

'Brainy' mice raise hope of better treatments for cognitive disorders

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Credit: Martha Sexton/public domain

It sheds light on the molecular underpinnings of learning and memory and could form the basis for research into new treatments for age-related cognitive decline, cognitive disorders such as Alzheimer's disease and schizophrenia, and other conditions.

The researchers altered a gene in mice to inhibit the activity of an enzyme called phosphodiesterase-4B (PDE4B), which is present in many organs of the vertebrate body, including the brain.

In behavioural tests, the PDE4B-inhibited mice showed enhanced [cognitive abilities](#).

They tended to learn faster, remember events longer and solve complex exercises better than ordinary mice.

For example, the "brainy mice" showed a better ability than ordinary mice to recognise another mouse that they had been introduced to the day before. They were also quicker at learning the location of a hidden escape platform in a test called the Morris water maze.

However, the PDE4B-inhibited mice also showed less recall of a fearful event after several days than ordinary mice.

The published findings are limited to mice and have not been tested in humans, but PDE4B is present in humans. The diminished memory of fear among mice with inhibited PDE4B could be of interest to researchers looking for treatments for pathological fear, typified by Post-Traumatic Stress Disorder (PTSD).

The PDE4B-inhibited mice also showed less anxiety. They spent more time in open, brightly-lit spaces than ordinary mice, which preferred dark, enclosed spaces.

Ordinary mice are naturally fearful of cats, but the PDE4B-inhibited mice showed a decreased fear response to cat urine, suggesting that one effect of inhibiting PDE4B could be an increase in risk-taking behaviour.

So, while the PDE4B-inhibited mice excelled at solving complex exercises, their low levels of anxiety could be counterproductive for a wild mouse.

Dr Steve Clapcote, Lecturer in Pharmacology in the University of Leeds' School of Biomedical Sciences, led the study. He said: "Cognitive impairments are currently poorly treated, so I'm excited that our work using mice has identified phosphodiesterase-4B as a promising target for potential new treatments".

The researchers are now working on developing drugs that will specifically inhibit PDE4B. These drugs will be tested in animals to see whether any would be suitable for clinical trials in humans.

Dr Alexander McGirr, a psychiatrist in training at the University of British Columbia, who co-led the study, said: ""In the future, medicines targeting PDE4B may potentially improve the lives of individuals with neurocognitive disorders and life-impairing anxiety, and they may have a time-limited role after traumatic events."

Dr Laura Phipps of Alzheimer's Research UK, who were not involved in the study, said:

"This study highlights a potentially important role for the PDE4B gene in learning and memory in [mice](#), but further studies will be needed to know whether the findings could have implications for Alzheimer's disease or other dementias. We'd need to see how this gene could influence memory and thinking in people to get a better idea of whether it could hold potential as a target to treat Alzheimer's.

"There is currently a lack of effective treatments for dementia and understanding the effect of genes can be a key early step on the road to developing new drugs. With so many people affected by dementia, it is

important that there is research into a wide array of treatment approaches to have the best chance of helping people sooner."

More information: McGirr A, Lipina TV, Mun H-S, Georgiou J, Al-Amri AH, Ng E, Zhai D, Elliott C, Cameron RT, Mullins JGL, Liu F, Baillie GS, Clapcote SJ, Roder JC. (2015). 'Specific inhibition of phosphodiesterase-4B results in anxiolysis and facilitates memory acquisition.' is published in *Neuropsychopharmacology*

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