Possible Parkinson's treatment successfully targets two major nerve systems

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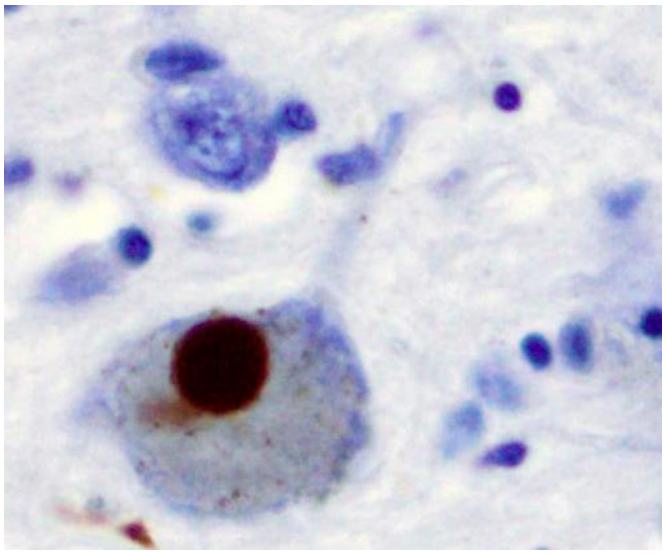

Immunohistochemistry for alpha-synuclein showing positive staining (brown) of an intraneural Lewy-body in the Substantia nigra in Parkinson's disease. Credit: Wikipedia

Scientists have discovered that a non-invasive technique which could one day be used to treat Parkinson's disease, can successfully target a highly specific group of brain cells which play a key role in development of the condition.

In 2015, scientists demonstrated that a form of gene therapy could target and stimulate a group of nerve cells affected by the disease, called cholinergic neurons. These cells degenerate as the disease progresses.

Now, thanks to brain imaging technology, they have discovered that their method, which targets cells that produce specific brain chemicals, can also successfully stimulate another type of neuron through cell-to-cell interactions.

In a study published in the journal *Neurotherapeutics*, Dr. Ilse Pienaar, Lecturer in Pharmacology at the University of Sussex, along with colleagues at Imperial College London and Invicro, a precision medicine company, reveal a clear communication pathway between cholinergic neurons and dopaminergic neurons, two major neurotransmitter systems found in the brain.

Dopaminergic neurons produce dopamine, but in Parkinson's disease, these levels are reduced as neurons deactivate and eventually die. This can cause a number of symptoms, including impaired movement.

Using a type of gene therapy in a rat model of Parkinson's, Dr. Pienaar and her colleagues targeted cholinergic neurons, only to realise that a therapeutic knock-on effect was also felt by dopaminergic neurons. The originally stimulated cell was able to evoke a positive reaction in the receptive cell type, restoring dopaminergic functions.

With both groups of nerve cells stimulated, test subjects were seen to make a complete recovery including showing no more signs of movement and postural impairment.

Dr. Ilse Pienaar, senior author of the study funded by the Medical Research Council, said: "When we used brain imaging, we found that as we activated cholinergic neurons, they then interacted directly with dopaminergic neurons.

"This seems to be a knock-on effect so by targeting this one set of neurons, we now know that we are able to also stimulate dopaminergic neurons, effectively restarting the production of dopamine and reducing symptoms.

"This is really important as it reveals more about how nerve systems in the brain interact, but also that we can successfully target two major systems which are affected by Parkinson's disease, in a

more precise manner."

In the gene therapy technique, the team used a harmless virus to deliver a genetic modification to cholinergic neurons in rats rendered Parkinsonian. They then administered a drug designed to act as a 'switch' and stimulate target neurons.

The technique could, in future, provide a less invasive and more effective way to treat Parkinson's patients. While the disease can currently be managed by drugs, these tend to become ineffective after five years and present a number of side effects. An alternative is an invasive surgical procedure called deep brain stimulation (DBS) which uses electrodes to send pulses into the brain. However, this treatment produces mixed results and researchers believe this is because it stimulates every cell type rather than just the specific cells affected by Parkinson's disease.

Dr. Pienaar said: "For the highest chance of recovery, treatments need to be focused and targeted but that requires a lot more research and understanding of exactly how Parkinson's operates and how our nerve systems work.

"Discovering that both cholinergic and dopaminergic neurons can be successfully targeted together is a big step forward.

"While this sort of gene therapy still needs to be tested on humans, our work can provide a solid platform for future bioengineering projects."

Lisa Wells, Head of CNS Discovery Applications at Invicro and co-author of this study commented: "It has been an exciting journey working with Dr. Pienaar's team to combine the two technologies to offer us a powerful molecular approach to modify neuronal signaling and measure neurotransmitter release. We can support the clinical translation of this "molecular switch" into clinical utility through live imaging technology."

According to Parkinson's UK, around 145,000 people in the UK are diagnosed with the disease, which has three main symptoms -shaking, slowness of movement and muscle stiffness.

More information: Puneet K. Sharma et al, DREADD Activation of Pedunculopontine Cholinergic Neurons Reverses Motor Deficits and Restores Striatal Dopamine Signaling in Parkinsonian Rats, *Neurotherapeutics* (2020). DOI: 10.1007/s13311-019-00830-4

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