# AsEH enzyme: A new pharmacological target against Alzheimer's disease

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A UB study published in the journal *Neurotherapeutics* has validated a new pharmacological target for Alzheimer's disease. The results show the inhibition of the enzyme soluble epoxide hydrolase (sEH) in murine models with the disease reduces the neuroinflammatory process, improving the endogen response of the organism and reducing the

neuronal damage and death that cause this type of dementia.

These results confirm the role of this enzyme in the evolution of Alzheimer's disease and pinpoint its inhibition as a potential strategic target for this disease and for others that feature neuroinflammation.

The new study is led by the lecturers of the Faculty of Pharmacy and Food Sciences Mercè Pallàs (Institute of Neurosciences), Santiago Vázquez (Institute of Biomedicine of the UB—IBUB) Carles Galdeano (IBUB), and Christian Griñán-Ferré (Institute of Neurosciences of the University of Barcelona—UBNeuro). Other participants are the experts of the Institute of Biomedical Research of Barcelona (IIBB)—from CSIC and IDIBAPS—the Autonomous University of Barcelona, the University of Santiago de Compostela and the California Davis University.

## A strategy focused on inflammatory processes

The drugs that are currently used to treat Alzheimer's disease have a limited efficiency and only in light phases of the disease. The therapeutic strategies of the last years have been specifically targeted at counterbalancing molecular paths such as the accumulation of amyloid beta and the formation of plaques in the brain, typical in this pathology. In the study, researchers used a new approach related to the inflammatory processes that contribute to unchain this disease and shape its pathogenesis.

"It is important to expand the research on the therapy to treat Alzheimer's towards new pharmacological targets, preferably related to pathophysiological pathways of the disease. In this case, our interest lied on sEH, since its inhibition showed powerful anti-inflammatory effects and some of its inhibitors were or had been in clinical phases in the treatment for hypertension, anti-inflammatory processes and neuropathic

pain," says Mercè Pallàs.

The enzyme sEH is present in the whole organism and which is relatively abundant in the murine and human brains. This enzyme makes the epoxyeicosatrienoic acids (EETs), molecules that reduce the inflammatory response under pathological conditions such as hypertension or diabetes, lose their anti-inflammatory activity and can even cause inflammation. Given these background, researchers analyzed the effects of the inhibition of she in two animal models with Alzheimer's disease, one regarded as familiar Alzheimer's and the other linked to the progress of the disease with advanced ages. The first part of the study showed that the expression of this enzyme increased in two animal models -compared to the control group- as well as in brain samples from patients with Alzheimer's. "These findings make the sEH to be linked to the progression of Alzheimer's and we can consider it to be a new pharmacological target," says the researcher.

## Drugs with neuroprotector effects

Once the sEH enzyme was considered a new therapeutic target, researchers validated it using three sEH inhibitors structurally different, one of them designed and synthetized by the group led by Santiago Vázquez. The results showed that all the used compounds, regardless of their chemical structure, were able to prevent cognitive deterioration in both animal models. "The oral treatment with different drugs allowed us to stop the cognitive damage and reduced all markers of the disease, such as the accumulation of amyloid plaques, tau phosphorylation, endoplasmic reticulum stress, and oxidative stress," says Mercè Pallàs.

Moreover, the new therapeutic strategy can have implications in the treatment of other pathologies. "sEH leading to an increase of endogen antiinflamatory defenses in the organism means the inhibitors of the enzyme can be an appropriate, efficient and safe therapy in pathologies

that feature inflammation," says Santiago Vázquez. The researcher adds that they are assessing new inhibitors of sEH patented by the University of Barcelona not only in models for Alzheimer's disease but also in models of Niemann-Pick type C disease, neuropathic pain and acute pancreatitis, all of them with an important inflammatory element.

**More information:** Christian Griñán-Ferré et al, Pharmacological Inhibition of Soluble Epoxide Hydrolase as a New Therapy for Alzheimer's Disease, *Neurotherapeutics* (2020). DOI: 10.1007/s13311-020-00854-1

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