Medical Xpress

Treatment of metabolic dysfunction could be a potential therapy for Alzheimer's disease

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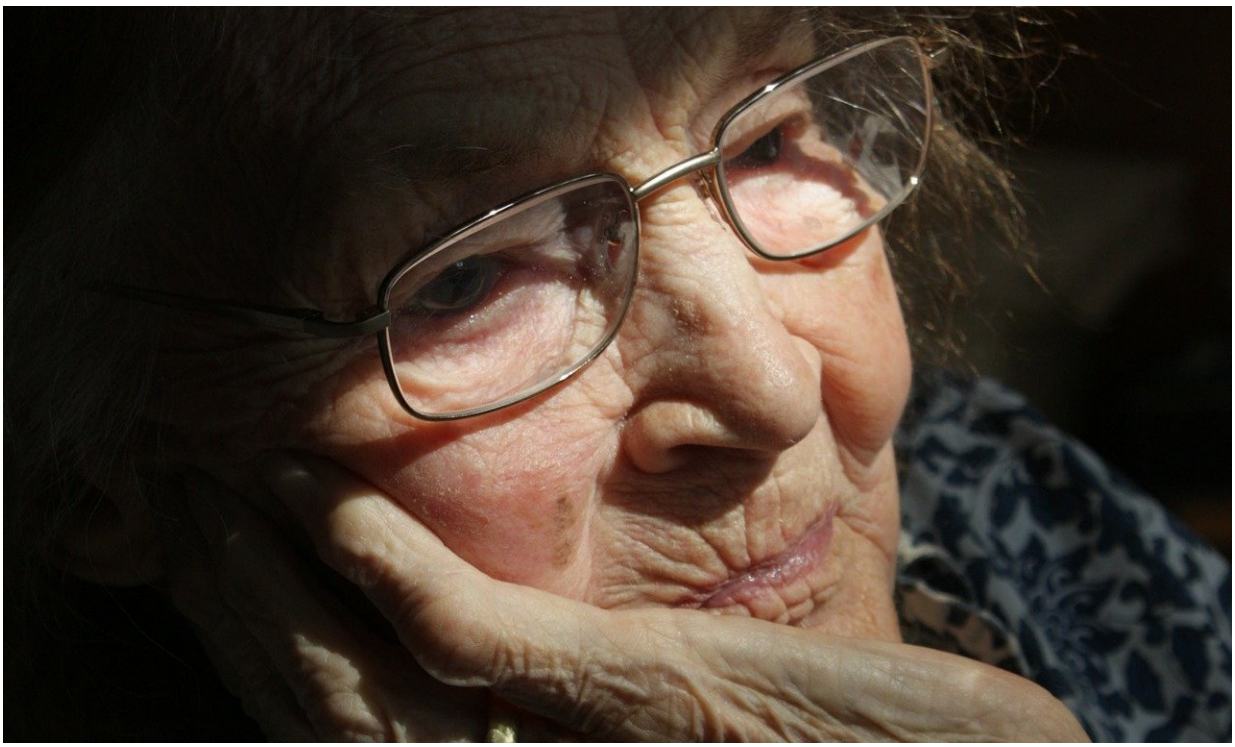

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A team of researchers led by Yale-NUS College has found evidence that metabolic dysfunction is a primary cause of Alzheimer's disease.

Alzheimer's disease is the most common neurodegenerative disease affecting the elderly worldwide, as well as one of the most common

causes of dementia. In Singapore, one in 10 people aged 60 or above is believed to suffer from dementia. After more than twenty years of research effort worldwide, scientists are still unable to identify the exact causes of Alzheimer's and no proven treatment is available. Two competing theories are currently proposed to explain the cause of Alzheimer's: the first is focused on the accumulation of a specific protein, called amyloid-beta protein, in the brain as the primary cause; whilst a second and more recent theory proposes that metabolic dysfunction, specifically a dysfunction of the cell's energy-producing machinery called mitochondria is responsible.

In a new study published in the scientific journal *eLife*, a team led by Assistant Professor Jan Gruber from Yale-NUS College discovered that metabolic defects occur well before any significant increase in the amount of amyloid-beta protein could be detected. The research used a tiny worm called Caenorhabditis elegans to identify these changes because it shares many similarities at the molecular level with human cells. A further breakthrough came when the team found that treatment of the worms with a common anti-diabetes drug called Metformin reversed these metabolic defects and normalised the worms' healthspan and lifespan.

"Current trials of Alzheimer's drugs targeting proteins have failed despite billions of dollars being invested. Based on the emerging strong links between mitochondrial dysfunction and Alzheimer's pathology, it might be better to adopt a preventative strategy by targeting metabolic defects, especially mitochondrial defects, directly and early, well before protein aggregates are even present," said Assistant Professor Gruber.

He further explained that metabolic and mitochondrial dysfunctions should be viewed as fundamental features of ageing in general and that age-dependent diseases, including Alzheimer's, should therefore be viewed as manifestations of ageing. Hence, it may be easier to prevent or

treat age-dependent diseases by targeting the mechanisms of ageing rather than treating individual diseases after symptoms occur.

More information: Emelyne Teo et al, Metabolic stress is a primary pathogenic event in transgenic Caenorhabditis elegans expressing pan-neuronal human amyloid beta, *eLife* (2019). DOI: 10.7554/eLife.50069

Provided by Yale-NUS College