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Faculté de biologie
et de médecine

Alzheimer's disease

The forgotten half of the brain to recover memory

A UNIL research team has succeeded in preserving the memory of Alzheimer's mice by boosting the metabolic functions of glial cells rather than those of neurons, a striking shift in treatment strategies.

Alzheimer's disease progressively affects memory until individuals lose their autonomy. It causes the death of neurons in brain regions where memory and learning mechanisms are located. Since treatment strategies focused on neurons have so far failed, researchers at the University of Lausanne (UNIL) decided to change the paradigm by turning to a cell type often overlooked by neuroscientists, and supposedly spared by Alzheimer's disease the: astrocytes. Astrocytes are part of the glial cell family and are known to structurally and functionally support neurons. The researchers focused on one of their proteins, UCP4, which is present in their mitochondria, the cells' powerhouse. By overexpressing UCP4 in astrocytes of Alzheimer's mice, the UNIL team succeeded in preventing degradation induced in neurons. The study, to be published in the journal *Glia*, shows that Alzheimer's mice treated early do not lose their memory with aging.

Alzheimer's disease affected 35.6 million people worldwide in 2015, according to WHO. The disease incidence is increasing, with a doubling of cases expected every 20 years. It affects essential cognitive functions such as memory, language, reasoning, and spatial orientation, up to a total loss of independence. Damage is attributed to the alteration of neurons that make up the brain areas important for memory and learning, in particular the hippocampus. The disease is characterized by the presence of plaques made of an accumulation of ß-amyloid protein between neurons, and by the presence of neurofibrillary tangles in the neurons. They progressively cause neuronal dysfunction until their death, explaining the decrease in volume of the hippocampus, and the loss of cognitive functions observed in patients.

To date, there is no cure, and the effectiveness of current approaches is questionable. "They are essentially indirect treatments that aim to increase cognitive functions such as memory and attention. The numerous studies and trials aimed at amyloid plaques or neurofibrillary tangles have produced disappointing results," says **Jean-Yves Chatton**, a neuroscience researcher and director of the Department of Fundamental Neurosciences at UNIL. It is therefore urgent to find new strategies to fight this dementia.

An intact memory

Rather than acting on neurons, plaques, or tangles, Jean-Yves Chatton's research team focused on astrocytes, glial cells often overlooked by neuroscientists. "Since direct approaches are not very effective, the idea was to find an indirect way to preserve neurons by relying on cells that are not themselves affected by the disease, and therefore theoretically healthy, and moreover known for their healing abilities towards neurons," says Jean-Yves Chatton.

For this study, his research team developed an approach to increase a specific function of astrocytes known to preserve neuronal death. The results show that this new strategy is able to counteract the pathological alterations observed in mice with Alzheimer's disease, such as early metabolic disruption, hippocampal atrophy, changes in neuron structure, and aberrant neuronal excitability. Remarkably, the memory of Alzheimer mice was preserved.

Boosting mitochondria in astrocytes

Astrocytes provide structural and functional support to neurons, notably through the exchange of substances that act on the neuronal plasticity mechanisms that underlie memory processes, or by providing energy. Astrocytes are also known to have respiration and energy production machinery - the mitochondria - and favor antioxidant conditions, which makes them particularly resistant to oxidative stress. "The early stages of the disease are precisely associated with hypometabolism and the presence of oxidative stress. All this places them in one way or another at the heart of the problem," explains **Nadia Rosenberg**, first author of the study and research assistant in the Department of Fundamental Neurosciences at UNIL.

With this in mind, Jean-Yves Chatton's laboratory sought to strengthen the antioxidant functions of astrocytes with the expectation of a protective effect on neurons. To do this, they focused on a protein, UCP4. The role of this protein is to lower the oxidation resulting from these mitochondria when they generate energy by consuming oxygen. A previous study showed that when UCP4 was overexpressed in the mitochondria of astrocytes, it improved the survival of neurons by a mechanism that for now is still poorly understood. "We produced viruses capable of infecting astrocytes and delivering UCP4 into their mitochondria," says the researcher. By doing this, they have succeeded in diverting Alzheimer's mice from their pathological trajectories.

A door open to new treatment strategies

The results of the study show that targeting astrocytes and their mitochondria is an effective strategy to prevent the neuronal decline observed in the early stages of the disease. The approach used in this study, delivering genes to mice using viruses, is the equivalent of gene therapy in humans. However, it is too early to speak of a potential treatment, especially since gene therapies are not yet perfected. On the other hand, the study opens up solid avenues of exploration. "We will now identify the molecules and mechanisms that link UCP4 to the development of Alzheimer's disease. This future research could lead to the identification of a drug treatment.

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