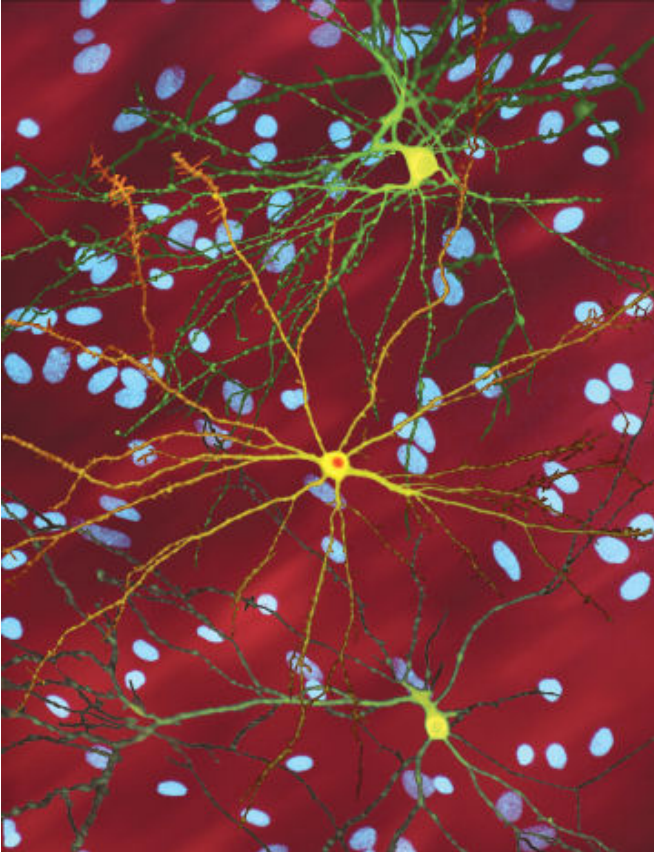


Researchers identify a molecular mechanism involved in Huntington's disease

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A montage of three images of single striatal neurons transfected with a disease-associated version of huntingtin, the protein that causes Huntington's disease. Nuclei of untransfected neurons are seen in the background (blue). The neuron in the center (yellow) contains an abnormal intracellular accumulation of huntingtin called an inclusion body (orange). Credit: Wikipedia/ Creative Commons Attribution 3.0 Unported license

Researchers from the Institute of Neurosciences of the University of Barcelona (UBNeuro) and the August Pi i Sunyer Biomedical Research Institute (IDIBAPS) described a mechanism, the increase of

proteinaceous synthesis, which takes part in the degeneration of the type of neurons that are affected in Huntington's disease, a genetic neurodegenerative disease. These results, published in the journal *Brain*, could help researchers design new therapies to treat this and other brain-affecting diseases.

The study is led by Esther Pérez-Navarro, lecturer at the Faculty of Medicine and Health Sciences of the UB and researcher at the August Pi i Sunyer Biomedical Research Institute (IDIBAPS). Other researchers from the University Pablo de Olavide have taken part in the study too.

Huntington's disease is a genetic neurodegenerative disease caused by the mutation of the huntingtin gene, which causes the early loss of striatal projection neurons, with effects in the motor coordination and cognitive and psychiatric damage. The new study analyzed the role in this proteinaceous synthesis altering process, a mechanism that allows neurons read the genetic code to synthesize proteins.

Improvement of motor coordination in mice

In order to study this mechanism, the researchers analyzed the total and phosphorylate levels of 4E-BP1, a protein that inhibits proteinaceous synthesis, in mice models with the disease. "The results show the total levels of the protein are reduced, while the phosphorylate levels increase in striatal projection neurons in mice with the disease, compared to control mice, so the protein synthesis increases, as seen in samples from patients' brains," says Esther Pérez-Navarro, also researcher at the Biomedical Research Networking Center on Neurodegenerative Diseases (CIBERNED).



Kinases and Phosphatases in Neuronal Function and Dysfunction Research Group, led by Esther Pérez-Navarro, lecturer at the Faculty of Medicine and Health Sciences of the UB and researcher at the August Pi i Sunyer Biomedical Research Institute (IDIBAPS). Credit: University of Barcelona (UB)

This study opens the door to identifying biomarkers to detect the [disease](#) before the first symptoms appear. In this sense, the researchers, in collaboration with the Unit of Movement Disorders in Hospital de la Santa Creu i Sant Pau, are studying whether the proteinaceous synthesis is also altered in other cells, such as blood cells and fibroblasts (skin cells). "The advantage of this study being conducted in Huntington's, associated with a genetic mutation, is that we can analyze these changes in carriers who do not show symptoms and we can make a long-term monitoring," says Esther Pérez-Navarro.

More information: Jordi Creus-Muncunill et al, Increased translation as a novel pathogenic mechanism in Huntington's disease, *Brain* (2019). [DOI: 10.1093/brain/awz230](https://doi.org/10.1093/brain/awz230)

Provided by University of Barcelona

To confirm this relation between inappropriate activity of proteinaceous synthesis and the disease, the researchers blocked this mechanism pharmacologically and observed improved motor function in mice, and that different molecular values were recovered in normal levels in the brains. "These results show an increase in the proteinaceous synthesis in the Huntington's disease is damaging and therefore, it represents a potential therapeutic target for new treatments such as a drug that can be administered in a non-invasive manner to normalize proteinaceous synthesis," says Pérez-Navarro.

A common mechanism in other brain diseases

Although this is the first time the proteinaceous synthesis alteration is related to this disease, this is a mechanism that was described in other neurodegenerative diseases such as Alzheimer's and Parkinson's, and other [mental disorders](#) such as autism. "Finding common mechanisms in different diseases affecting the brain makes it more attractive, since the same therapy could benefit different diseases," says Pérez-Navarro.

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