Experimental treatment prevents Alzheimer's-associated weight gain in mice

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Treatment with a bile acid derivative known as TUDCA (tauroursodeoxycholic acid) can mitigate metabolic abnormalities associated with Alzheimer's disease, such as alterations in food intake

and body weight, improving the patient's quality of life, according to the findings of a study conducted at the University of Campinas (UNICAMP) in the state of São Paulo, Brazil.

Experiments with mice showed that TUDCA combats these metabolic abnormalities by reducing food intake and increasing energy expenditure, as well as improving respiratory quotient, an indicator of metabolic efficiency based on the body's use of carbohydrates, proteins and lipids to produce energy, and a means of adjusting nutritional therapy. TUDCA acts on the hypothalamus, a brain region with multiple connections to other parts of the central nervous system and peripheral tissues.

In a healthy organism, TUDCA helps with digestion. It is produced in the liver and stored in the gallbladder. Its main medical use is to treat liver disease.

The study involved mice with a disorder similar to Alzheimer's induced by injection of streptozotocin (Stz), a cytotoxin and antibiotic widely used in experiments with rodents. The results may well turn out to be repeatable in humans, according to Helena Cristina de Lima Barbosa, a professor at the university's Institute of Biology (IB-UNICAMP).

"It's possible that the same benefits will be observed in patients. Taking into consideration the clinical data published so far, this extrapolation could be valid," she told Agência FAPESP.

Barbosa was the principal investigator for the study, which is described in an article in the journal *Scientific Reports*.

The study was conducted at the Obesity and Comorbidities Research Center (OCRC), a Research, Innovation and Dissemination Center (RIDC) funded by FAPESP and hosted by UNICAMP. It was part of the

master's research of Lucas Zangerolamo, with a scholarship from FAPESP.

"In our study, the Alzheimer's model animals displayed altered feeding behavior associated with higher body weight and lower energy expenditure. We set out to investigate the variables involved in this process, and detected an increase in inflammatory markers directly associated with dysregulation of the hypothalamus," Zangerolamo explained.

The study was designed to investigate the effects of TUDCA on hypothalamic appetite control and energy homeostasis in an Alzheimer's animal model. The scientists used three experimental groups: healthy mice treated with a placebo, streptozotocin-induced Alzheimer's mice also treated with placebo, and streptozotocin-induced Alzheimer's mice treated with 300 milligrams of TUDCA per kilogram once a day.

The control and intervention groups were kept in the same conditions and in individual cages for ten consecutive days. Food intake was measured every two days.

The mice treated with TUDCA displayed lower food intake, higher energy expenditure and a higher respiratory quotient, reduced fluorescence and gene expression of inflammatory markers in the hypothalamus, and normal expression of orexigenic (appetite-stimulating) neuropeptides AgRP and NPY.

Leptin-induced signaling of p-JAK2 and p-STAT3 in the hypothalamus of the mice improved. Downregulation of these phosphylated proteins is associated with weight gain.

"The inflammation that leads to dysfunctional behavior may be associated with the hypothalamus," Barbosa said. "TUDCA reduced the

inflammation and improved leptin signaling to induce satiety, leading to a reduction in food intake. Less inflammation of the hypothalamus permitted an overall improvement in the organism."

Dementia on the rise

According to an epidemiological study published in April 2021 in *Revista Brasileira de Epidemiologia*, Brazil had the second-highest prevalence of dementia in the world in 2016, with Alzheimer's disease accounting for about 70% of cases. Between 2007 and 2017, the number of deaths due to dementia increased 55% (more than deaths from breast, prostate and liver cancer combined). The prevalence of Alzheimer's in Brazil could quadruple by 2050.

The authors are researchers at the Federal University of Pelotas (UFPel) and the Federal University of Rio Grande do Sul (UFRGS) in Brazil, and the University of Queensland in Australia.

They also say Alzheimer's patients are more likely to be diagnosed with diabetes, depression, Parkinson's disease and stroke than elderly adults without Alzheimer's.

Alzheimer's is a neurodegenerative disorder caused by an accumulation and extracellular deposition of amyloid beta precursor protein in the hippocampus, a brain region that plays a major role in memory. This process leads to neuron death, memory impairment, a gradual cognitive decline and potentially dementia. Aging is the main risk factor.

Between 50% and 60% of Alzheimer's patients have non-cognitive metabolic abnormalities, such as alterations in food intake and body weight. Some become obese and diabetic, with high blood pressure and bad cholesterol. They are often insulin-resistant, losing the ability to use glucose in their peripheral tissue.

Obesity is one of the world's worst public health problems, according to the World Health Organization (WHO), which estimates that 2.3 billion adults will be overweight by 2025, and 700 million will be obese (with a body mass index above 30).

Safety of TUDCA

Clinical trials involving patients with amyotrophic lateral sclerosis, another progressive neurodegenerative disease, have shown that TUDCA is safe for humans and well absorbed by the organism when administered orally.

In the case of Alzheimer's, previous studies showed that treatment with TUDCA reduced the accumulation of amyloid beta in mice, attenuating the damage caused by a mechanism that has yet to be fully elucidated.

According to Zangerolamo, the researchers are currently studying the effects of TUDCA on senile mouse models to see if similar results can be obtained.

More information: Lucas Zangerolamo et al, Energy homeostasis deregulation is attenuated by TUDCA treatment in streptozotocin-induced Alzheimer's disease mice model, *Scientific Reports* (2021). DOI: 10.1038/s41598-021-97624-6

Natan Feter et al, Who are the people with Alzheimer's disease in Brazil? Findings from the Brazilian Longitudinal Study of Aging, *Revista Brasileira de Epidemiologia* (2021). DOI: 10.1590/1980-549720210018

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