Researchers identify an action mechanism for a drug against Alzheimer' disease

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A study conducted on mice published in the journal *Geroscience* has identified the action mechanism of a promising compound against Alzheimer's disease, developed by the team of Medical Chemistry and

Pharmacology at the University of Barcelona. The new drug belongs to a family of molecules that, when bound to imidazole I2 receptors, these cause a reduction in neuroinflammation and an improvement in cognition and other markers of the progression of this disease, the most prevalent among dementias. The results show that these beneficial effects would occur when the calcineurin pathway is modulated. According to the researchers, this preclinical study opens the door to the development of new therapies against Alzheimer's, a disease that has not been cured yet, and also against other neurodegenerative diseases.

The article results from the collaboration of two research teams from the Faculty of Pharmacy and Food Sciences, led by Mercè Pallàs, member of the Institute of Neurosciences (UBNeuro), and Carmen Escolano, from the Institute of Biomedicine of the University of Barcelona (IBUB). The study is also signed by UB researchers Christian Griñán Ferré, Foteini Vasilopoulou, Sergio Rodríguez Arévalo, Andrea Bagán and Sònia Abás.

Late-onset Alzheimer's disease murine model

The new compound, which presents a high affinity and selectivity regarding imidazole I2 receptors, has been designed and synthetized by the group on medical chemistry led by Carmen Escolano. These receptors are in several organs and take part in multiple physiological processes (analgesia, inflammation, nervous system diseases, etc.). Moreover, they are related to neurodegenerative processes and they seem to increase in the brain of people with Alzheimer's disease.

Previous studies carried out by this research group have shown the positive effect of this family of compounds on the evolution of Alzheimer's. "Following these results, our goal was to determine the mechanism and parameters that change when the drug is given to animal models, specifically to mice with neurodegeneration linked to aging,

which is considered linkable to late-onset Alzheimer's. That is, the one in which the symptoms start around the age of 65, " notes Carmen Escolano.

In the experiment, the researchers analyzed different markers of disease progression, as well as short- and long-term behavioral and memory tests, to study the effects of treatment on the behavior and memory of mice. The results show a significant improvement in the animals that received the drug, compared to the control group. "The new molecule improved cognition and alleviated the anxiety in mice. In addition, we were able to confirm at a molecular level that the treatment with this molecule reduced the typical neuroinflammation and oxidative stress in Alzheimer's, and it decreased specific markers of the pathology, such as tau protein or beta amyloid," says Mercè Pallàs.

The study also enabled researchers to deduce the mechanism of action of the new compound. "Our findings provide evidence that the molecular changes that take place after treatment are related to the calcineurin pathway, an enzyme phosphatase responsible for the production of inflammatory mediators such as cytokines or the reduction of neuronal plasticity," notes Carmen Escolano.

"These results", continues the researcher, "open up new possibilities for this family of imidazole I2 receptor ligands, as the cognitive improvement they produce in animal models of neurodegeneration is determined by the mechanism of action described."

More information: Foteini Vasilopoulou et al, I2 imidazoline receptor modulation protects aged SAMP8 mice against cognitive decline by suppressing the calcineurin pathway, *GeroScience* (2020). DOI: 10.1007/s11357-020-00281-2

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