Neuronal gateway to essential molecules in learning and memory discovered on atomic scale

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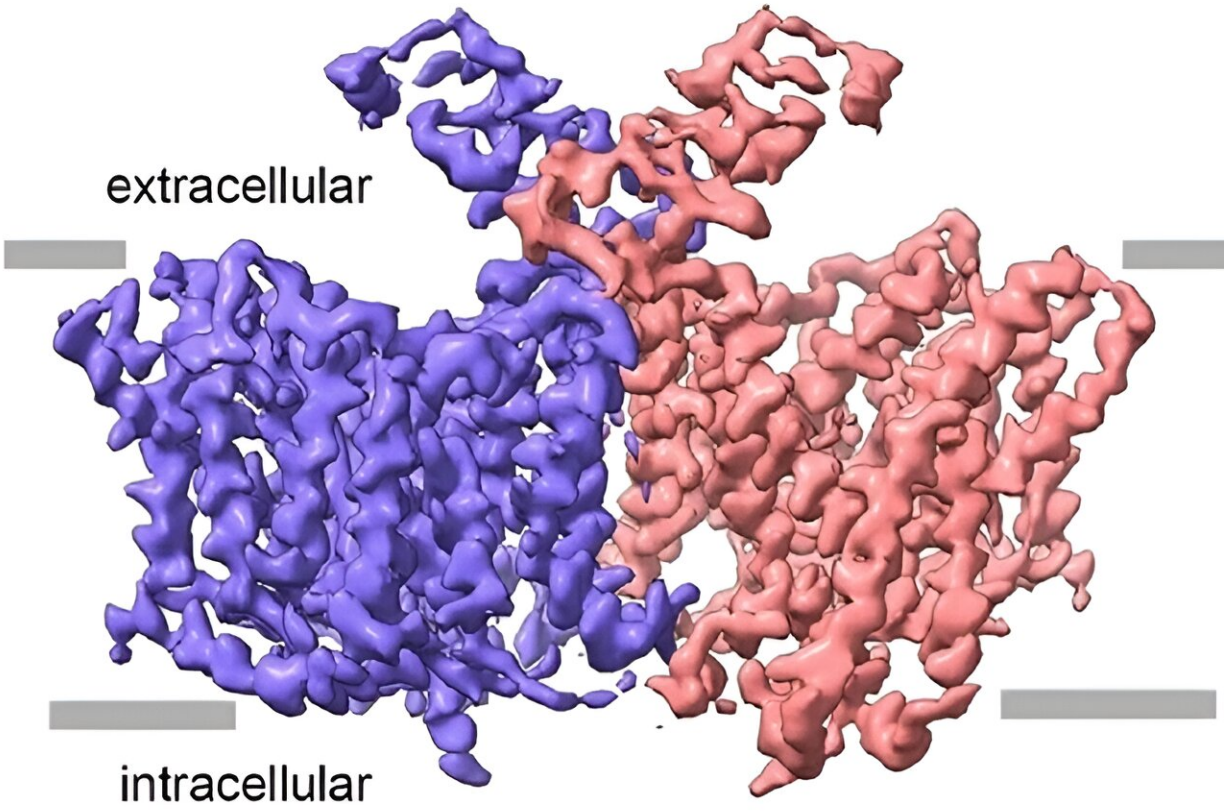

The discovery of the structure and mechanism of action of the Asc1 protein, which is the in-and-out pathway of neurons for crucial amino acids in cognitive processes, could help in the design of drugs against schizophrenia, stroke and other neurological diseases. Credit: University of Barcelona

Learning from an experience, remembering an anecdote or changing an attitude are examples that reveal how all our behavior is the result of the exchange of chemical compounds—neurotransmitters—between neurons. Unraveling what exactly happens at the molecular level when neurons "talk" to each other at synapses is crucial for understanding the human brain in general and, in particular, for helping to solve mental health problems.

Now, a study has observed and described the structure of a protein in the membrane of neurons that acts as a gate that opens and closes. It is the protein Asc1/CD98hc (Asc1), which acts as a specific transporter for certain key amino acids for learning and memory.

