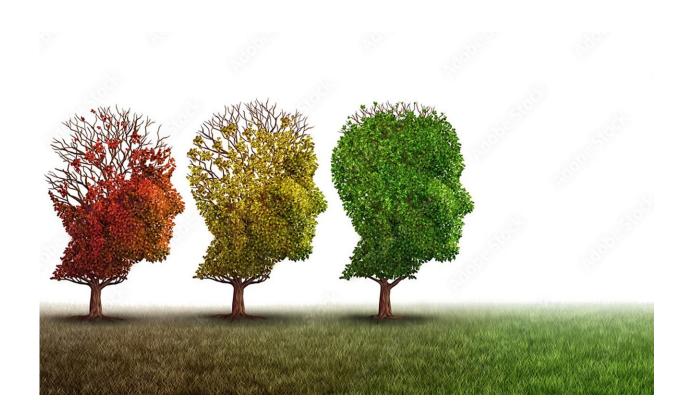


Research team identifies new treatment target for Alzheimer's disease

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Alzheimer's disease is the leading cause of dementia and disability in old age. Credit: Lancaster University

Researchers at the University of Leeds and Lancaster University in the



UK have identified a new potential target for the treatment of Alzheimer's disease—PDE4B. Their work is <u>published</u> in *Neuropsychopharmacology*.

Alzheimer's disease is the leading cause of dementia and disability in old age. As the number of people diagnosed with Alzheimer's disease is on the increase, new treatments are urgently needed to improve the quality of life for people living with the disease.

PDE4B is an enzyme inside cells that breaks down a molecule known as cyclic AMP, which regulates a range of cellular processes. Based on an Australian study that identified the PDE4B gene as a risk factor for developing Alzheimer's disease, the UK team investigated whether reducing PDE4B activity might protect against Alzheimer's disease pathology and be a useful treatment approach. To this end, they introduced a gene for reduced PDE4B activity into an Alzheimer's disease (AD) mouse model that develops amyloid plaques in the brain, a key pathological feature of the disease.

The researchers observed that AD mice showed memory deficits in maze tests, but memory was unimpaired in AD mice with genetically reduced PDE4B activity. Using functional brain imaging, the team found the metabolism of glucose, the main source of energy in the brain, was impaired in AD mice, like that seen in patients with the disease. However, AD mice with genetically reduced PDE4B activity showed healthy levels of glucose metabolism in the brain.

To understand the mechanisms involved, the researchers next looked at gene and protein expression levels in the brain. This identified increased inflammation in the brains of AD mice, like that seen in Alzheimer's disease patients, but inflammation was lower in AD mice with



genetically reduced PDE4B activity.

Similar effects were seen for a range of other proteins involved in Alzheimer's disease pathology. Overall, these data suggest that reducing PDE4B activity might be a useful approach for the treatment of Alzheimer's disease, although more research is needed to validate the use of drugs that target the enzyme.

Dr. Steven Clapcote, the lead researcher, from the University of Leeds, said, "Reducing the activity of the PDE4B enzyme had a profound protective effect on memory and <u>glucose metabolism</u> in the AD mouse model, despite these mice showing no decrease in the number of <u>amyloid plaques</u> in the brain. This raises the prospect that reducing PDE4B activity may protect against <u>cognitive impairment</u> not only in Alzheimer's disease but also in other forms of dementia, such as Huntington's disease."

Dr. Neil Dawson, a co-author of the paper, from Lancaster University, echoed these sentiments: "These results offer real hope for the development of new treatments that will benefit patients with Alzheimer's disease in the future. It was intriguing to find that reducing PDE4B activity by just 27% could dramatically rescue memory, brain function and inflammation in the AD mice. The next stage is to test whether PDE4B inhibiting drugs have similar beneficial effects in the AD mouse model, to test their potential efficacy in Alzheimer's disease."

More information: Paul Armstrong et al, Protective effect of PDE4B subtype-specific inhibition in an App knock-in mouse model for Alzheimer's disease, *Neuropsychopharmacology* (2024). <u>DOI:</u> 10.1038/s41386-024-01852-z



Provided by Lancaster University

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