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Scientists block action of hallmark dementia protein in mice

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A research team at King's College London has used a new approach to study a hallmark dementia protein called tau in mice, revealing that a drug called phenylbutyrate can protect against damage caused by the protein.

The findings are published in the journal *Brain* and funded by Alzheimer's Research UK and the Wellcome Trust.

One of the key hallmark features of Alzheimer's is an abnormal build-up of a protein called tau in the brain, but there are several different neurodegenerative diseases that are caused by abnormal tau. These so-called 'tauopathies' can have a range of symptoms from memory and thinking problems to severe movement disorders.

The team, led by Dr Diane Hanger at the Maurice Wohl Clinical Research Institute, King's College London, studied donated brain tissue from the London Neurodegenerative Diseases Brain Bank at King's College London. They had previously identified a fragment of tau protein that was found in the brains of people with a tauopathy called progressive supranuclear palsy and wasn't present in healthy brains.

They bred mice to produce low levels of this form of the tau protein, which they called Tau35. Despite only producing a relatively low level of the protein, the mice developed memory, thinking and movement problems that became progressively worse with age. The findings indicate the importance of the tau protein in orchestrating damage in the

brain in diseases like Alzheimer's. The researchers then studied the function of nerve cells in the mice in more detail. The study revealed that the tau fragment caused defects in how the cells get rid of unwanted or damaged proteins – one mechanism through which tau could damage nerve cells in the brain.

When the mice were eight and a half months old they started experiencing significant memory and motor symptoms. At this stage, they were treated daily for six weeks either with an injection of phenylbutyrate or sterile water as a control. Phenylbutyrate is a drug already used to treat urea cycle disorders – inherited metabolic disorders that affect how ammonia is removed from the bloodstream. Previous research had suggested the drug could target some aspects of Alzheimer's in mice and it has also been explored in clinical studies for cancer, cystic fibrosis and neurodegenerative diseases like motor neurone disease and Huntington's disease. After treatment with phenylbutyrate, the mice showed improvements to their memory and motor symptoms suggesting phenylbutyrate could rescue damage caused by the tau protein.

Dr Diane Hanger, said, "Tau protein is becoming an increasingly attractive target for the development of new medicines for dementia, because it's central to several different neurodegenerative diseases including Alzheimer's. This new approach to studying the effect of low levels of tau protein in mice helps us to recreate aspects of these diseases in a way that more closely represents what's seen in patients. By studying these mice, we're starting to identify key mechanisms driving damage in the brain and we hope that teams across the world can use this method to study these complex diseases and search for new treatments."

"Phenylbutyrate is a drug already being investigated for benefits in a range of conditions and it was interesting to see it may also have the potential to protect against damage caused by tau protein in mice. The

findings are an important basis for future drug development studies to understand the mechanism through which phenylbutyrate may protect against neurodegeneration and whether this could point us towards new treatments. In future we're keen to continue building on our new approach to learn more about the mechanisms driving neurodegeneration in these mice, with the aim of identifying promising targets for the development of new treatments."

Dr Simon Ridley, Director of Research at Alzheimer's Research UK, said, "The human brain is a hard-to-reach organ, making it difficult to study the molecular changes in diseases like Alzheimer's in a living system. This study has allowed the research team to better understand how tau can damage cells in diseases like Alzheimer's, as well as a range of other neurodegenerative diseases associated with the protein. It's important to expand the tools researchers have to study the diseases that cause dementia, as they provide a way both to understand these diseases and to screen new drugs.

"While clinical trials in people will always be the gold standard to prove the benefit of any new drug for diseases like Alzheimer's, research in mice is an important part of the drug development process. We must continue to invest in research to understand the biology of the different forms of dementias as well as using this to narrow down the most promising new therapeutic approaches to drive towards clinical trials."

More information: Marie K. Bondulich et al. Tauopathy induced by low level expression of a human brain-derived tau fragment in mice is rescued by phenylbutyrate, *Brain* (2016). DOI: 10.1093/brain/aww137

Provided by Alzheimer's Research UK