Parkinson’s disease and alpha-synuclein: on the hunt for novel therapeutics

Professor Stephan Witt

Parkinson’s disease affects 1-2% of the population over 65 years of age and is the most commonly occurring movement disorder. The disease is caused by selective degeneration of dopaminergic neurons in a region of the mid-brain called the substantia nigra. Although their numbers are few, these dopamine-producing neurons play an important role in the control of multiple brain functions, including voluntary movement, as well as a broad array of behavioural processes such as mood, reward, addiction, and stress. Loss of these neurons can lead to slow movement, rigidity and unstable posture. The affected neurons often show aggregates called Lewy bodies, whose main component is the protein alpha-synuclein. Although highly expressed in the brain, alpha-synuclein is also present in red blood cells, highly expressed in the brain, alpha-synuclein. Although

Professor Stephan Witt and his team have been studying the roles of two such compounds, called phosphatidylcholine (PC) and phosphatidylethanolamine (PE) in modulating the solubility of alpha-synuclein. One source of PE in cells is an enzyme called phosphatidylethanolamine decarboxylase (PSD). Other sources of PE include enzymes in the cytoplasm, the fluid that fills a cell, and in the endoplasmic reticulum (ER), which acts as the manufacturing and packaging component of the cell.

The group at LSU Health Shreveport discovered a 60% reduction in PE in yeast cells when they deleted the gene for PSD. They also found that this resulted in ER stress, defects in trafficking of materials within the cell, accumulation of alpha-synuclein and severely inhibited growth. The group were able to produce similar results using a worm model, C. elegans. These worms express human alpha-synuclein in their neurons, so they make a good model for Parkinson’s disease in humans. Both experiments showed that moderate levels of human alpha-synuclein and low levels of PE were toxic. Interestingly, moderate levels of alpha-synuclein or low PE levels have little or no toxicity on their own; it is only the combination of the two which is extremely toxic.

Professor Witt also investigated whether it is possible to reduce this level of toxicity and found that administration of a single compound called ethanolamine could rescue the toxicity of low PE and alpha-synuclein. Ethanolamine does this by stimulating the synthesis of PE through a particular enzymatic pathway. Overall, they concluded that low PE in cells causes traffic jams of aggregated alpha-synuclein on the internal highways of the cell and that these traffic jams ultimately kill the cell.

RE-DEFINING EXISTING DRUGS

Loading on from this, Professor Witt’s team went on to screen the Prestwick library of Food and Drug Administration (FDA) approved drugs for drugs which would abolish the toxicity of alpha-synuclein in yeast cells with low PE levels. They chose drugs based on reports that they were able to rescue the slow growth phenotype of yeast cells without the gene for PSD, and which expressed human alpha-synuclein. Their work screened 1121 drugs and identified three possible candidates: cyclosporine (CsA), which is a powerful immunosuppressant, melflufenxate (MFX) and sulfaphenazole (SUL), which is an antibiotic. Previous studies suggest that these drugs work in different ways. Cyclosporine is thought to prevent alpha-synuclein induced damage to mitochondria, the energy-producing powerhouse of the cell. Melflufenxate hydrolyses into choline, which can increase the level of PE in cells and unclog the traffic jams. Sulfaphenazole has been reported to induce autophagy in cells, a process by which the cells can self-destruct and safely decrease the level of alpha-synuclein.

Firstly, the drug candidates were tested for their ability to inhibit ER stress in yeast cells, a phenomenon which may also be associated with an increase in alpha-synuclein aggregation and increased cell death. The yeast cells didn’t contain the gene for PSD, and therefore produced about 50% of the basal level of PE. Whilst SUL decreased ER stress to the greatest extent compared to the control, CsA decreased ER stress to a lesser extent and MFX slightly increased it.

The drugs were then tested in a worm neurodegeneration model, which could be used to mimic Parkinson’s disease
in humans. All three drugs were able to rescue dopaminergic neuron loss, and in fact protected the dopaminergic neurons that expressed alpha-synuclein, but not PSD, from degeneration. One way this neuroprotection is thought to occur is through a reduction in alpha-synuclein gene expression. However, Professor Witt determined that alpha-synuclein expression was unchanged following treatment with the drug candidates, but that the neuroprotection may occur via different pathways for each drug. MFX may scavenge free radicals, which cause damage to the body, CsA may inhibit pores associated with calcium transport, which may cause both neurodegeneration and cardiac damage, and SUL may inhibit cell death pathways. CsA and MFX had previously been reported to protect against neurodegeneration, but this work presents the first report that SUL is able to protect against alpha-synucleinduced dopaminergic neuron loss.

**Professor Witt’s work could potentially be used, singly or in combination, to protect against alpha-synuclein associated pathology in cells derived from patients with Parkinson’s disease. If this is indeed the case, there is the possibility that by interfering with the pathways by which alpha-synuclein causes disease, we could develop novel therapeutic strategies to tackle a distressing degenerative disorder.**

**WHAT COMES NEXT**

The next question is whether the drug candidates identified by Professor Witt’s work could potentially be used, singly or in combination, to protect against alpha-synuclein associated pathology in cells derived from patients with Parkinson’s disease. If this is indeed the case, there is the possibility that by interfering with the pathways by which alpha-synuclein causes disease, we could develop novel therapeutic strategies to tackle a distressing degenerative disorder.