Promising drug for Parkinson's disease: Study supports fast track to clinical trials

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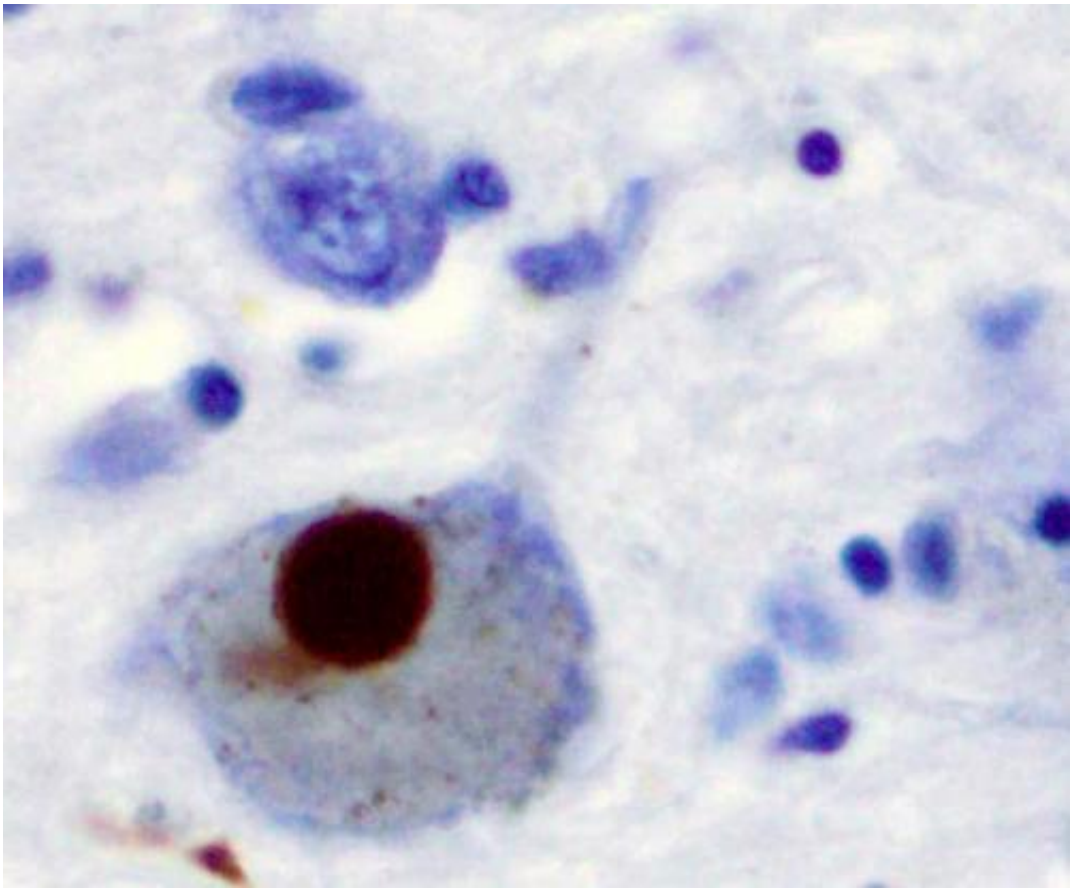

Immunohistochemistry for alpha-synuclein showing positive staining (brown) of an intraneural Lewy-body in the Substantia nigra in Parkinson's disease. Credit: Wikipedia

A drug which has already been in use for decades to treat liver disease

could be an effective treatment to slow down progression of Parkinson's disease, scientists from the University of Sheffield have discovered.

The pioneering research led by academics from the Sheffield Institute of Translational Neuroscience (SITraN), in collaboration with scientists from the University of York, supports the fast-tracking of the drug ursodeoxycholic acid (UDCA) for a clinical trial in Parkinson's patients.

Dr Heather Mortiboys, Parkinson's UK Senior Research Fellow from the University of Sheffield, explained: "We demonstrated the beneficial effects of UDCA in the tissue of LRRK2 carriers with Parkinson's disease as well as currently asymptomatic LRRK2 carriers. In both cases, UDCA improved mitochondrial function as demonstrated by the increase in oxygen consumption and cellular energy levels."

Oliver Bandmann, Professor of Movement Disorders Neurology at the University of Sheffield and Honorary Consultant Neurologist at Sheffield Teaching Hospitals NHS Foundation Trust, added: "Whilst we have been looking at Parkinson's patients who carry the LRRK2 mutation, mitochondrial defects are also present in other inherited and sporadic forms of Parkinson's, where we do not know the causes yet. Our hope is therefore, that UDCA might be beneficial for other types of Parkinson's disease and might also show benefits in other neurodegenerative diseases."

The research is also the first to demonstrate beneficial effects of UDCA on dopaminergic neurons, the nerve cells affected in Parkinson's disease, in a fly model of Parkinson's disease which carries the same genetic change as some patients with the condition.

The study published in the journal *Neurology* is funded by Parkinson's UK, the Wellcome Trust and the Norwegian Parkinson Foundation.

A mutation in the LRRK2 gene is the single most common inherited cause of Parkinson's disease. However, the precise mechanism that leads to Parkinson's is still unclear.

Defects in mitochondria, and as a consequence reduced energy levels, are a factor in a number of diseases that affect the nervous system including Parkinson's and Motor Neuron Disease. Nerve cells have a particularly high energy demands, therefore defects in the cell's energy generators will crucially affect their survival.

Professor Bandmann added: "Following on from the promising results of our in vitro drug screen, we were keen to further investigate and confirm the potential of UDCA in vivo - in a living organism.

"UDCA has been in clinical use for decades and thus could be advanced to the clinic rapidly if it proves beneficial in clinical trials."

Collaborators Rebecca Furmston, White Rose PhD student, and Dr Chris Elliott, from the University of York's Department of Biology, demonstrated the beneficial effects of UDCA in vivo using the fruit fly (Drosophila melanogaster). In fruit flies, the mitochondrial defects caused by the LRRK2 mutation to dopaminergic neurons can be monitored through the progressive loss of visual function. Flies carrying the mutation maintained their visual response when fed with UDCA.

Dr Elliott said: "The treatment of fruit flies carrying the faulty LRRK2 gene with UDCA showed a profound rescue of dopaminergic signalling. Feeding the flies with UDCA partway through their life slows the rate at which the fly brain then degenerates. Thus, mitochondrial rescue agents may be a promising novel strategy for disease-modifying therapy in LRRK2-related Parkinson's."

Dr Arthur Roach, Director of Research and Development at Parkinson's

UK, which part-funded the study, said: "There is a tremendous need for new treatments that can slow or stop Parkinson's.

"Because of this urgency, the testing of drugs like UCDA, which are already approved for other uses, is extremely valuable. It can save years, and hundreds of millions of pounds.

"It's particularly encouraging in this study that even at relatively low concentrations the liver drug still had an effect on Parkinson's cells grown in the lab.

"This type of cutting-edge research is the best hope of finding better treatments for people with Parkinson's in years, not decades."

More information: Mortiboys, H., Furmston, R., Bronstad, G., Aasly, J., Elliott, C., Bandmann, O. (2015) UDCA exerts beneficial effect on mitochondrial dysfunction in LRRK2G2019S carriers and in vivo. *Neurology* 85:1-7

Provided by University of Sheffield