The article, published in the journal *Nature Communications*, was led by teams from the University of Barcelona (UB), the Institute for Research in Biomedicine (IRB Barcelona), the Spanish National Cancer Research Center (CNIO) and the Rare Diseases Networking Biomedical Research Center (CIBERER).

A protein linked to mental illness

The activity of the Asc1 protein has been linked to different types of mental pathologies. Therefore, understanding its three-dimensional structure will allow the development of new drugs for these pathologies.

"Modulating Asc1 activity could be a therapeutic strategy for conditions such as stroke and schizophrenia. Determining the structure of Asc1 at atomic resolution is important because it can help in the search for compounds that modify its activity," says expert Óscar Llorca (CNIO).

"The collaboration between the UB, IRB Barcelona and the CNIO has been key to unraveling the mysteries of Asc1 and gaining unprecedented insight into its structure and function. The discovery not only sheds light

on the complex cellular machinery underlying fundamental cognitive processes, but also brings us closer to the development of more precise therapeutic interventions for a range of neurological disorders," adds Manuel Palacín, lecturer at the Department of Biochemistry and Molecular Biomedicine of the UB's Faculty of Biology and head of the Amino Acid Transporters and Disease Lab at IRB Barcelona.

In addition to the experts Óscar Llorca and Manuel Palacín, Ekaitz Errasti-Murugarren, professor at the Department of Physiological Sciences at the UB's Faculty of Medicine and Health Sciences, also participated in the study. The first authors are Josep Rullo-Tubau (IRB Barcelona) and María Martínez-Molledo (CNIO).

Transporting molecules crucial for cognitive functions

Every cell in the body has gates in its membrane for exchanging substances with the outside environment. These are proteins that open and close continuously according to the needs of the cell. Specifically, they open inwards, capture molecules—for example, an amino acid—with a modification in their structure, release them and open outwards, or vice versa.

The Asc1 protein is found mainly in neurons of the hippocampus and cerebral cortex in the brain. It specializes in moving two key amino acids—namely D-serine and glycine—into or out of the neuron for the neural connections—the synapses—involved in learning, memory and brain plasticity, which is the ability of the nervous system to modify circuits in response to new environments.

Fluctuations in the supply of these amino acids have been linked to schizophrenia, stroke, ALS and other neurological diseases. There have

long been attempts to design drugs that regulate Asc1 activity to treat these diseases, but unsuccessfully. A detailed understanding of the atomic structure of Asc1 provides essential information to achieve this.

Caught when opening inside

The Asc1 protein was purified by the expert Josep Rullo-Tubau at IRB Barcelona, and transferred to the CNIO so that María Martínez-Molledo could observe it with cryoelectronic microscopy and, thus, determine the structure of Asc1 in 3D and high resolution using these images. With the cryoelectronic microscopy technique, the molecules are frozen at high speed and observed under electron microscopes. Advanced imaging techniques are then used to interpret the information.

The observed structure shows Asc1 when it has been trapped at a stage where the gate was open toward the inside of the cell, just when it was waiting to receive an amino acid to be transported. "From its atomic structure, we were able to predict which parts of the protein seem important for binding the amino acid to be transported, and the possible mechanism for transporting it out of the cell," says Llorca.

The groups of the experts Víctor Guallar (Barcelona Supercomputing Center) and Lucía Díaz (Nostrum Biodiscovery) made these predictions about the functioning of the transporter, which were tested by Rullo-Tubau by measuring the effect of specific mutations in Asc1. This study was complemented by Rafael Artuch (Hospital Sant Joan de Déu) and the Biostatistics and Bioinformatics scientific platform at IRB Barcelona, headed by Camille Stephan-Otto Attolini.

One protein with two modus operandi

The findings help explain another peculiarity of Asc1. While the rest of

the family of transporters to which it belongs—called HATs—can only exchange amino acids—that is, transport one amino acid into the cell when they take out another, or vice versa—Asc1 can take out one amino acid without the need to introduce another, and open and close in a vacuum. This mode of transport is called diffusion.

The results obtained on the molecular structure of Asc1 provide data to better understand the function performed by each of the transport modes.

More information: Josep Rullo-Tubau et al, Structure and mechanisms of transport of human Asc1/CD98hc amino acid transporter, *Nature Communications* (2024). DOI: 10.1038/s41467-024-47385-3

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