve?

The AMBLED trial aimed to investigate a drug called Foliglurax, also known as PXT002331. Back in 2016, this drug was shown to be safe and well tolerated in people without Parkinson's. And the latest stage of the study involved testing the drug in people with Parkinson's for the first time. The study took place at 46 sites across six European countries, including the UK. It recruited 157 people who were taking levodopa, had been diagnosed with Parkinson's for more than 3 years, and who experienced wearing off and dyskinesia. These participants were randomly assigned to receive either a low or high dose of the experimental treatment or a placebo (dummy drug). They took this twice a day for a month alongside their levodopa medication.

How does Foliglurax work?

In Parkinson's, levels of the chemical messenger glutamate are altered as the brain tries to compensate for the lack of dopamine. Excessive activity related to glutamate is believed to play a role in why some experience levodopa-induced dyskinesia. Foliglurax has been developed to reduce glutamate signalling and rebalance the brain. There is already an approved drug that reduces glutamate signalling which can be prescribed to treat Parkinson's symptoms — amantadine. In the UK amantadine is normally prescribed with other Parkinson's medications to treat tremor and rigidity. While helpful, it can have side effects and does not work for everyone.

The results

Unfortunately, Lundbeck have announced that the results from the phase 2 trial of Foliglurax in people with Parkinson's failed to show sufficient beneficial effects. Those receiving the active drug treatment had no significant reduction in 'off' time compared to the placebo group. Foliglurax also failed to improve dyskinesia.

What's next?

A publication of the full results of the AMBLED trial will follow this initial announcement. Whilst these results are disappointing there are other drugs being investigated to help with the side effects of levodopa. Indeed, one promising drug, called NLX-112, has recently been shown to reduce dyskinesia in marmosets. It is hoped that this drug will enter clinical trials by the end of 2020.

 *Written by Dr Katherine Fletcher, Research Communications Officer at Parkinson's UK*

TAKE PART

For people who wish to participate in studies, please visit our **Take Part Hub**, a post code searchable database of studies actively recruiting participants. The Hub is updated weekly with new studies, so please do check it regularly: https://www.parkinsons.org.uk/research/take-part-research

And for those people not online, you can call our free, confidential Helpline on **0808 800 0303** and our trained Advisors will be able to discuss what you are interested in and put you through to the Research team to find studies for you.

Links to studies that can be completed from home:

1. **The USP Project - Exploring and understanding the scope and value of the Parkinson's nurse in the UK:** Annette Hand and Sarah Brown from Northumbria University are looking to demonstrate the scope, value and efficiency of specialist nurses working in the field of Parkinson's.

   Link:
   https://www.parkinsons.org.uk/research/usp-project-exploring-and-understanding-scope-and-value-parkinsons-nurse-uk

   Who: 400 people affected by Parkinson's are needed. This can be anyone diagnosed with Parkinson's or family and friends who are interested in sharing their thoughts.

   What: Completing a one off online survey which should take no more than 45 minutes. You may be approached at a later date about a face to face interview if interested.

2. **Swallowing difficulties in people with Parkinson's:** The aim of the study is to produce a report that can be used by staff in the NHS to improve care delivery. They will also produce information to

support patients and their families with the care they should receive.

Link: https://www.parkinsons.org.uk/research/swallowing-difficulties-people-parkinsons

Who: As many people as possible who have Parkinson's and have been admitted to hospital in the last 18 months. During the hospital admission you must have experience swallowing, eating or drinking problems. They are also interested in hearing from partners and family members who have supported the above people.

What: Completing a short, one off, online questionnaire that should take no more than 5 minutes.

Need to chat to someone? Our helpline and Parkinson's local advisers are here to answer any questions you have about the symptoms of Parkinson's. You can call them on 0808 800 0303.

Thank you for supporting research!

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