Cage Fighting for Parkinson's Disease: How can we prevent the abnormal spread of proteins

Research

Parkinson's disease (PD) is a significant global problem, affecting 10 million people worldwide. In Australia alone, 1 in every 350 Australians suffer from PD, with 32 new cases diagnosed each day. Given that the prevalence of PD is estimated to double by 2030, the search for an effective treatment for the disease is critical. Currently, the limited treatments available for PD treat only the symptoms and do not actually modify the brain mechanisms that contribute to the disease.

A major contributor to the spread of Parkinson's disease throughout the brain is the transmission of an abnormally folded protein called alpha synuclein from brain cell to brain cell. Alpha synuclein normally helps to maintain communication between brain cells. In PD, for reasons that are not yet understood, the alpha synuclein begins to misfold and aggregate. While some of this alpha synuclein forms clumps called Lewy bodies within brain cells, alpha synuclein may also be released from brain cells into the space between cells. There, it can be taken up by neighbouring brain cells, triggering the misfolding and aggregation of the protein alpha synuclein within those cells. In this way, the pathology of PD can spread throughout the brain and lead to the emergence of the characteristic motor and non-motor symptoms of PD.

In our research, we aimed to develop a novel protein nanocage system and investigate whether it could capture alpha synuclein. This is particularly exciting, as it represents a first of its kind treatment, focusing on an aspect of the pathology of PD that is currently not targeted in any other available therapeutic. Additionally, by stopping the transmission of alpha synuclein from brain cell to brain cell, it may actually modify the brain mechanisms that underlie the development of PD, halting the spread of disease throughout the brain.

Outcome

The Brain Foundation funding allowed us to conduct experiments to understand the key properties of protein nanocages, such as the rate at which they disassemble, how they come back together, and how safe they are for administration in the brain. These experiments were critical, as they provide us with the foundational knowledge necessary to understand how to utilise the nanocages to develop a new treatment strategy for PD. For example, this work provides important insights into the dosage likely needed to see a beneficial effect or the best route of administration into the body. Excitingly, the Brain Foundation funding also allowed us to engineer our protein nanocage system to bind to alpha synuclein. This is the first time that a protein nanocage has been used to bind an unmodified foreign protein and provides key proof of concept that our nanocage system can be used to target the abnormal transmission of alpha synuclein in the brain in PD. With this critical preliminary data, we can now move on to the next step in development, assessing whether our system stops the spread of alpha synuclein between cells in experimental models, thereby preventing the emergence of the symptoms of PD.

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